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The relationship between the Ki-67 proliferative index, histological grade, and prognosis in soft tissue sarcomas

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Soft tissue sarcomas are rare malignant tumors characterized by high histological heterogeneity. The study aimed to evaluate the relationship between the Ki-67 proliferative index, the degree of histological differentiation, and prognosis in soft tissue sarcomas. A total of 158 patients were included in the study, and histological evaluation was performed according to the FNCLCC system. The Ki-67 proliferative index was determined using immunohistochemical methods and compared with histological grades. The analyses demonstrated a statistically significant association between the Ki-67 index and the degree of histological differentiation ($p<0.001$). A predominance of high-grade tumors was observed in patients with high Ki-67 levels. In addition, a certain discrepancy was noted between Ki-67–based grading and the FNCLCC system based on mitotic activity. The results indicate that the Ki-67 proliferative index is a useful prognostic marker in soft tissue sarcomas. However, its assessment in conjunction with other morphological and clinical parameters is considered more appropriate.

Keywords: *Soft tissue tumors, sarcoma, proliferative index, prognosis*

INTRODUCTION

Soft tissue sarcomas are rare malignant neoplasms of mesenchymal origin, accounting for approximately 1% of all malignant tumors (Siegel et al., 2019). These tumors are characterized by marked histological diversity, variable clinical behavior, and heterogeneous prognosis. Encompassing more than 100 distinct histological and molecular subtypes, soft tissue sarcomas represent a complex group of malignancies, with each subtype exhibiting its own specific clinical course and prognostic features (Gamboa et al., 2020; Fletcher et al., 2013). The rarity and heterogeneity of the disease complicate early diagnosis and the selection of optimal treatment strategies. Prognosis and standard therapeutic approaches for soft tissue sarcomas vary depending on the clinical stage of the tumor. Currently, the staging system proposed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is considered the most widely used system for staging soft tissue sarcomas (Danieli and Gronchi, 2023).

In modern oncological practice, the degree of morphological differentiation, the TNM staging system, mitotic activity, angiogenesis, and the proliferative index (Ki-67) are regarded as the main prognostic indicators for assessing the prognosis of soft tissue sarcomas (Machado et al., 2021). Ki-67 is a proliferation marker protein expressed in all phases of the cell cycle except the G0 phase. It is widely accepted as a reliable proliferative marker and has prognostic significance in various tumor types, including soft tissue sarcomas (Ogino et al., 2013; Laurila et al., 2022).

A comprehensive analysis of these factors allows for an accurate determination of patients' survival prospects and appropriate treatment strategies.

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Considering all of the above, the present study aimed to determine the prognostic significance of the Ki-67 proliferative index in soft tissue sarcomas and to assess its reliability in the evaluation of histological grade.

MATERIALS AND METHODS

A total of 158 patients aged 20–70 years were included in the study, of whom 70 were men and 88 were women. Predefined inclusion criteria were applied for patient selection. In all patients, the histological diagnosis of soft tissue sarcoma was confirmed. The diagnosis was established based on excision or incision biopsy specimens, and histological evaluation was performed according to the FNCLCC histological grading system. The TNM classification of soft tissue sarcomas (UICC/AJCC) was assessed for each patient. All patients underwent pre-planned clinical and laboratory examinations in line with the study protocol.

RESULTS AND DISCUSSION

The age distribution of the patients included in the study showed that soft tissue sarcomas predominantly occur in middle-aged and older populations. The mean age was 56.9±14.5 years, with the largest proportion of patients being over 60 years old (n=77), indicating that the disease is more frequently detected in later stages of life. Regarding sex distribution, female patients predominated (n=88), while the number of male patients was 70. Morphological diagnosis was primarily performed via excision or incision biopsy (n=119), indicating that in the majority of cases, histological confirmation was obtained directly from the tumor tissue.

Analysis of the histological types of tumors showed that the most frequently encountered morphological type was fibrohistiocytic tumor (n=66). This was followed by liposarcoma (n=19), malignant mesenchymal tumors (n=16), and synovial sarcoma (n=11). Less commonly observed were pleomorphic sarcoma (n=7), rhabdomyosarcoma (n=4), and other rare morphological types. This diversity confirms the high histological heterogeneity of soft tissue sarcomas.

Evaluation of histological differentiation revealed that a significant proportion of patients had tumors that were low- or poorly differentiated. Grade III tumors were identified in 61 patients, while Grade IV (anaplastic) tumors were observed in 9 patients. This finding indicates a predominance of biologically aggressive tumors in the studied population. Analysis of the anatomical location of tumors showed that the most frequent site was the lower extremities (n = 99). The upper extremities (n = 30) and the lumbosacral region (n = 12) were the next most common sites. Tumors in the head and neck regions were rarely observed (Diagram 1). The majority of tumors were localized in the lower extremities (62.7%), which corresponds to the typical anatomical distribution of soft tissue sarcomas.

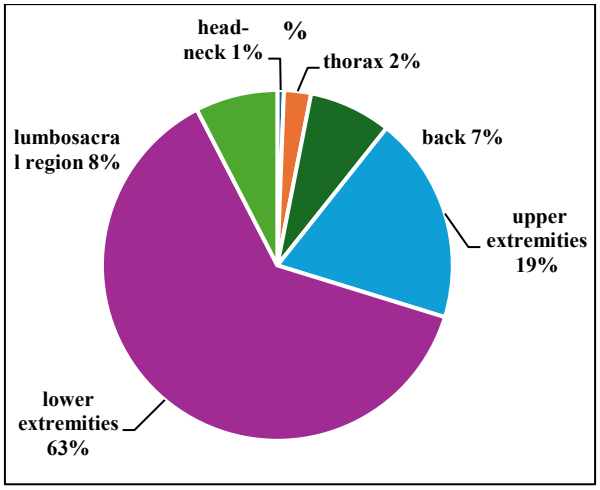

Diagram 1. Distribution of soft tissue sarcomas by anatomical location.

According to the TNM classification, the majority of tumors were classified in the higher T categories (T3–T4), indicating large tumor size and the presence of invasion into surrounding structures. Evaluation of regional lymph nodes showed no metastases in most patients (N0, n=95). Distant metastases were recorded in a small number of patients (M1, n=4). Assessment of the Ki-67 index, a marker of cellular proliferation, revealed elevated values in a proportion of patients. Especially, cases with a Ki-67 index above 40% were observed. In terms of mitotic activity, tumors with a high mitotic count were observed, reflecting the aggressive biological behavior of the tumors.

Table 1. Multivariate model of prognostic factors in soft tissue sarcomas.

Factors	Category	HR (95% Confidence Interval	p-value
Sex	Females (compared to males)	1.18 (0.72–1.94)	0.51
Age group	≥60 years (compared to <60 years)	2.36 (1.21–4.58)	0.013
Tumor location	Lower extremities (compared to other locations)	1.64 (0.89–3.02)	0.11
Histological differentiation grade	Grade III–IV (compared to Grade I–II)	3.27 (1.67–6.41)	0.014
TNM stage	Stage III–IV (compared to Stage I–II)	4.12 (2.01–8.45)	<0.001
Ki-67 index	≥40% (compared to <40%)	2.58 (1.29–5.18)	0.016
Mitotic activity	High (compared to low/moderate)	2.21 (1.01–4.86)	0.027
Angiogenesis	Severe (compared to low/moderate)	1.97 (0.96–4.05)	0.034

Table 2. Distribution of patients by histological grade according to the Ki-67 proliferative index.

Ki-67 activity level (%)	Low grade (Grade I–II)	Moderate grade (Grade III)	High grade (Grade IV)	Total (n)
≤30 %	32	25	3	60
31–40 %	7	11	2	20
≥41 %	5	25	48	78
Total	44	61	53	158

Based on angiogenesis indicators, pronounced vascularization was noted in some patients. During staging, the majority of patients were classified as stage III (n = 42), while early stages (I–II) were relatively less common. This finding indicates that the diagnosis was made at a late stage in most patients. Treatment strategies were primarily based on a combined approach. The most frequently applied method was surgical treatment, with extensive tumor resection performed in the majority of patients (n = 143). In some cases, amputation or exarticulation was carried out. Chemotherapy and radiotherapy were used as adjunctive treatments, particularly for high-stage and poorly differentiated tumors.

Based on the results of the multivariate prognostic model, several clinical and morphological factors were found to be significantly associated with disease progression. Patients aged ≥60 years were observed to have an increased risk ($p = 0.013$). Histological differentiation grade emerged as an important prognostic factor. Tumors of Grade III–IV were associated with a higher risk compared to Grade I–II tumors ($p = 0.014$). Additionally, TNM stage III–IV was significantly associated with poorer prognosis ($p < 0.001$).

A Ki-67 index of ≥40% and high mitotic activity was also considered indicators of a more aggressive clinical course. Cases with pronounced angiogenesis showed a tendency for increased risk. These results indicate that the biological characteristics of the tumor play a key role in the clinical progression of the disease.

In this study, differences between approaches based on the Ki-67 proliferative index and mitotic activity in the assessment of histological differentiation grade in soft tissue sarcomas using biopsy specimens were compared. In addition, the impact of various prognostic factors, including histological grade, on the survival of patients with soft tissue sarcomas was analyzed. The analyses demonstrated a notable discrepancy between Ki-67–based grading and the FNCLCC system based on mitotic activity in the evaluation of histological differentiation grade. In 14.6% of the studied patients, the histological grade determined by Ki-67–based assessment did not correspond to that defined by the FNCLCC system. Furthermore, the Ki-67–based grading system was found to be characterized by higher reproducibility in the assessment of histological grade (Table 2).

At the same time, a high Ki-67 index was associated with a more aggressive clinical course of the disease, highlighting its potential prognostic significance. A statistically highly significant association was identified between the Ki-67 proliferative index and histological differentiation grade (χ^2 test, $p < 0.001$). The proportion of high-grade (Grade IV) tumors was significantly higher in patients with strong Ki-67

activity compared with those exhibiting weak Ki-67 activity. Odds ratio analysis demonstrated that strong Ki-67 activity increased the risk of developing Grade IV tumors by approximately 34-fold.

CONCLUSION

The assessment of the Ki-67 proliferative index during immunohistochemical analysis may depend on a number of technical and methodological factors. Fixation time, the antibodies used, staining protocols, and evaluation methods are considered the main factors that can influence Ki-67 results. In order to minimize these effects, immunohistochemical staining procedures were standardized in the present study, and all specimens were processed in the same laboratory. Nevertheless, the possibility of variability in the intensity and distribution of Ki-67 staining among different tissue specimens cannot be completely excluded.

The analyses also demonstrated a noticeable discrepancy between grading based on the Ki-67 proliferative index and histological grading based on mitotic activity. This discrepancy indicates that, although Ki-67 is a sensitive marker reflecting the biological characteristics of the tumor, its results may depend on various technical and interpretative factors. Therefore, the Ki-67 index should not be used in isolation for the assessment of histological grade but rather evaluated in conjunction with other morphological and clinical parameters. These findings further emphasize that, while the Ki-67 proliferative index is a useful prognostic biomarker in soft tissue sarcomas, methodological standardization and a comprehensive approach are essential for its proper interpretation.

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CONFLICT OF INTEREST

The author declares no conflict of interest related to this study.

AUTHOR CONTRIBUTIONS

Tamara Guliyeva conceived and designed the study, supervised the research process, participated in the histopathological evaluation, and prepared the initial manuscript draft. Samira Safarova contributed to data collection, immunohistochemical analysis, statistical evaluation, and interpretation of the results. Azer Amiraslanov provided scientific supervision, contributed to study design, critically revised the manuscript for important intellectual content, and approved the final version. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

AI STATEMENT

The authors confirm that no artificial intelligence (AI) tools were used to generate, analyze, interpret, or validate the scientific data presented in this study. Any AI-assisted technologies, if used, were limited solely to language editing, grammar correction, or formatting support. The authors take full responsibility for the originality, accuracy, and integrity of the manuscript.

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