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Factors affecting the Survival of Soft Tissue Sarcoma Patients of the Extremities at Cipto Mangunkusumo Hospital, Indonesia

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Abstract

Introduction. The strategy for treating limb soft tissue sarcoma (STS) is challenging due to delayed diagnosis and the non-specific clinical picture, leading to the mortality of nearly 50% of newly diagnosed patients. Various therapeutic modalities have been applied to increase the survival of patients with extremity soft tissue sarcoma. However, clinicopathological factors can influence the survival rate and thus affect the effectiveness of therapy. This study aims to determine the numbers and factors influencing overall survival five years after treatment for patients with soft tissue sarcoma of the extremities at Dr. Cipto Mangunkusumo General Hospital (CMGH) in 2011-2015.

Method. A prognostic study was run on patients with complete histopathology who underwent treatment during 2011-2015. Data analysis using the Kaplan-Meier method, cox regression test, and Cox regression with time-dependent variable.

Results. A total of 42 were enrolled in the study. The median survival after therapy for patients was six years (3 months – 8.25 years), with a five-year survival of 52.4%. Factors affecting five-year survival were surgical procedures in limb-saving surgery (HR 0.852 95% CI 0.68 – 1.07, p = 0.163).

Conclusion. The five-year survival rate of soft tissue sarcomas of the extremities was 52.4%. Overall survival is affected by higher-grade sarcoma, incomplete therapy, and worse clinical stage.

Keywords: survival, extremity soft tissue sarcoma, prognosis

Introduction

Soft tissue sarcoma (STS) is a malignancy of mesenchymal origin, with more than 50 histopathological subtypes identified. The incidence of STS is low, about 1% of all malignancies.[1] However, STS remains a heavy burden in surgical oncology. It is the leading cause of death due to malignancy in the 14-29 year age group. Furthermore, STS accounts for 7-10% of all childhood cancers.[2]

The strategy for treating STS is quite challenging. Nearly 50% of all newly diagnosed patients die during the first year.[1] The diagnosis of STS is often delayed due to non-specific clinical pictures. Thus, it is quite often that the cancer already has local extension or metastasis when diagnosed.[1,3] Histopathologically, soft tissue tumors are difficult to differentiate between malignant and benign based, particularly in a small biopsy specimen.[1] This often results in an unplanned excision requiring more intensive surgery.[4,5] A previous study by Dogan et al. (2019) reported that the 5-year local control rate was 77%, and the five-year survival rate was 71.8% among newly diagnosed STS patients.[6] The prognostic study by Toulmonde et al. (2014) showed that age, sex, tumor location, tumor size, histopathological subtype, tumor grade, bone/neurovascular involvement, incision margin, adjuvant radiotherapy, and adjuvant chemotherapy are prognostic factors that influence STS patients' survival.[7]

Although various studies have been conducted on STS's survival rates and risk factors, there has yet to be a similar study in Indonesia. This study aims to determine the numbers and factors influencing the overall survival rate five years after therapy for patients with soft tissue sarcoma of the extremities at a tertiary hospital in Indonesia in 2011-2015.

Method

A survival analysis proceeded using the cohort retrospective method. Patients diagnosed with STS of the extremities treated with definitive surgery at Dr. Cipto Mangunkusumo National General Hospital from 2010 to 2015 were enrolled in the study consecutively. Those with incomplete medical records were excluded. The diagnosis of extremities STS was instituted based on histopathological results. Clinical characteristics taken from the subjects were age, clinical stage, tumor grade, tumor margin, the completeness of the therapy, radiotherapy, and chemotherapy. The outcome was the overall survival rate and determining factors among soft tissue sarcoma of the extremities measured from the day of surgery. Survival analysis used the Kaplan-Meier curve and Cox regression analysis with hazard ratios (HR): a 5% error bound and 95% confidence interval limit. The power was considered to be 90%.

The Committee of Ethics, Faculty of Medicine, Universitas Indonesia, approved the study number KET-524/UN2.F1/ETIK/PPM.00.02/2021.

Results

Forty-two subjects who met the criteria were enrolled in the study. The baseline characteristics of subjects are presented in Table 1.

Table 1. Subjects' characteristics

Variables	n (%)
Age (years)	51 (7 – 89)
Gender	
– Male	26 (61.9%)
– Female	16 (38.1%)
Follow-up period (years)	6 (0.25 – 8.5)
Tumor site	
– Upper extremity	8 (19%)
– Lower extremity	34 (81%)
Tumor size	
– <5 cm	10 (23.8%)
– ≥5 cm	32 (76.2%)
Regional node involvement	
– N0	34 (81%)
– N1	8 (19%)

Table 2. Subjects' characteristics (continued)

Variables	n(%)
Metastasis	
– M0	27 (64.3%)
– M1	15 (35.7%)
Clinical stage	
– Early (IA, IB, IIA, IIB)	19 (45.2%)
– Advanced (III)	8 (19.1%)
– Metastasis (IV)	15 (35.7%)
Grade	
– Low-grade	12 (28.6%)
– High-grade	30 (71.4%)
Tumor margin	
– R0	21 (50%)
– R1	13 (31%)
– R2	8 (19%)
Surgical intervention	
– Amputation	22 (52.4%)
– Limb-saving surgery	20 (47.6%)
Completeness of treatment	
– Complete	26 (61.9%)
– Incomplete	16 (38.1%)
Recurrence	
– Yes	22 (52.4%)
– No	20 (47.6%)
Comorbidity	
– Diabetes mellitus	10 (23.8%)
– Hypertension	9 (21.4%)
– Others	6 (14.3%)

The overall median survival was 5 (0.25 – 8.5) years, while the five-year survival was 52.4%. The Kaplan-Meier curve is presented in Figure 1.

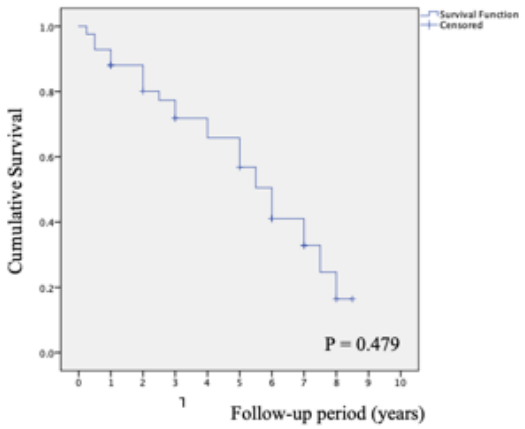

Figure 1. The overall survival analysis of the subjects in this study

Of the clinical characteristics analyzed, tumor grade, the completion of treatment, and stages were factors affecting overall survival, i.e., higher–grade tumor, incomplete treatment, and metastasis ($p < 0.05$). The results of the analysis are presented in Table 2.

Table 2. Risk factors affecting the overall survival rate of STS patients

Factors	HR	CI 95%	p– value
Grade			
Low–grade			
High–grade	4.110	1.00-16.96	0.050
Completion of treatment			
Complete			
Incomplete	2.647	1.03-6.79	0.043
Clinical stage			
Early	Ref	Ref	0.005
Advanced	9.863	0.67-1.10	0.239
Metastases	1.476	1.02-2.13	0.039

Discussion

Among 42 subjects enrolled, tewnty survived for more than five years postoperatively; a 5-year survival rate was 52.4%. This result aligns with a retrospective cohort study by Acem et al. (2020) using international collaborative data between 2000 and 2016, which found a 5-year survival rate of 52.1%,[8] and a study by Hashimoto et al. (2020) that soft tissue sarcoma of the extremities at the age of 17-39 years was 57.1%.[9]

Histologically, soft tissue sarcomas were classified according to the origin of soft tissue cells.[1,9] In this study, the soft tissue sarcomas of the extremities were mostly high-grade (70%). The results are in line with the study of Puri and Gulia (2011) that as many as 71% of patients with soft tissue sarcomas were classified as high-grade.[10] In some tumors, histopathological subtype determines the degree of malignancy. Rhabdomyosarcoma, synovial sarcoma, and Ewing's tumor were classified as high-grade soft tissue sarcoma. On the other hand, liposarcomas are well differentiated, except for undifferentiated, round cell, and pleomorphic liposarcomas, which were included in the high-grade group.[9] Leiomyosarcoma and non-liposarcoma are associated with more frequent distant recurrences. High-grade lesions are at higher risk for metastasis within the first thirty months.[10]

Surgical intervention is the primary treatment for soft tissue sarcomas of the extremities. This study showed that most of the extremity soft tissue sarcoma patients had a free incision margin of 50%. The incision margin is significantly related to the survival of patients with STS of the extremities. The results align with the results of a meta-analysis that the incision margin was associated with the survival of soft tissue sarcomas of the extremities.[12] The incision margin was proven to be closely related to the risk of local recurrence. The 5-year local recurrence rate is 11% for radical margins, 5% for broad margins, and 21% for marginal resection of soft tissue sarcomas in the thigh. Moreover, the local recurrence rate in the R0 group was lower than in the R1 group.[12]

Most subjects in this study had metastases (IV) clinical stage (42.9%). In stage IV STS, the lesion has already metastasized to the lymph nodes or other distant sites, regardless of lesion size, location, or histologic grade. It is also associated with a higher risk of recurrence.[1,2] In this study, most of the subjects underwent amputation by 52.4%. An amputation is a surgical option in patients whose tumors cannot be completely resected. Amputation may be necessary in those patients to minimize the risk of distant site recurrence. In addition, patients with recurrence, untreatable pain, bleeding, or function may also benefit from limb amputation.[13]

This study has several limitations. Despite a retrospective study, this study was merely conducted in one health service center and subjected to be confirmed by a multicenter study.

Conclusions

The five-year survival rate for patients with soft tissue sarcomas of the extremities was 52.4%, and is affected by higher–grade, incomplete therapy, and metastasis.

Disclosure

The authors declare no conflict of interest.

Role of authors

Conceptualization EDY, KSM, DK, AK, Data curation EDY, KSM, DK, AK,, Formal analysis EDY, KSM, AK, Funding acquisition EDY, KSM, Investigation EDY, KSM, AK, Methodology EDY, KSM, DK, AK, Project administration EDY, KSM, Resources EDY, DK, Software AK, Supervision EDY, DK, AK, Validation EDY, KSM, DK, Visualization EDY, KSM, AK, Writing original draft preparation EDY, KSM, AK, Writing review and editing EDY, KSM.

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