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The Prediction of Overall Survival With The Use of The Sarculator In Operated Soft Tissue Sarcoma of The Extremities: Monocentre Experience

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ABSTRACT

Soft tissue sarcomas are rare malignancies with poor prognosis and more than 100 histologic subtypes. Due to their poor prognosis, accurate prognosis cannot be made by the staging system alone. Therefore, normograms have been developed for sarcoma patients. In this study, it was aimed to investigate the real-life data of prognosis prediction of sarculator normogram.

Retrospective observational research was used in our study and the records of 146 patients were reviewed. The study included 50 patients who met the study criteria. The prognostic factors in sarcoma patients were analyzed in the study. Tumor size, tumor grade, age, and histologic subtype of the tumor were examined. In addition, all patients were graded using the sarcoma normogram and divided into percentile groups.

The study's patient population had a median age of 47 years. 37 months was the median overall survival time. Patients with tumor grade 3 showed a statistically lower overall survival than those with grade 1 according to univariate analysis. Among patients divided into three groups according to Sarculator scoring, the high-risk group had a statistically significant difference of 23 months, the intermediate-risk group of 39 months, and the good-risk group of 93 months.

Increased tumor size and grade were statistically significantly associated with poor survival, which was consistent with the literature. Statistically significant 5-10 year survival data were obtained in patients divided into 3 groups and compared with sarcolator. Thus, the accuracy of the Sarcolator was confirmed with real-world data.

Keywords: Softtissuesarcoma, nomograms, prognosis

Introduction

Sarcomas account for less than 1% of adult malignancies, of which 80% are of soft tissue origin. Sarcoma is a very heterogeneous disease, with more than 100 histological subtypes(1-4). Liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic are the three most prevalent subtypes (5).The prognosis of soft tissue sarcomas is poor, and some factors such as stage at diagnosis, tumor size, grade, tumor subtype, and tumor location are effective in prognosis (5-7). Local or locally advanced sarcomas are primarily treated with surgical resection with negative margins (8). Postoperative radiotherapy (RT) and adjuvant chemotherapy may be added depending on tumor size and grade (9).

CurrentAmericanJointCommittee on Cancer (AJCC) softtissuesarcoma (STS) staging is derived from data examining prognostic factors in patients with extremity STS (10,11). Although the stage of disease predicts prognosis in soft sarcomas of the extremities, this prediction is inadequate. Nomograms have been developed for sarcomas because of the inability to accurately predict prognosis with staging alone. Nomograms are a more accurate way to provide prognostic information to both patients and physicians. Nomograms can guide the information needs of the patient and the treatment plan of the physician (12,13). The most recent nomogram is the one used by Memorial Sloan Kettering Cancer Center (MSKCC). According to this nomogram, 12-year survival predictions are made using tumor size, tumor depth, tumor location, patient age, histologic subtype, and data (14,15). While the MSKCC nomogram could be used for all types of soft tissue sarcomas, a new nomogram was developed for extremity soft tissue sarcomas (16). In the extremity soft tissue sarcoma nomogram, survival rates and incidence of distant organ metastases are estimated using age, tumor size, tumor grade, and histologic subtype (16). The Sarculator Nomogram is a prognostic tool developed from a large series of patients and validatedin many

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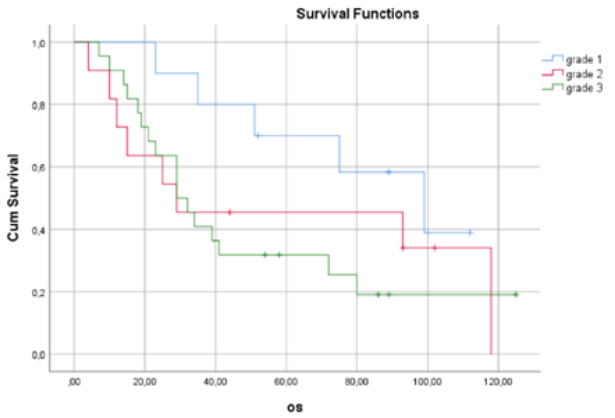

Fig. 1. Overall Survival Between Grades

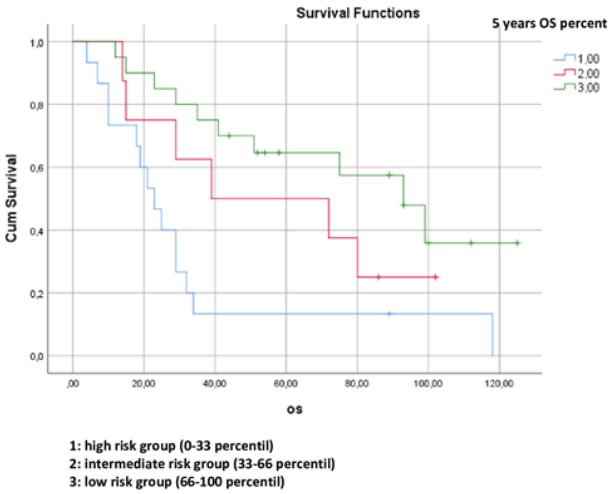

Fig. 2: 5-year Overall Survival (OS) Between Groups

patients, available online and free of charge (13). We aimed to investigate the real-world data of the nomogram in extremity soft tissue sarcoma by applying it to our patients in this study.

Materials and Methods

Patients with soft tissue sarcoma who were admitted to Dicle University and treated between November 2011 and November 2019 were included. This was a retrospective observational study and the records of 146 patients were reviewed. Patients younger than 18 years, patients with secondary malignancies, patients who were mentally unstable, patients whose treatment was not continued at our center, and patients with missing data were excluded from the study. Additionally, patients with gastrointestinal stromal tumors, Ewing sarcoma, peripheral, alveolar/embryoid rhabdomyosarcoma, desmoplastic small round cell tumor, and desmoid tumor were disqualified. Of the 146 patients screened, 50 patients between 18 and 80 years of age whose follow-up and treatment were completed at our center and for whom all data were available were included in the study. Adjuvant and neoadjuvant chemotherapy consisted of ifosfamide (2500 mg/m2 IV 1-3 days), mesna (2500 mg/m2 IV 1-3 days), and adriamycin (60 mg/m2 IV day 1). The tumors were graded as grade 1, 2, and 3 according to the French National Federation of Cancer Centers (17). In relation of age with survival, each yearly increase in age was analyzed in relation to survival. In the relationship of tumor size increase with survival, the relationship of each 1-cm increase with survival was examined.

Our patients were staged using the Sarculator nomogram, which is used in soft tissue sarcomas. In this nomogram, prognosis was predicted using tumor size (0-35 cm), patient's age (18-100), tumor histology (categorical variable: leiomyosarcoma, dedifferentiated pleomorphic sarcoma, liposarcoma, others), tumor grade (categorical variable: 1,2,3). Patients were divided from the 33rd and 66th percentile of sarculator points. Patients were divided into three risk groups: high, intermediate, and low. Comparisons between groups were made using the 5-year and 10-year overall survival statistics.

Statistical Analysis: The Kolmogorow-Smirnov test was used to determine whether numerical data had a normal distribution. For values that were not normally distributed, the median, minimum, and maximum were utilized. Univariate analysis was used to evaluate the variables. Variables with $P \leq 0.1$ were included in the multivariate analysis. Prediction of 5-year and 10-year OS was calculated using sarculator. Patients were divided into 33rd percentile and 66th percentile with sarculator results. High-risk, intermediate-risk, and low-risk patient categories were established. To estimate overall survival (OS), the Kaplan-Meier test was utilized. The OS was outlined as the interval between a diagnosis and death from any cause. Censoring was done on patient data that were still alive at the time of the research. The log-rank test was used to evaluate OS differences across groups.The statistical significance level was set at 5% in calculations. SPSS (IBM, version 25) statistical software package was used for the analysis of our study.

Results

There were 50 patients total in the study, with 30 men and 20 women. The median age of the patients was 47 years (43-52). The most common histologic subtype was undifferentiated pleomorphic sarcoma. Table 1 displays general patient characteristics. Median tumor size was 9 cm (2-47). The median overall survival was 37 (4-126) months for total population; 99(52-145) monthsin grade 1, 29 (24-

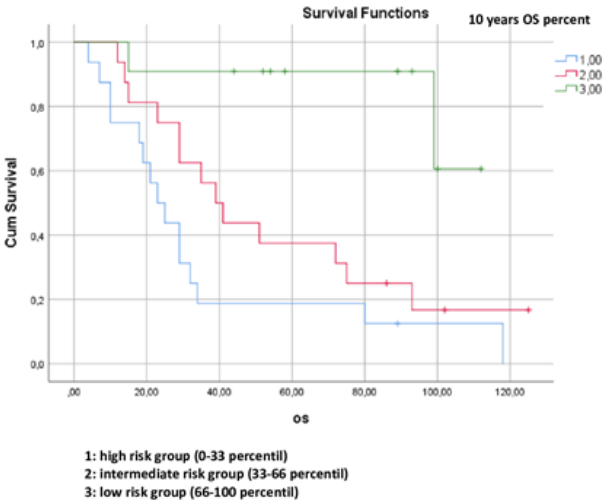

Fig. 3. 10-Year Overall Survival (OS) Between Groups

106) months in grade 2, and 29 (4-39) months in grade 3.

On univariate analysis, worse survival was linked to growing tumor size. (P: 0.032, HR: 1.008, Cl: 0.98-1.03). Patients with grade 3 tumors fared worse than those with grade 1 tumors in terms of survival. (P: 0.044, HR: 1.68, Cl: 1.01-2.80) (Figure 1). According to univariate analysis, no significant difference was found in terms of age, histologic subtype, and R1 and R2 resection. Comparing histologic subtypes did not reveal any statistically significant differences in survival (Table 2). Tumor grade was not substantially related to poor survival on multivariate analysis, whereas tumor size was associated with poor survival (P: 0.011, HR: 1.04, Cl: 1.01-1.08) (Table 3).

Patients were divided into three groups with 2 break points in the 33th and 66th percentiles according to the sarculator scoring, the groups' 5-year overall survival (OS) rates differed statistically significantly from one another OS 23 (15-30) months in the high-risk group, 39 (25-98) months in the intermediate group, and 93 (64-121) months in the low-risk group) (Figure 2). There was a statistically significant difference of 23 months between the groups for 10-year survival (15-30) in the high-risk group, 39 months (27-50) in the intermediate-risk group, and the median was not reached in the good group (p:0.013) (Figure 3).

Discussion

The AJCC classification is used to predict the prognosis of soft tissue sarcomas (10,11). However, since the AJCC classification does not provide adequate prognostic prediction, additional prognostic indices are needed for the physician's treatment decision. Therefore, nomograms have been developed to predict the prognosis of soft tissue sarcomas. In our study, we investigated the applicability of the Sarculator nomogram in extremity soft tissue sarcomas.

First, we compared the data obtained in our study with the literature; the most common histologic subtype in soft tissue sarcomas in guideline reviews is liposarcoma (5,18). In our study, the most common histologic subtype was undifferentiated pleomorphic sarcoma with a frequency of 24% and liposarcoma with a frequency of 18%. This might be connected to the few patients. The small number of patients may have contributed to the lack of a statistically significant difference in survival with regard to age and tumor histological subtypes in the study analysis. According to numerous studies, soft tissue sarcoma patients with larger tumors had a lower chance of survival. (6,19,20). In line with the literature, our analysis found that larger tumors were related with poorer outcomes (P: 0.032 HR: 1.008, Cl: 0.98-1.03). Poorer survival data occur with increasing tumor size.

Increasing histologic grade is an indicator of distant organ metastasis of malignancy and poor overall survival (1,5,18,21). In our study, overall survival was 99 (52-145) months in patients with grade 1, 29 (24-106) months in grade 2, and 29 (4-39) months in grade 3. Univariate analysis revealed that patients with tumor grade 3 had statistically lower overall survival than patients with tumor grade 1, which was consistent with the literature. (P: 0.044, HR: 1.68, Cl: 1.01-2.80). Based on these results, it should be predicted that large, high-grade tumors have a significant chance of recurrence and poor survival. Adjuvant chemotherapy/radiotherapy should be considered for this group of patients.

In examining the real-world consistency of the sarculator nomogram in our study, we obtained 93 months of overall survival data in the low-risk group above the 66th percentile. For the intermediate group, this time frame was 39 months, whereas for the high-risk patients it was 23 months. This difference was statistically significant. There was a statistically significant difference in 10-year survival between the groups. In the studies that analyzed survival using the Sarculator, adjuvant chemotherapy provided additional benefit only in the high-risk groups as classified by the Sarculator. Chemotherapy had no additional contribution in the low-risk group (22,23).

Our study had limitations such as single center, small number of patients and retrospective study. This study should be supported by integrating the sarculator nomogram into prospective studies investigating the role of adjuvant therapy in soft tissue sarcoma. In conclusion, our study demonstrated that the sarculator nomogram accurately predicts 5 - and 10-

Table 1: General Characteristics of Patients

	N (%)
Age (median, range)	47 (43-52)
Gender	
Female	20 (40)
Male	30 (60)
Histolojic subtypes	
Undifferentiated pleomorphic sarcoma	12 (24)
Liposarcoma	9 (18)
Fibrosarcoma	7 (14)
Leiomyosarcoma	6 (12)
Other subtypes	16 (32)
Grade	
1	12 (24)
2	11 (22)
3	24 (48)
Unknown	3 (6)
The treatment received	
Neoadjuvan	7 (14)
Adjuvan	23 (46)
Radiotherapy	
Yes	26 (52)
No	24 (48)

Frequency analysis of patients characteristics

Table 2: Univariate Analysis

	HR	Cl	P
Age	1.008	0.98-1.03	0,472
Tumor size	1.049	1.01-1.08	0,032
Grade			
Grade 2 vs* grade 1	1.81	0.5-5.7	0,301
Grade 3 vs grade 1	1.68	1.01-2.80	0,044
Resection			
R1 vsR2	1.01	0.4-2.4	0,9
Histolojic subtypes			
Liposarcoma vs other	0.9	0.4-2.3	0,9

Univariate Logistic Regression, Enter Method
*versus

Table 3: Multivariate analysis

	HR	Cl	P
Tumor size	1.04	1.01-1.08	0,011
Grade			
Grade 2 vs* grade 1	2.1	0.6-6.6	0,183
Grade 3 vs grade 1	2.04	0.7-5.8	0,181

Multivariate logistic regression, enter method, backward style
*versus

year overall survival with real-world data. We believe that the Sarculator should be more actively used in future studies of adjuvant treatment of soft tissue sarcoma. We anticipate that it will help physicians make adjuvant treatment decisions and help patients satisfy their curiosity about the prognosis of their disease.

Ethics Approval: Gazi Yasargil Training and Research Hospital Clinical Research Ethics Committee approved the study protocol: (number anda date: 324-04.07.2019)

Conflict of Interests: Authors have declared no conflict of interest for this article.

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