Med & Health Aug 2024; 19(2): 526-536 https://doi.org/10.17576/MH.2024.1902.13

ORIGINAL ARTICLE

Reevaluating the Prognostic Value of Histopathological Parameters in Soft Tissue Sarcoma of the Extremities

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Received: 29 Jan 2024 / Accepted: 11 Mac 2024

ABSTRAK

Pelbagai sistem dan penarafan bertujuan untuk menghubungkan parameter morfologi dan klinikal dengan prognosis sarkoma tisu lembut. Walau bagaimanapun, literatur sedia ada menunjukkan penemuan yang tidak konsisten. Kajian retrospektif ini mengkaji nilai ramalan prognostik parameter histopatologi yang biasa digunakan dalam meramal kelangsungan hidup pesakit sarkoma tisu lembut di anggota badan. Kajian ini melibatkan 122 pesakit dan menilai parameter seperti nekrosis tumor, kiraan mitosis, skor pebezaan tumor, dan status sempadan tumor. Hasil kelangsungan hidup dianalisis berdasarkan pembolehubah histopatologi ini. Kadar kelangsungan hidup 5 tahun adalah 48%, dengan jangka hayat median selama 88 bulan. Di kalangan pesakit, 87.7% (n = 107) mempunyai sempadan bebas tumor. Analisis statistik, termasuk Analisis Kelangsungan Kaplan-Meier dan regresi Bahaya Berkadar Cox, mendapati bahawa tiada satu pun daripada parameter ini menunjukkan nilai prognostik yang signifikan (p>0.05). Kajian ini mendapati bahawa tiada parameter histopatologi yang dikaji menunjukkan kepentingan prognostik terhadap kelangsungan hidup jangka panjang di kalangan pesakit sarkoma tisu lembut selama tempoh pemantauan 10 tahun.

Kata kunci: Analisis kelangsungan hidup; histopatologi; malignan tisu lembut; prognosis; sempadan tumor

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ABSTRACT

Various staging and grading systems aim to correlate morphological and clinical parameters with the prognosis of soft tissue sarcoma. However, the existing literature offers inconsistent findings. This retrospective cross-sectional study investigated the prognostic value of common histopathological parameters in predicting the survival of extremity soft tissue sarcoma patients. The study comprised 122 patients, and it evaluated parameters like tumour necrosis, mitotic count, tumour differentiation score, and tumour margin status. The survival outcomes were analysed concerning these histopathological variables. The 5-year survival rate was 48%, with a median survival of 88 months. Of the patients, 87.7% (n = 107) had tumour-free margins. Statistical analyses, including Kaplan-Meier Survival Analysis and Cox Proportional Hazard regression, revealed that none of these parameters exhibited significant prognostic value ($p>0.05$). This study found that none of the histopathological parameters examined demonstrate prognostic significance for long-term survival among soft tissue sarcoma patients over a 10-year follow-up period.

Keywords: Histopathology; prognosis; soft tissue malignancy; survival analysis; tumour margin

INTRODUCTION

Soft tissue sarcomas (STSs) are uncommon malignancies, accounting for less than 1% of adult cancer cases (Dadia & Grimer 2007; Harati & Lehnhardt 2017; United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute 2020). They represent a diverse group of rare malignant tumours within the realm of musculoskeletal soft tissue malignancies, constituting 60-70% of cases and encompassing a wide spectrum of histologic types and prognoses (Alamanda et al. 2012; Coindre 2006; Coindre et al. 1996; Dadia & Grimer 2007; Gronchi et al. 2005; Harati & Lehnhardt 2017; Sbaraglia et al. 2021; Zagars et al. 2003). Various staging and grading systems have been developed to establish correlations between morphological and clinical parameters and prognosis, aiming to guide optimal treatment for each patient (Coindre et al. 2001; Guillou et al. 1997). However, these systems have generated conflicting findings, which cast uncertainty on the utility of these prognostic factors.

Some studies emphasise the importance of histopathological parameters in determining tumour grade (Biau et al. 2012; Büyükceran et al. 2022; Coindre 2006; Coindre et al. 1996; Hashimoto et al. 1992; Liang et al. 2020; Liu et al. 2010; Stojadinovic et al. 2002). Histological grade, often seen as the single most vital prognostic factor for predicting survival and disease-free intervals, has been emphasised

in some reports (Gronchi et al. 2005; Stojadinovic et al. 2002; Weitz et al. 2003; Zagars et al. 2003). Multivariate analyses have suggested that a combination of parameters, including tumour necrosis, mitotic count, and tumour differentiation, is essential for grading sarcomas. Moreover, factors such as tumour histology, grade, and mitotic activity have been identified as significant determinants of survival (Brennan et al. 2014; Liu et al. 2010; Weitz et al. 2003). However, the applicability of these parameters to all sarcoma types remains a matter of debate (Hashimoto et al. 1992; Weitz et al. 2003; Zagars et al. 2003).

Prognostic relevance is also a subject of ongoing debate. While some studies highlight their significance, others challenge their prognostic value (Bilgeri et al. 2020; Goertz et al. 2020; Gronchi et al. 2005; Harati & Lehnhardt 2017; Jang et al. 2021; Liu et al. 2010; Matheron et al. 2022; Palm et al. 2023; Sambri et al. 2021; Shafiq et al. 2022; Sheoran et al. 2022; Weitz et al. 2003; Zagars et al. 2003). Positive microscopic resection margins have been observed to notably influence local recurrence-free survival. They independently forecast distant recurrence-free survival rates and disease specific survival rates for all patients. When surgical margins are negative, the overall disease-specific 5-year survival rate is 83%, whereas positive margins lead to a lower rate of 75% (Stojadinovic et al. 2002).

In the present study, we delved into the prognostic value of histopathological parameters for the survival of patients with STS, particularly tumour margin, mitotic count, tumour differentiation score, and tumour necrosis.

MATERIALS AND METHODS

A retrospective cross-sectional study was conducted using a convenience sampling method to recruit participants, following the acquisition of ethical approval from the institutional review committee (USMKK/JEPeM/17120736). The study focused on patients treated for soft tissue sarcoma (STS) at an orthopaedic oncology and reconstruction clinic of a local tertiary hospital, spanning from January 2011 to December 2020. The inclusion criteria comprised adult patients specifically diagnosed with STS of the extremities, while cases involving retroperitoneal STS or STS in locations other than the extremities were excluded. Additionally, patients with incomplete medical records or those whose various histological parameters could not be ascertained due to sampling challenges or technical issues were also excluded.

Comprehensive medical records and histopathological reports were obtained from the institution's pathology laboratory database. An experienced pathologist assessed the status of tumour margins, mitotic count, tumour differentiation score, and tumour necrosis. All patients underwent wide resection followed by local radiotherapy, and adjuvant chemotherapy was administered to specific groups of patients, including those aged below 40, high-risk groups, or those with pulmonary metastases.

Tumour margins were assessed from the gross tumour specimen. Tumour-free margins were defined as microscopically negative margins, while microscopically positive margins had tumour involvement at the inked margin (Liu et al. 2010). Mitotic counts were conducted under high magnification (400x) in 10 high-power fields (HPF)) (Figure 1A). The mean count per HPF (measured 0.1734 mm^2) was recorded and categorised into scores i.e. Score 1 (0-9 mitoses per 10 HPF); Score 2 (10-19 mitoses per 10 HPF); Score 3 (20 mitoses per 10 HPF). Tumour differentiation scores were evaluated using the French Federation of Cancer Centre (FNCLCC) system (Coindre et al. 2001; Guillou et al. 1997). A score of 1 indicated sarcomas closely resembling normal adult mesenchymal tissue (Figure 1A). When the histologic typing was certain, sarcomas were given a score of 2 (Figure 1B). A score of 3 indicated embryonal and undifferentiated sarcomas. The presence of necrosis was determined by the observation of necrotic areas in any excised tumour slides (Figure 1C). The number of slides taken from the tumour usually depends on the size of the tumour mass. Data was recorded using a pre-designed proforma sheet and analysed through Kaplan-Meier survival, univariable, and multiple Cox regression analyses.

RESULTS

The mean age of the entire cohort of patients was 52.6 years, with 59% being male. The overall median survival was 88 months, with a 5-year

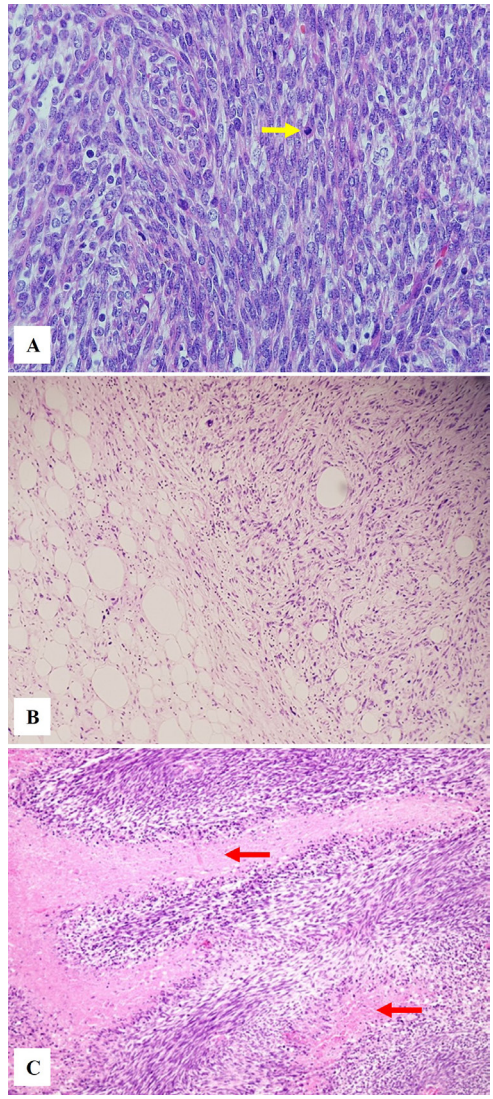

FIGURE 1: Examples of cases from the study to illustrate the histological parameters. (A) Synovial sarcoma (x400 magnification) showing mild nuclear pleomorphism and occasional mitosis (yellow arrow): score 1 grading, no necrosis, and FNCLCC score 1; (B) Dedifferentiated liposarcoma (x200 magnification) showed well-differentiated area (left side) and high grade non-lipogenic sarcoma (right side): score 3 grading, no necrosis, and FNCLCC score 2; (C) Pleomorphic sarcoma (x200 magnification) with geographical type of tumour necrosis: score 3 grading, presence of necrosis (red arrows), and FNCLCC grade 2

survival rate of 48.4%. A summary of demographic data for all patients was provided in Table 1.

The median survival time according to histopathological parameters was presented in Table 2. Tumour-free margins were observed in 87.7% of patients (n = 107). Analysis revealed a median survival of 88 months for patients with tumour-free margins. Analysing mitotic count revealed that patients with low mitotic counts (0-9 mitoses per 10 HPF) had a median survival of 64 months, compared to patients with high mitotic counts (20 mitoses per 10 HPF) who had a median survival of 97 months. Patients with a tumour differentiation score of 1 had a higher median survival rate (142 months) compared to scores 2 and 3, which had median survival rates of 88 months and 97 months, respectively. The median survival time for STS patients with tumour necrosis was 88 months, while those without necrosis had a substantially longer median survival (142 months). None of the histopathological parameters showed significant differences in log-rank test results (all $p>0.05$). Kaplan-Meier survival curves for patient-related histopathological parameters were depicted in Figure 2.

TABLE 1: Demographic characteristics of the patients involve in the study (n = 122)

Variables	Mean (SD)	n (%)
Age (years)	52.61 (18.59)	
Gender		
Male		50 (41.0)
Female		72 (59.0)
Death (5 years)		
No		59 (48.4)
Yes		63 (51.6)
Tumour necrosis		
No		83 (68.0)
Yes		39 (32.0)
Mitotic count		
Score 1: 0-9 mitoses per 10 HPF		53 (43.4)
Score 2: 10-19 mitoses per 10 HPF		50 (41.0)
Score 3: 20 mitoses per 10 HPF		19 (15.6)
Tumour differentiation score		
Score 1		39 (32.0)
Score 2		18 (14.8)
Score 3		65 (53.3)
Tumour free margin		
No		15 (12.3)
Yes		107 (87.7)

Notes: SD: standard deviation; HPF: high-power field

Univariable Cox regression analyses showed that tumour-free margin, mitotic count, tumour differentiation score, and presence of tumour necrosis did not serve as prognostic

TABLE 2: Survival time according to the histopathological parameters (n = 122)

Variables	Median survival time (95% CI)	Log-rank statistic (df)	p-value
Tumour necrosis			
No	142.00 (0.00, 289.91)	0.09	0.771
Yes	88.00 (51.72, 124.28)		
Mitotic count			
Score 1:0–9 mitoses per 10 HPF	64.00 (51.75, 76.25)	1 vs 2:0.02	0.888
Score 2:10–19 mitoses per 10 HPF	88.00 (58.48, 117.52)	1 vs 3:1.66	0.198
Score 3:20 mitoses per 10 HPF	97.00 (0.00, 203.11)	2 vs 3:1.27	0.262
Tumour differentiation score			
Score 1	142.00 (24.50, 259.50)	1 vs 2:3.58	0.059
Score 2	88.00 (88.00, 88.00)	1 vs 3:0.03	0.867
Score 3	97.00 (53.09, 140.91)	2 vs 3:1.88	0.171
Tumour free margin			
No	0.00 (0.00,0.00)	0.83	0.362
Yes	88.00 (52.53, 123.47)		

Notes: CI: confidence interval; df: degrees of freedom.

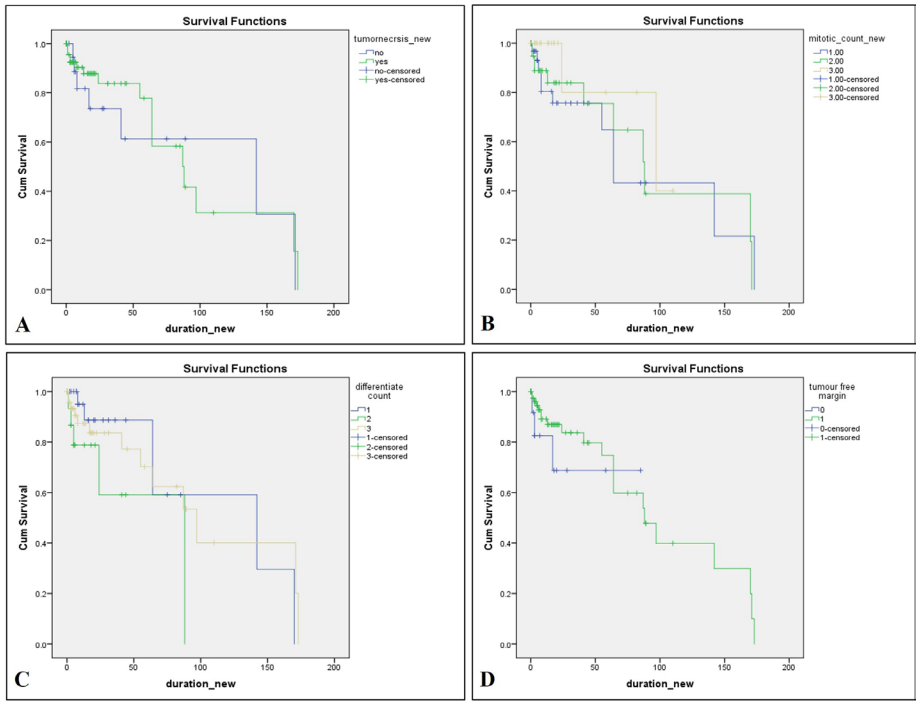

FIGURE 2: Kaplan-Meier survival curves according to the patient-related histopathological parameters for STS: (A) presence of tumour necrosis, (B) mitotic count, (C) tumour differentiation score, and (D) tumour free margin

factors for STS patient survival (Table 3). Even though none of these factors were found significant in univariable Cox regression analysis, they were all included in multiple Cox regression using the backward stepwise method, and all variables were found to be non-significant.

DISCUSSION

STS is a rare and heterogeneous group of malignancies influenced by multiple factors that contribute to its prognosis and survival. Histopathological parameters have been proposed as primary prognostic factors, influencing the decisions on adjuvant chemotherapy. In this study, the 5-year survival rate stood at 48.4%, and the overall median survival duration reached 88 months. While most patients presented with large tumours exceeding 5 cm, our results were consistent with reports from other tumour centres. Liu et al. (2010) and Hashimoto et al. (1992) reported 5-year overall survival rates for local extremity sarcomas of 41% and 43.6%, respectively. The National Cancer Intelligence Network (NCIN) in the United Kingdom reported an enhancement in the 5-year survival rate, which increased from 51% during the 1990s to 55% post-2000. This improvement was attributed to the centralised management of sarcomas (Dadia & Grimer 2007; Francis et al. 2013). A review of 10,000 patients from the Memorial Sloan Kettering Cancer Centre indicated that extremity sarcomas with a local recurrence rate of around 25% over a decade exhibited a disease-specific death prevalence of approximately 40% during the same period. The primary determinants of outcome and prognosis were identified as histologic subtype and grade (Brennan et al. 2014).

A study with 1,116 STS patients found

TABLE 3: Histopathological parameters as prognostic factors for soft tissue sarcoma analysed using univariable Cox regression (n = 122)

Variables	b	Crude HR (95% CI)	Wald statistics	p-value
Tumour necrosis				
Yes	0	1	0.08	0.773
No	-0.13	0.88 (0.36, 2.16)		
Mitotic count				
Score 0: 0-9 mitoses per 10 HPF	0	1	0.01	0.918
Score 1: 10-19 mitoses per 10 HPF	-0.05	0.96 (0.41,2.26)	1.40	0.237
Score 2: 20 mitoses per 10 HPF	-0.92	0.40 (0.09,1.83)		
Tumour differentiation score				
Score 1	0	1	2.39	0.122
Score 2	0.97	2.62 (0.77, 8.92)	0.02	0.884
Score 3	0.07	1.08 (0.40, 2.93)		
Tumour free margin				
Yes	0	1	0.81	0.365
No	-0.17	0.88 (0.65, 1.35)		

Notes: HR: hazards regression; HPF: high-power field

that factors including tumour necrosis, cellularity, tumour differentiation, mitotic activity, cellular pleomorphism, nuclear atypia, the extent of the myxoid area, the amount of fibrous stroma, and histological grading significantly predicted outcomes for STS patients (Hashimoto et al. 1992). However, when subjected to multivariate analysis, only histological grading and the extent of tumour necrosis emerged as statistically significant predictors of prognosis. Histologic grading was found to be prognostically significant for the survival of STS patients (Alamanda et al. 2012; Coindre 2006; Coindre et al. 1996; Hashimoto et al. 1992). The commonly employed histological grading systems include the FNCLCC and the United States National Cancer Institute (NCI) system. These systems incorporate a range of histological and morphological factors in their assessments. To assign grades 1 or 3, the NCI utilises a combination of histological type, mitotic rate, pleomorphism, and cellularity. Meanwhile, the FNCLCC system determines a score based on the assessment of mitotic rate, amount of tumour necrosis, and tumour differentiation score to assign grades (Coindre et al. 2001; Guillou et al. 1997). Nevertheless, the analysis in this study found no statistically significant contribution of any of these histopathological parameters to the final survival. Patients with low or intermediate-grade sarcomas exhibited the most favourable survival rates, and younger patients with high-grade sarcomas receiving systemic adjuvant chemotherapy exhibited better survival. High-grade sarcomas, especially in elderly individuals, presented poor survival outcomes, regardless of the histological parameters considered.

In the present study, most resected tumours achieved good surgical margins (87.7%). Nevertheless, the study revealed that a free tumour margin did not significantly affect the final survival of our STS patients. While low-grade sarcomas have been reported to survive multiple surgical procedures for recurrence without systemic metastases, other studies have indicated the prognostic significance of free surgical margins (Biau et al. 2012; Liu et al. 2010; Matheron et al. 2022; Palm et al. 2023; Gouin et al. 2022; Shafiq et al. 2022; Stojadinovic et al. 2002; Zagars et al. 2003). Recent literature emphasises the importance of margins in achieving local disease control, though it shows less significant correlations between margins and overall patient survival (Gouin et al. 2022; Gronchi et al. 2005; Harati & Lehnhardt 2017; Matheron et al. 2022; Weitz et al. 2003).

Limitations and Recommendations

While the study offers valuable insights into the prognostic value of histopathological parameters in extremity STS patients, it is important to acknowledge its limitations. Firstly, the relatively modest sample size may have limited the statistical power of our analysis, though our status as a primary tumour referral centre helped to ensure a reasonably substantial cohort size. Notably, exclusion of retroperitoneal STS cases was

necessary due to their heterogeneous prognosis and survival outcomes. Instances with inconclusive or insufficient results on histopathological parameters were also excluded, reflecting the challenge in diagnosing STS. Strict inclusion and exclusion criteria were adhered to, mitigating the impact of confounding variables and ensuring the homogeneity of our study population. While we aimed for a more objective assessment by analysing histopathological parameters based on specific sarcoma types, the rarity of these malignancies posed challenges in categorisation. Nevertheless, it is important to highlight that diverse sarcoma types universally employ these histopathological parameters as prognostic factors.

Despite these limitations, the study provides a foundation for further research in this important area of STS prognosis. Moving forward, future research should prioritise prospective studies to establish the prognostic value of these parameters, despite the practical challenges posed by the heterogeneity and rarity of these malignancies. Collaboration with other institutions or tumour registries could facilitate pooling of data from larger cohorts for robust statistical analyses. Multicentre studies may help to capture a more diverse patient population and enhance the external validity of findings and improve the generalisability of results. Additionally, exploring genetic and genomic factors and employing advanced statistical techniques like propensity score matching or hierarchical modelling may enhance the validity and robustness of analyses. By addressing these recommendations, future research endeavours can overcome the limitations identified in the current study and provide a more comprehensive understanding of the prognostic factors influencing STS outcomes.

CONCLUSION

The present study highlights the complex and multifaceted nature of STS prognosis. The findings indicate that the commonly considered histopathological parameters may not serve as robust prognostic indicators for STS patient survival. This raises questions about the adequacy and applicability of existing prognostic models for this rare and diverse group of malignancies. Further research and a more nuanced approach to prognostication are warranted to improve outcomes for STS patients. These findings contribute to the ongoing discourse in the field of STS and call for a re-evaluation of the prognostic value of histopathological parameters. This conclusion is drawn based on a 10-year follow-up.

ACKNOWLEDGEMENT

The authors express their appreciation to Jawatankuasa Etika Penyelidikan Manusia (JEPeM-USM), for granting approval for the study (USMKK/JEPeM/17120736). No financial support was received by the authors for the execution of this research.

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