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Original article

FACTORS AFFECTING OUTCOMES IN EXTREMITY AND TRUNK SOFT TISSUE SARCOMAS

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Abstract

Introduction: Complete surgical resection with negative margins remains the cornerstone of treatment for soft tissue sarcomas (STS). However, the prognostic significance of surgical margin status remains controversial, as outcomes are influenced by multiple tumor- and patient-related factors. This study aimed to evaluate the association between surgical margin status and local recurrence (LR), distant metastasis (DM), and overall survival (OS).

Material and methods: A prospective study included 44 patients with STS who underwent surgical treatment. Demographic, tumor-related, treatment, LR, DM, and survival data were analyzed. Statistical analysis included the Chi-square test, Fisher's exact test, Kaplan–Meier survival analysis, and Log-rank test.

Results: LR occurred in 31.8% of patients and DM in 20.9%. Positive surgical margins were associated with a higher incidence of LR, although the difference was not statistically significant. Surgical margin status was also not significantly associated with OS. In contrast, high-grade and larger tumors showed a consistent trend toward less favorable oncological outcomes.

Conclusion: Surgical margin status was not significantly associated with LR or OS in this cohort. The observed trends suggest that tumor grade and size may have a greater influence on prognosis than surgical margin status alone. The prognostic significance of surgical margins should therefore be interpreted in the context of tumor biology, size, anatomical location, disease stage, and treatment strategy.

Keywords: soft tissue sarcoma, local recurrence, distant metastasis, overall survival

Introduction

Soft tissue sarcomas (STS) comprise a diverse group of malignant mesenchymal tumors characterized by considerable biological and morphological heterogeneity. According to the 2020 WHO classification, this group includes approximately 80 distinct tumor entities, which

are differentiated based on their morphological, immunohistochemical, and molecular characteristics. Individual subtypes demonstrate specific patterns regarding age at presentation, anatomical distribution, biological behavior, and prognosis[1].

Over the past two decades, survival outcomes among patients with STS have shown a gradual improvement. Prognosis is influenced by several clinicopathological factors, including patient age, histological subtype, tumor size, and histological grade. Despite advances in treatment and patient management, the overall 5-year survival rate across all STS subtypes remains approximately 55%. More accurate estimation of an individual's prognosis and risk can be achieved through the use of validated prognostic nomograms, which integrate multiple clinical and pathological variables[2,3].

Surgical resection remains the cornerstone of treatment for adults with localized STS and should ideally be performed by surgeons with specific expertise and training in sarcoma surgery. Assessment of tumor resectability should be undertaken by a specialized multidisciplinary sarcoma team, taking into consideration the disease stage, tumor location, relationship to surrounding anatomical structures, and patient-related comorbidities[4]. The aim of this study was to evaluate the impact of surgical margin status on LR, DM, and OS in patients with STS and to determine the prognostic significance of additional clinicopathological factors.

Material and methods

This prospective cohort study included patients with histologically confirmed STS who underwent surgical treatment at a single sarcoma center between January 2024 and July 2026. A total of 44 patients who fulfilled the predefined eligibility criteria were included in the final analysis. Eligible patients were adults diagnosed with STS of the extremities or trunk with localized disease confirmed by appropriate staging with contrast-enhanced computed tomography (CT). Patients were required to have a minimum follow-up period of 12 months following tumor excision, unless LR, DM, or death occurred within this period, with death considered as a competing event. Patients were excluded if histopathological documentation was unavailable, if metastatic disease was present at initial presentation, or if they had another active malignancy or advanced comorbidities. Patients who did not attend scheduled follow-up examinations regularly were also excluded in order to ensure the completeness and consistency of the collected data. Additional exclusion criteria comprised dermatofibrosarcoma protuberans, extraskeletal Ewing sarcoma or osteosarcoma, abdominal or retroperitoneal STS, and atypical lipomatous tumors (ALT). Demographic, clinical, histopathological, and treatment-related data were obtained from the patients' medical records. The variables of interest included age, sex, histological tumor grade (G1, G2, G3), surgical margin status (R1, R2, R3), disease stage, oncological treatment, including neoadjuvant and/or adjuvant chemotherapy and radiotherapy, as well as the occurrence of LR, DM, and OS. The study was approved by the Faculty of Medicine in Skopje Institutional Review Board (03-6470/12).

Study outcomes

The primary study outcomes were the occurrence of LR and local recurrence-free survival (LRFS). LRFS was defined as the interval between definitive surgical treatment and the first documented LR, or the date of the last follow-up for patients who remained free of LR. Secondary outcomes included OS and the development of DM. OS was defined as the time from the date of definitive surgical intervention to death from any cause or the date of the last documented follow-up for patients who remained alive.

Statistical analysis

Categorical variables were summarized using absolute and relative frequencies, whereas continuous variables were expressed as mean ± standard deviation or median with

interquartile range, according to the distribution of the data. Comparisons between categorical variables were performed using Pearson's chi-square (χ^2) test or Fisher's exact test, where appropriate. Differences in age between groups were assessed using the independent-samples Student's t-test. Follow-up duration was estimated using the Kaplan-Meier method. LRFS and OS were analyzed using Kaplan-Meier survival curves, with differences between groups assessed using the log-rank test. The association between individual clinicopathological factors and LRFS was evaluated using univariable Cox proportional hazards regression. Results were expressed as hazard ratios (HRs) with corresponding 95% confidence intervals. For binary comparisons, odds ratios (ORs) with 95% CI were calculated. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 32.0.0.0 (139) (IBM Corp., Armonk, NY, USA).

Results

The study included 44 patients, of whom 20 were male and 24 female. Ten tumors were classified as low-grade sarcomas and 34 as high-grade sarcomas. In seven patients, the tumor was <5 cm in size, while in 37 it was >5 cm. Eight tumors were superficially located and 36 were deeply located. R0 resection was achieved in 30 patients, and R1/R2 resection in 14 patients. Staging data were available for 35 patients, of whom 10 had early-stage disease, i.e. stage I-II, and 25 had advanced-stage disease, i.e. stage III-IV. Twenty patients did not receive oncological therapy, while 24 received chemotherapy, radiotherapy, or a combination of both. The median duration of follow-up, estimated by the Kaplan-Meier method, was 17 months (95%CI: 10.12-23.88 months; interquartile range: 8-26 months).

Local recurrence and association with clinicopathological characteristics

During follow-up, LR occurred in 14 of 44 patients (32.8%). LR was observed in 9 of 30 patients with R0 resection (30.0%), and in 5 of 14 patients with R1 resection (35.7%) with no significant association between margin status and LR (Fisher's exact test, p=0.738). LR increased with tumor grade (G1, 10.0%; G2, 25.0%; G3, 42.3%), although the overall association was not significant (χ^2=3.684; p=0.158), with a borderline linear trend (p=0.058). After dichotomization, LR occurred in 1 of 10 low-grade (10.0%) and 13 of 34 high-grade tumors (38.2% p=0.132). LR occurred in 1 of 7 tumors <5 cm (14.3%) and 13 of 37 tumors >5 cm

Table 1. Distribution of patients by histological subtype

Histological subtype	Frequency	Percent
Liposarcoma	1	2.3
Leiomyosarcoma	2	4.5
UPS	6	13.6
MFS	7	15.9
Fibrosarcoma	1	2.3
MPNST	5	11.4
Rhabdomyosarcoma	3	6.8
Myxoid liposarcoma	7	15.9
Sarcoma, NOS	1	2.3
Myxoinflammatory fibroblastic sarcoma	1	2.3
DDLS	6	13.6
Low grade fibromyxoid sarcoma	3	6.8
Solitary fibrous tumor	1	2.3
Total	44	100

UPS-undifferentiated pleomorphic sarcoma, MFS-myxofibrosarcoma, MPNST-malignant peripheral nerve sheet tumor, DDLS-Dedifferentiated liposarcoma

(35.1%, p=0.401), and in 3 of 8 superficial (37.5%) and 11 of 36 deep tumors (30.6%; p=0.695). Patients with LR were older than those without LR (62.57±18.16 *vs*. 55.13±17.58 years; p=0.203). LR occurred in 30% of male and 33.3% of female patients. The distribution of patients according to histological subtype is presented in Table 1. The anatomical distribution of tumors is presented in Table 2. The types of surgical intervention are summarized in Table 3.

Table 2. Anatomical distribution of tumors

Location	Frequency	Percent
Upper arm	1	2.3
Forearm	2	4.5
Hand	3	6.8
Pelvis	4	9.1
Thigh	21	47.7
Knee	4	9.1
Lower leg	7	15.9
Trunk	2	4.5
Total	44	100

Table 3. Distribution according to the type of surgical intervention

Type of surgery	Frequency	Percent
Excision	37	84.1
Amputation	5	11.4
Disarticulation	1	2.3
Hemipelvectomy	1	2.3
Total	44	100

Local recurrence-free survival

Median LRFS was 20 months (95% CI: 16.57-23.43), with estimated 12- and 24-month LRFS rates of 67.4% and 44.3%, respectively. LRFS did not differ according to the surgical margin status (log-rank p=0.917); median LRFS was not reached after R0 resection and was 20 months after R1 resection. Median LRFS was 18 months in high-grade tumors *versus* not reached in low-grade tumors (p=0.132), and 19 months in tumors >5 cm *versus* not reached in

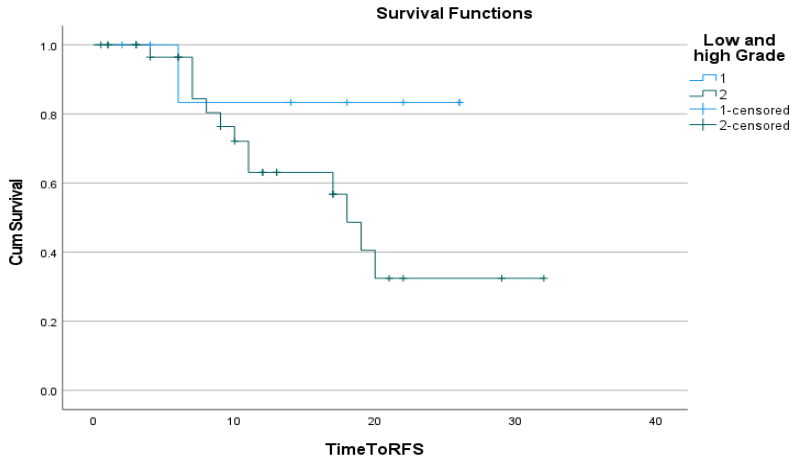

Fig. 1. Kaplan-Meier analysis demonstrated numerically shorter LRFS among patients with high-grade tumors; however, the difference did not reach statistical significance (log-rank χ^2 =2.267, p=0.132). The median LRFS was 18 months in the high-grade tumor group, whereas the median was not reached in the low-grade tumor group.

those <5 cm (p=0.320) (Figure 1). No difference was observed according to tumor depth (p=0.999). In patients with available staging data, median LRFS was 17 months in advanced-stage disease and was not reached in early-stage disease (p=0.227). In univariate Cox analysis, high-grade tumors (HR=4.20; 95% CI: 0.54-32.26; p=0.169) and tumors >5 cm (HR=2.68; 95% CI: 0.35-20.83; p=0.344) were associated with higher estimated hazards of LR, although neither association was statistically significant.

Distant metastases

DM developed in 9 of 43 patients (20.9%). The lungs were the most common site of metastatic disease, accounting for 8 of the 9 patients with DM (88.9%), while bone metastasis was documented in one patient.

Overall survival

During follow-up, 7 of 44 patients (15.9%) died. Median OS was not reached, with estimated 12- and 24-month OS rates of 84.8% and 80.3%, respectively. OS did not differ significantly according to tumor grade (log-rank p=0.634) or surgical margin status (log-rank p=0.927).

Oncological treatment

LR occurred in 2 of 20 untreated (10.0%) and 12 of 24 treated patients (50.0%) (χ^2 = 8.046; p=0.005; OR=9.00; 95% CI: 1.70-47.60). Treated patients had shorter LRFS (median, 18 months *vs*. not reached; log-rank χ^2=4.564; p=0.033) (Figure 2). All treated patients had high-grade tumors compared with 50% of untreated patients (p<0.001). Tumors >5 cm were also more frequent among treated patients (95.8% *vs*. 70.0%; p=0.035; OR=9.86; 95% CI: 1.07-90.65).

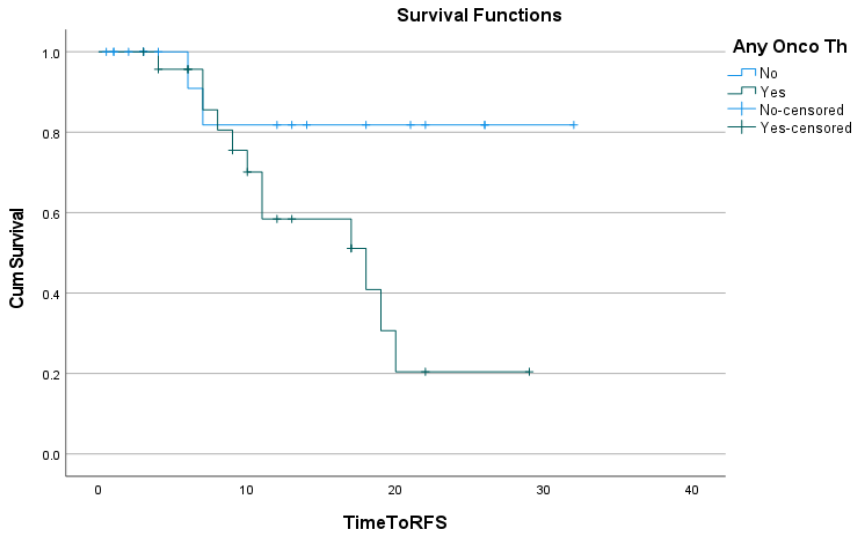

Fig. 2. LRFS differed significantly according to receipt of oncological treatment. Patients who received oncological treatment had significantly shorter LRFS compared to those who did not receive such treatment (log-rank χ^2 = 4.564; p = 0.033). The median LRFS was 18 months in the treated group, whereas the median was not reached in the untreated group.

Discussion

In this prospective cohort study, we evaluated the clinicopathological characteristics and factors associated with LR, DM, and OS in patients with STS. The main findings indicate that high-grade tumors were associated with less favorable oncological outcomes, including a higher frequency of LR and shorter LRFS, although these differences did not reach statistical

significance. Surgical margin status was not significantly associated with either LR or LRFS. Patients who received oncological treatment demonstrated shorter LRFS; however, this finding should be interpreted cautiously, as systemic and/or radiation treatment was preferentially administered to patients with adverse prognostic characteristics, particularly high-grade and larger tumors. Therefore, the observed association is likely attributable to confounding by indication rather than representing a detrimental effect of oncological treatment itself.

In our cohort, an R0 resection was achieved in 30 patients, whereas 14 patients had R1 or R2 resections. During follow-up, LR developed in 14 of 44 patients (32.8%). LR occurred in 9 of 30 patients with R0 resection (30.0%) and in 5 of 14 patients with R1 resection (35.7%). No statistically significant association was identified between surgical margin status and LR (Fisher's exact test, $p = 0.738$). These findings differ from those reported by Pisters, Novais, and Stojadinovic, who identified surgical margin status as an independent prognostic factor for LR and disease-related mortality[5–7]. Similar associations have also been reported by other authors[5-9]. The absence of a statistically significant association between margin status and LR in our study should be interpreted in the context of the limited sample size and relatively small number of events. In addition, the prognostic impact of surgical margins in STS is influenced by several factors, including tumor grade, size, anatomical location, histological subtype, and the relationship between the tumor and surrounding critical structures. In selected cases, a close or microscopically positive margin may be accepted when further resection would result in substantial functional impairment, particularly when combined with radiotherapy. Therefore, margin status should not necessarily be considered an isolated determinant of oncological outcome but rather as one component of a broader multidisciplinary treatment strategy.

High-grade soft tissue sarcomas demonstrated a higher frequency of LR and numerically shorter LRFS in our cohort. Although statistical significance was not reached, the observed pattern is consistent with the established role of tumor grade as an important marker of tumor biological aggressiveness. Histological grade is widely recognized as one of the major prognostic factors in STS and is associated with local disease control, development of DM, and disease-specific survival[10]. In our cohort, LR occurred in 42.3% of grade 3 tumors compared with 25.0% of grade 2 and 10.0% of grade 1 tumors. Furthermore, patients with high-grade tumors had a median LRFS of 18 months, whereas the median was not reached in the low-grade group. Although these differences were not statistically significant, the consistent direction of the findings supports the biological plausibility of an association between higher tumor grade and an increased risk of LR.

Tumor size showed a similar pattern. Patients with tumors measuring >5 cm had a higher frequency of LR and numerically shorter LRFS than those with smaller tumors, although the differences did not reach statistical significance. This observation is consistent with the recognized prognostic importance of tumor size in STS. The lack of statistical significance in our study may, at least in part, reflect the limited number of patients and events, which restricts the statistical power to detect clinically meaningful associations.

The relationship between oncological treatment and outcomes requires particularly cautious interpretation. In the present study, LR occurred more frequently among patients who received oncological treatment, and treated patients had significantly shorter LRFS in the unadjusted Kaplan–Meier analysis. However, all patients who received oncological treatment had high-grade tumors, and the majority had tumors larger than 5 cm. These findings indicate that treatment allocation was strongly associated with unfavorable baseline tumor characteristics. Importantly, when the analysis was restricted to patients with high-grade tumors, the association between oncological treatment and LR was no longer statistically significant, nor was the difference in LRFS. This attenuation of the association supports the presence of confounding by indication and demonstrates why the unadjusted comparison between treated

and untreated patients should not be interpreted as evidence that oncological treatment worsens outcomes.

Previous studies have demonstrated improved disease control and survival outcomes with appropriately selected multimodal treatment strategies in patients with STS[11-13]. The role of radiotherapy and systemic therapy, however, depends on tumor grade, size, location, stage, resectability, and individual patient characteristics. Consequently, patients receiving neoadjuvant or adjuvant treatment frequently represent a higher-risk population than those treated with surgery alone. In observational studies, this treatment-selection process can produce an apparent association between treatment and poorer outcomes even when the treatment itself is beneficial. The present findings should therefore be interpreted primarily as evidence of differences in baseline risk between treatment groups rather than as an estimate of the independent effect of oncological treatment.

Several limitations should be considered when interpreting the findings of this study. The most important limitation is the relatively small sample size, which substantially limits statistical power and increases the probability of type II error. This is reflected in the wide confidence intervals observed for several estimated associations. The relatively short median follow-up of 17 months also limits the assessment of long-term oncological outcomes, particularly because LR and DM in STS may occur several years after primary treatment. Furthermore, the histopathological heterogeneity of STS and the limited number of outcome events, including LR, DM, and deaths, precluded more detailed analyses of individual histological subtypes and restricted the feasibility of multivariable modelling. Another important limitation is the non-random allocation of oncological treatment. Treatment decisions were influenced by adverse prognostic characteristics, particularly high histological grade and larger tumor size, resulting in substantial confounding by indication. Consequently, the observed differences between treated and untreated patients cannot be interpreted as an independent treatment effect.

Despite these limitations, the present study provides prospective real-world data on the clinical course of patients with STS treated at a specialized center. The findings suggest that tumor biological characteristics, particularly histological grade and tumor size, may have a greater influence on oncological outcomes than could be demonstrated for individual treatment-related variables in this relatively small cohort. Although surgical margin status was not significantly associated with LR, LRFS, DM, or OS, achieving a negative surgical margin remains an important principle of oncological surgery and an essential objective whenever technically and functionally feasible.

Conclusion

Overall, the results suggest that the prognostic significance of surgical margins should be interpreted within the broader context of tumor biology, size, anatomical location, disease stage, and treatment strategy. The observed trends towards poorer outcomes among patients with high-grade and larger tumors are consistent with the established biological behavior of STS. Larger prospective cohorts with longer follow-up and sufficient numbers of outcome events are required to better define the independent contribution of surgical margins and multimodal oncological treatment to local control, metastatic progression, and survival.

Conflict of interest statement. None declared.

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