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Evaluation of the factors affecting survival and local recurrence in thigh soft tissue sarcomas

Savaş Yıldırım, MD[1], Mert Çiftdemir, MD[2], Fethi Emre Ustabaşıoğlu, MD[3], Funda Üstün, MD[4], Ufuk Usta, MD[5]

[1]Department of Orthopedics and Traumatology, Lüleburgaz State Hospital, Kırklareli, Türkiye
[2]Department of Orthopedics and Traumatology, Trakya University Faculty of Medicine, Edirne, Türkiye
[3]Department of Radiology, Trakya University Faculty of Medicine, Edirne, Türkiye
[4]Department of Nuclear Medicine, Trakya University Faculty of Medicine, Edirne, Türkiye
[5]Department of Pathology, Trakya University Faculty of Medicine, Edirne, Türkiye

ABSTRACT

Objectives: The aim of this study was to evaluate the factors affecting local recurrence and survival in patients with soft-tissue sarcomas located in the thigh.

Patients and methods: This retrospective cross-sectional study evaluated 41 soft tissue sarcoma patients (21 males, 20 females; mean age: 57.9±13.7 years; range, 18 to 90 years) with thigh involvement between January 2010 and December 2020. All surgical intervention was performed by one surgeon with an experience of 15 years in orthopedic oncologic surgery. Epidemiological, radiological, histopathological, and metabolic features, as well as surgical and oncological treatments and prognoses, were assessed. The data was statistically analyzed to determine factors affecting local recurrence and survival in these cases, staged using Enneking and the American Joint Committee on Cancer classifications.

Results: Liposarcomas were the most common type of tumor (39%), followed by undifferentiated pleomorphic sarcomas (32%). Tumors >10 cm were associated with decreased survival rates. High-grade tumors, tumor necrosis, Ki-67 index >20%, and positive surgical margins were also associated with lower survival rates. Metastatic patients had significantly lower survival rates. Local recurrence was significantly more frequent in patients with positive surgical margins. Survival rates were significantly lower in metastatic patients.

Conclusion: There are many factors that affect local recurrence and survival of soft tissue sarcomas. The size of the mass, the presence of necrosis, a high Ki-67 index, positive surgical margins, and the presence of metastasis are the main factors that should be taken into consideration.

Keywords: Local recurrence, soft tissue sarcoma, survival, thigh.

Soft tissue sarcomas (STS) are rare, nonepithelial malignant tumors with mesenchymal origin, mostly located in retroperitoneal area and proximal extremities. Soft tissue sarcomas account for fewer than 1% of all human malignancies.[1] Incidence of STS is four to five times that of primary malignant bone tumors. Seventy-five percent of STS are located in extremities.[2] The most frequent localization is the thigh region.[2]

Most sarcomas present as painless and gradually enlarging, often deep-seated soft tissue masses. Due to their indolent clinical features and rare incidence, STS are often ignored by the patient or misinterpreted as benign lesions by physicians. These interpretation errors cause delays in diagnosis and may have a negative contribution to the prognosis. Although there are multiple factors that contribute to prognosis and survival in STS, rarity of STS and diversity of

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Correspondence: Savaş Yıldırım, MD. Lüleburgaz Devlet Hastanesi Ortopedi ve Travmatoloji Kliniği, 39750 Lüleburgaz, Kırklareli, Türkiye.

E-mail: drsavasyldrm@gmail.com

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the tumor subtypes often cause confusion regarding diagnosis, prognosis, and lack of standardization in treatment among physicians.[3] To eliminate this ambiguity in diagnosis and treatment, it is essential that the factors affecting survival and prognosis in STS should be clearly and precisely defined and well-known by the physicians. This study is focused on thigh-located STS cases to study a more homogeneous tumor subtype since the thigh is the most prevalent site for STS. The aim of this study was to evaluate the factors affecting local recurrence (LR) and survival in STS cases located in the thigh.

PATIENTS AND METHODS

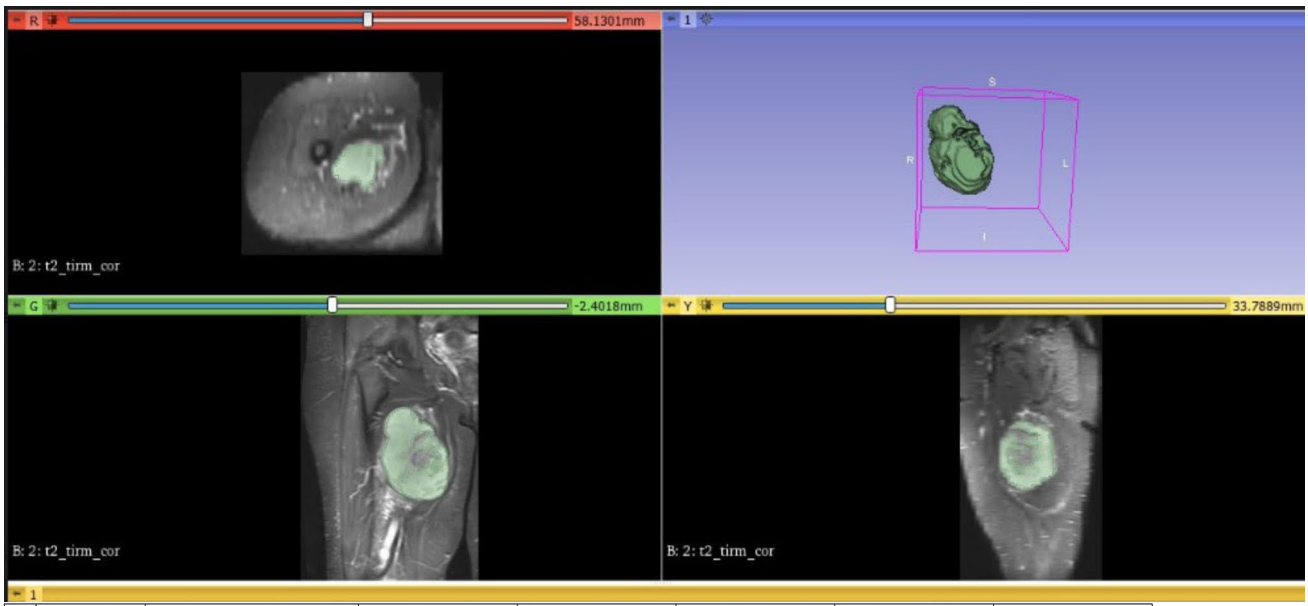
In this retrospective cross-sectional study, data of all patients with histopathologically proven extremity STS treated surgically between January 2010 and December 2020 were collected from the archives of the Bone and Soft Tissue Tumors Council of Trakya University Hospital. A total of 74 cases were found in the database. Patients with STS located other than in the thigh and patients with incomplete data were excluded, and finally, 41 patients (21 males, 20 females; mean age: 57.9±13.7 years; range, 18 to 90 years) were enrolled in the study. All surgical intervention were performed by one surgeon with an experience of 15 years in orthopedic oncologic surgery.

Epidemiological, clinical, radiological, and laboratory data regarding age, sex, tumor site, histopathological (HP) tumor types, HP tumor volumes, surgical excision types, surgical margins, tumor grades, Ki-67 index, and tumor necrosis ratio were collected from the hospital automation and picture archiving and communication system (PACS) of the hospital. Histopathological tumor volumes were calculated in gross examination of the specimen.[4] Surgical margins were classified using the residual tumor (R) classification.[5] For statistical significance, leiomyosarcoma, chondrosarcoma, and angiosarcoma cases were grouped as others, and all sarcomas included in the study were classified as liposarcomas (LS), undifferentiated pleomorphic sarcomas (UPS), fibroblastic tumors (FT), malignant peripheral nerve sheath tumors (MPNST), and others (OT) in terms of their HP origins.

Radiological tumor volumes for each case were calculated using an open-source program (3D Slicer version 4.10.2; https://www.slicer.org/). Magnetic resonance images were extracted from PACS hardware in the DICOM (Digital Imaging and Communications in Medicine) format and uploaded into the program. Exact contours of the masses were selected semiautomatically using intensity-based algorithms from the "segment editor" tab. Redundant selection areas were deleted with the "scissors" and "erase" tools. Anatomical three-dimensional models of the segmented lesions were created, and parameters such as the volume and surface area of the lesion were automatically measured by the software using the "segment statistics" tool from the "quantification" tab (Figure 1). Additionally, the radiological dimensions of the tumors were measured and noted in their longest axis on magnetic resonance imaging. All radiological interpretations were performed by the radiologist member of the tumor council.

Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)-computed tomography (CT) views of patients were evaluated using maximum intensity projection views on the workstation. Metabolic tumor volume (MTV), total lesion glucose (TLG), mean standardized uptake value (SUV_{mean}), and maximum standardized uptake volume (SUV_{max}) were calculated as PET-CT parameters.[6] Metabolic tumor volume was defined as the area surrounded by the 42% isocontour around the maximum PET voxel of the lesion using PET VCAR (Volume Computer Assisted Reading) software (Advanced Workstation 4.4; GE HealthCare Technologies Inc., Chicago, IL, USA). Metabolic tumor volume is the sum of the volume of voxels with standardized uptake volumes that exceed a certain threshold in a tumor. Total lesion glucose is calculated by multiplying the MTV with the SUV_{mean} value.

All data were combined for staging the patients using both Enneking and the American Joint Committee on Cancer (AJCC) staging systems.[7,8] Details about oncological treatment of patients, such as neoadjuvant and adjuvant therapy protocols, clinical progress, and last follow-up dates were collected from the Institutional Oncologic Center records. There is no clear treatment protocol regarding the effectiveness of adjuvant chemotherapy and radiotherapy treatments. These treatment methods were not used in low-grade patients with negative surgical margins and without distant metastases upon the decision of the musculoskeletal system council, which is an expert board of medical oncologists and radiation oncologists. Only adjuvant chemotherapy was given to three patients, only adjuvant radiotherapy was given to eight patients, and adjuvant chemotherapy with radiotherapy was given to 15 patients. All the collected data were evaluated and statistically analyzed to determine the factors affecting LR and survival in STS cases located in the thigh.



	A	B	C	D	E	F	G
1	Segment	Number of voxels (voxels)	Volume (mm^3) (1)	Volume (cm^3) (1)	Surface area (mm^2)	Volume (mm^3) (2)	Volume (mm^3) (2)
2	Segment_1	69245	429242	429.242	52361.1	431011	431.011

FIGURE 1. Three-dimensional modeling and volume calculation of the mass on magnetic resonance images.

Statistical analysis

Statistical analysis was done with IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Normality analyses of quantitative data were performed with the Kolmogorov-Smirnov test. Data that did not fit the normal distribution were compared with the Mann-Whitney U test. The Pearson chi-square test was used to compare qualitative

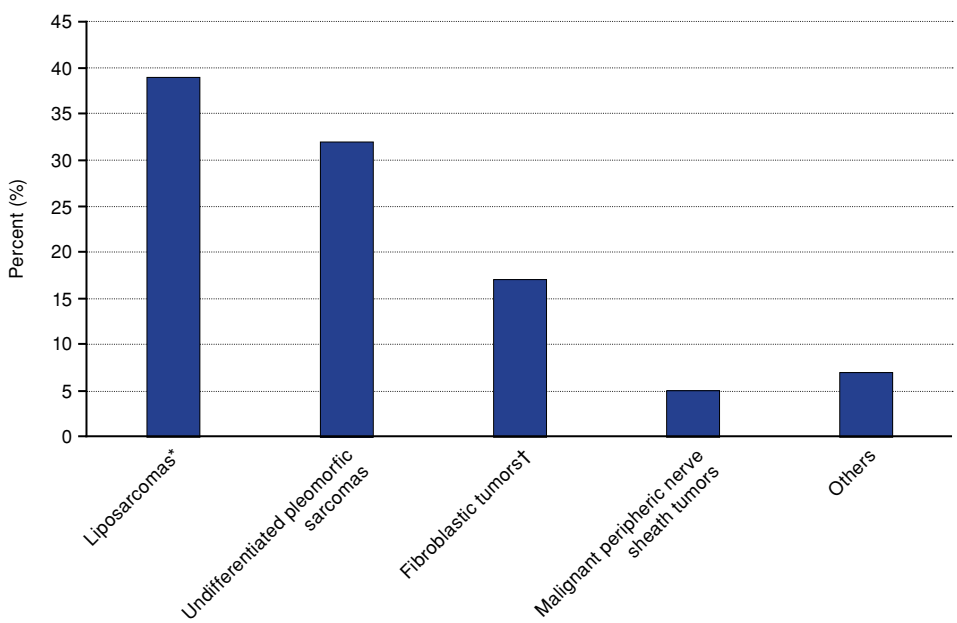


FIGURE 2. Histopathological origins of the tumors.
* 5 low-grade, 2 dedifferentiated, 6 myxoid and 3 pleomorphic liposarcomas; † 2 fibromyxoid sarcomas, 2 fibrosarcomas and 3 high-grade myxofibrosarcomas.

data. Survival analysis was performed using the Kaplan-Meier test. A Cox regression test was used in multivariate analysis. Data are presented with mean ± standard deviation, frequency (percentage), and the 95% confidence interval. A p-value <0.05 was considered statistically significant.

RESULTS

There were liposarcomas in 16 patients (39%), undifferentiated pleomorphic sarcomas in 13 (32%), fibroblastic tumors in seven (17%), malignant peripheral nerve sheath tumors in two (5%), high-grade leiomyosarcoma in one (2%), extraskeletal myxoid chondrosarcoma in one (2%) and angiosarcoma in one (2%) patient according to the 2020 World Health Organization Soft Tissue and Bone Tumors classification (Figure 2).

The mean radiological tumor volume was 463±560.5 cm^3 (range, 10 to 1,967 cm^3) in the study group. Radiological dimensions of the tumors in their longest axis were compared. Seven (17.1%) STS had a size between 5 to 10 cm, and 34 (82.9%) had a size >10 cm. Radiological dimensions and radiological tumor volumes had no statistically significant effect on LR, but survival was decreased significantly in patients with tumors >10 cm (p=0.039).

Preoperative PET-CT was performed only in 22 (52%) patients. Thorax and abdomen CT were the staging tools used for the rest of the patients. In PET-CT, the mean SUV_{max} was 14.07±11.5 (range, 2.3 to 37), the mean SUV_{mean} was 6.30±5.6 (range, 1 to 21.8), the mean MTV was 344.98±406.52 cm^3 (range, 15.7 to 1,609 cm^3), and the mean TLG was 2,117.98±3,464.3 (range, 53 to 11,745.7). Of the 22 patients with preoperative PET-CT, 18 had high-grade tumors, and four had low-grade tumors. There was no statistically significant difference between metabolic parameters (SUV_{max}, SUV_{mean}, TLG, and MTV) and LR and survival in both high and low-grade tumors.

The mean HP tumor volume was 1,460±1,758.2 cm^3 (range, 36 to 7,830 cm^3). According to HP grades, 25 (60%) STS were classified as high-grade, and 16 (40%) were classified as low-grade. Histopathological grades of the tumors showed no statistical significance on LR; however, survival rates were significantly lower in patients with high-grade tumors (p=0.017). Tumor necrosis was present in 26 (63.5%) STS, while no necrosis was present in 15 (36.5%). The mean Ki-67 index was 29% in the entire study group. The mean Ki-67 index was 44% in high-grade and 5% in low-grade STS. Survival was significantly lower in patients with tumor necrosis and a Ki-67 index higher than 20% (p=0.024 and p=0.007, respectively).

The patients were evaluated for surgical margins according to R classification.[4] Sixteen (39%) patients

TABLE I
Survival and local recurrence according to Enneking and AJCC staging systems

	Survival		Local recurrence		
	Alive	Dead	Yes	No	Total
Enneking classification					
IA	7	0	6	1	7
IB	6	2	5	3	8
IIA	2	1	2	1	3
IIB	8	5	9	4	13
III	6	4	6	4	10
Total	29	12	28	13	41
p	0.016		0.839		
AJCC classification					
IA	1	0	1	0	1
IB	12	2	10	4	14
IIIA	2	0	2	0	2
IIIB	8	6	9	5	14
IV	6	4	6	4	10
Total	29	12	28	13	41
p	0.012		0.758		

AJCC: American Joint Committee on Cancer; Chi-square; p<0.05.

had a positive surgical margin and were classified as R2. Of the remaining 25 (61%) patients with negative surgical margins, seven (17%) were classified as R1 (17%), and 18 (44%) were classified as R0. Local recurrence was significantly more frequent in R2 patients (p=0.044). There was no statistically significant relation between R classification and survival rates (p>0.05).

Thirty-three (80%) patients applied to our institution for the first time without applying to another hospital. Eight (20%) patients were referred to our institution due to recurrences that developed after various treatments performed in other hospitals. Ten (24.4%) of 41 patients presented with metastatic tumors. At admission, five (50%) had lymph node metastasis, four (40%) had pulmonary metastasis, and one (10%) patient had bone metastasis. Patients were staged using both Enneking and AJCC classifications.[7,8] Numerical data regarding Enneking and AJCC staging systems are given in Table 1. Both staging systems were found to have a significant relationship with survival (p=0.016 and p=0.012, respectively).

TABLE II
All statistical data

	LR	Survival
Age	0,654	0.043*
Histopathological tumor types	0.734	0.011*
The longest axis on MRI (≥10 cm)	0.845	0.039*
SUV_{max}	0.797	0.274
SUV_{mean}	0.866	0.758
Total lesion glucose (TLG)	0.164	0.183
Histopathological tumor volume (HTV)	0.922	0.057
Radiological tumor volume (RTV)	0.390	0.079
Metabolic tumor volume (MTV)	0.249	0.100
Tumor grades	0.960	0.017*
Tumor necrosis	0.598	0.024*
Ki-67 (>%20)	0.658	0.007*
Surgical margin	0.044*	0.854
Enneking classification	0.839	0.016*
AJCC classification	0.758	0.012*
Adjuvant treatment	0.492	0.664
Metastasis†	0.517	0.015*
Metastasis‡	0.819	0.002*
Local recurrence (LR)	-	0.105

* Significant Statistics p<0.05; † Presence of metastases at the time of admission; ‡ Development of metastases during follow-up.

All patients were evaluated multiple times during their diagnostic and therapeutic workflow in the Bone and Soft Tissue Tumors Council of Trakya University Hospital. No neoadjuvant oncological treatment was offered to any patient. According to postoperative definitive HP analysis, staging, and patient-specific variables, 26 (63%) patients received adjuvant oncological treatment. Adjuvant treatment protocols consisted of only chemotherapy in three (7%), only radiotherapy in eight (20%), and chemotherapy and radiotherapy combined in 15 (37%) patients. No adjuvant oncological treatment was given to 15 (37%) patients. Adjuvant oncological treatment had no statistically significant effect on LR (p>0.05). Patients with pulmonary metastases had significantly lower survival rates (p=0.002).

Finally, the effect of LR on survival was investigated; LR did not significantly affect survival (p>0.05). All statistical data are summarized in Table 2.

Local recurrences were observed in 13 (31.7%) patients. Of the 13 cases with LR, eight were already referred to our institution from external centers due to LR. In five (12%) patients, new LRs were observed during the follow-up. The mean duration of LR was 20±17.98 (range, 2 to 60) months. Twelve (29.2%) of the patients included in the study died due to tumor-related causes during follow-up. Twenty-nine (70.7%) patients were alive at the end of the study. The mean follow-up period of the patients who died was 30.6±33.1 (range, 12 to 124) months. The mean follow-up period of the surviving patients was 52.1±32.76 (range, 12 to 124) months. The mean age at which the deceased patients were diagnosed was 62.7±14.8 years, whereas the mean age at which the survivors were diagnosed was 55.9±13 years.

DISCUSSION

Soft-tissue sarcomas are rare and mortal tumors with mesenchymal origin. Course and prognosis of STS are highly influenced by various factors: the location of the tumor, HP origin, HP grade, tumor size, surgical margins, and neo/adjuvant oncological treatment. There are studies that scrutinize prognostic factors in STS in the literature. However, there is no complete consensus on this issue. Factors affecting LR and survival in patients with STS located in the thigh were evaluated in this study.

A study reported that advanced age has negative impact on survival rates in STS patients.[9] In this

study, there was a significant relationship between age at diagnosis and survival (p=0.043). The mean age at diagnosis was 55.93±13 years in surviving cases and 62.75±14.8 years in deceased patients. A statistical significance was found between HP tumor types and the mean age at diagnosis. The mean age at diagnosis was significantly older in the UPS group compared to the rest of the HP tumor types (p=0.002).

Histopathologic diagnosis of the tumors affects patient survival in STS. Brennan et al.[10] compared dedifferentiated LS and UPS and showed a significant difference in favor of LS in disease-specific survival. Survival times in LS cases were significantly longer than in UPS cases (p=0.011) in our study. There was no significant difference between LR.

The most common symptom of STS is a palpable, painless soft tissue mass.[11,12] Studies reported significant relationship between the long axis of the tumor and survival when the tumors were clinically classified as <5 cm, 5-10 cm, and >10 cm on the long axis at first presentation.[13,14]

Histopathologic grading is a prominent prognostic factor for survival in patients with STS.[15,16] Our results confirm that HP grading is significantly related to survival in STS patients (p=0.017). There was no significant relationship between HP grading and LR (p>0.05).

A direct relationship between the necrosis rate detected after neoadjuvant chemotherapy and prognosis in STS has been reported in the literature.[17-19] In a meta-analysis, the rate of LR was increased, and survival decreased in cases with necrosis rate <90% after neoadjuvant chemotherapy.[18] However, no correlation between prognosis and necrosis rate was found in another study.[17] Only the presence of tumor necrosis in HP specimens was evaluated since none of the patients received neoadjuvant oncological therapy in our study. Decreased survival was found significantly related to presence of tumor necrosis (p=0.024).

Various immunohistochemical markers are used for HP diagnosis and grading. The most common immunohistochemical marker is the Ki-67 index. This marker represents the proliferating tumor cells and is related to poor prognosis in STS.[20] Tumors with a Ki-67 index >20% are regarded as high-grade, rapidly metastasizing tumors with lower survival rates. Moreover, Ki-67 is an independent marker for distant metastases and tumor-related deaths.[13,21] In our study, STS with a Ki-67 index >20% was significantly related to shorter survival (p=0.007).[22] No correlation was present between the Ki-67 index and LR (p>0.05). A significant decrease in survival was present in patients with tumors >10 cm in our study (p=0.039). Tumor size had no effect on LR.[22]

Positron emission tomography-CT is not the conventional staging tool for STS.[1] Nearly half of our patients were staged using PET-CT. The rest of the patients were staged using conventional thorax-abdomen CT. In the literature, SUV_{max} has been shown to be associated with prognosis in various epithelial tumor types, including pulmonary, esophagus, and head and neck cancers.[23,24] This relationship was also reported in small and heterogeneous cases of STS.[25,26] The precise role of the preoperative 18F-FDG PET-CT scan and its power and ability to predict survival and LR in STS are still debated. Sambri et al.[26] found low SUV_{max} values in synovial sarcoma and myxoid LS, but they were high in UPS. Authors suggested that 18F-FDG PET-CT may be an appropriate staging and follow-up tool for patients only with specific STS histotypes. In our study, the mean SUV_{max} levels in MPNST and UPS cases were significantly higher than in LS and FT cases (p=0.015 and p=0.035, respectively). According to our results, none of the PET-CT had a significant effect on survival and LR. We attribute the inadequacy of PET-CT parameters to heterogeneity of the HP subgroups, low number of cases undergoing PET-CT examination, and lower metabolic activity of STS.

Staging systems have an important place in predicting prognosis.[1,12] The most commonly used staging systems in STS are Enneking and AJCC classifications. The AJCC classification is based on tumor dimensions, regional lymph node involvement, and distant metastases.[7] Enneking classification is based on tumor grade, anatomic compartments and distant metastases.[8] Both AJCC and Enneking classifications were evaluated against survival in this study, and shorter survival was found in Enneking IIB-III and AJCC IIIB-IV patients (p<0.05).

Surgical treatment of STS should aim for wide resection. Positive surgical margins after resection increase the risk of LR.[5,27-29] Adjuvant treatment in patients with failed local control may cause additional morbidities and higher amputation rate.[29] Yildiz et al.[16] found increased LR rates in patients with positive surgical margins. Gundle et al.[5] reported that R classification best determines the risk of LR. In our study, surgical margins were evaluated using the R classification. Local recurrences were increased in patients with positive surgical margins (p=0.044); however, positive surgical margins

were not significantly correlated with survival.[22] Furthermore, no significant relationship was present between the R classification and LR and survival (p>0.05).[22]

Although limb-sparing surgery with wide surgical excision is one of the determinant factors for prognosis in STS, studies have shown significant improvement in local control with addition of adjuvant RT to limb-sparing surgery.[30,31] Beane et al.[30] demonstrated that local RT has no significant positive effect on survival. The effectiveness of adjuvant chemotherapy on both local control and distant metastases in STS is also controversial.[32] There was no significant difference in terms of LR and survival between the groups that received and did not receive adjuvant oncologic treatment (p>0.05).[32] These treatment methods, which have harms as well as benefits, were not used, particularly in low-grade patients with negative surgical margins and without distant metastases, upon the decision of the musculoskeletal system council, which is an expert board of medical oncologists and radiation oncologists. Only adjuvant chemotherapy was given to three patients, only adjuvant radiotherapy was given to eight patients, and adjuvant chemotherapy with radiotherapy was given to 15 patients.

Sarcomas tend to metastasize through the hematogenous route. Most common site of distant metastasis is lungs. Willeumier et al.[14] stated that the presence of distant metastasis is a poor prognostic factor for survival in patients with high-grade sarcoma. Survival was significantly decreased in patients who both had pulmonary metastases at the time of admission and who developed pulmonary metastases during treatment and follow-up in our study (p<0.05).

It has shown that the development of LR does not have a significant effect on disease-related survival.[16,32] No significant relationship was found between LR and survival (p=0.156).

The limitations of the study are the small number of patients, not having a more homogeneous group in terms of HP diagnosis, and the fact that PET was not performed on all patients.

In conclusion, UPS and LS were the most common HP subgroups. A positive surgical margin was the only factor affecting the development of LR. Metabolic parameters were found to have no statistically significant effect on LR and survival. Patient age at diagnosis, HP subtype and grade of STS, tumor size, presence of tumor necrosis, high Ki-67 index, advanced tumor stage, and development of pulmonary metastases were the factors that shortened the survival. Furthermore, LR did not significantly affect survival.

Ethics Committee Approval: The study protocol was approved by the Trakya University Faculty of Medicine Dean's Office Scientific Research Ethics Committee (date: 09.11.2011, no: 18-02). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concepted, designed and wrote the manuscript: M.Ç.; Made literature review, data collection, critical radiological analysis and revised the manuscript: F.E.U.; Performed the data collection, processing and statistical analysis: S.Y.; Performed data collection, analysis and interpretation of data: F.Ü.; Made literature review, supervision critical revision and interpretation of data: U.U.

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