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Factors affecting prognosis and treatment strategies in metastatic soft tissue sarcomas: twenty years of experience

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Abstract. – OBJECTIVE: In this study, we aimed to reveal the general clinicopathological features, treatment features, and factors that could predict overall survival in metastatic soft tissue sarcomas, a very rare and heterogeneous disease group.

PATIENTS AND METHODS: This study was a retrospective cohort study. Patients monitored with metastatic soft tissue sarcoma between January 2001 and January 2021 were evaluated retrospectively. Patients aged 18 years and over, histopathologically diagnosed with metastatic STS, and unsuitable for operations, such as local curative surgery or metastasectomy, were included in the study.

RESULTS: A total of 179 patients in the metastatic stage and monitored in our center were included in the study. The median follow-up period was 8.4 months (IQR, 3.4-14.4). 58 (32.4%) patients were de-novo metastatic, and 121 (67.6%) patients developed metastasis later. The median age was 53.2 (Range: 18.8-87.6 years), and 101 (56.4%) patients were male. The most common primary location was the lower extremity (87) (48.6%). The most common histological subtypes were synovial sarcoma (38) (21.2%), pleomorphic sarcoma (37) (20.7%), and liposarcoma (26) (14.5%). The majority were grade 3 tumors (n=131, 73.2%). Having ECOG PS 2-3 (HR=2.829, 95% CI 1,667-4.800, $p<0.001$), having tumor grade as 3 (HR=1.748, 95% CI 1.150-2.656, $p<0.009$), receiving palliative chemotherapy (HR=0.294, 95% CI 0.144-0.600, $p<0.001$), and receiving two or more lines of chemotherapy among those palliative receivers (HR=2.505 95% CI 1.696-3.700, $p<0.001$) were independent predictive factors of mortality.

CONCLUSIONS: Survival in metastatic soft tissue sarcoma is better in patients with good ECOG performance status, low tumor grades, and who have received palliative chemotherapy. Receiving more than one line of palliative systemic treatment for progressive disease improves survival.

Key Words:
Metastatic soft tissue sarcoma, Palliative chemotherapy, Performance status.

Introduction

Soft tissue sarcoma (STS) is a heterogeneous group of malignant tumors of mesenchymal origin with more than 60 determined histological subtypes. It constitutes 1% of all adult cancers[1,2]. Although it is usually diagnosed during the local disease period, approximately 15% of patients are de-novo metastatic[3,4]. In 40%-50% of patients diagnosed with local disease, distant organ metastasis develops later[4,5]. The lung is the most common site of metastasis[6,7]. The average overall survival is around 8 to 18 months for patients with advanced disease, depending on the underlying histological type and treatment modality[6-9].

Systemic chemotherapy is the mainstay of treatment in metastatic disease. Doxorubicin and ifosfamide-based chemotherapies constitute the basis of the treatment in both adjuvant therapy and metastatic disease[10,11]. In the following stages, depending on the underlying histological type, combination regimens containing gemcitabine, trabectedin, eribulin, pazopanib are other treatment alternatives[12-14]. A meta-analysis[15] evaluating randomized studies reported a response rate of 15% and a PFS of 2-4 months with doxorubicin, ifosfamide, or dacarbazine monotherapy. Moreover, the combination of these drugs increased response rates to 20%-40%. However, no significant improvement in overall survival was achieved.

Studies[16-18] on the localized disease suggest that age, histological subtype, grade, tumor size, and location are associated with prognosis. Only

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a few studies[4,5] evaluate the treatment strategy and the factors associated with prognosis in metastatic STS, which is relatively rare and has a poor prognosis.

This study aims to reveal general clinicopathological features, treatment modality, and factors that may predict overall survival in STS, a rare and heterogeneous disease group.

Patients and Methods

This study was a retrospective cohort study. Patients monitored with metastatic STS between January 2001 and January 2021 were evaluated retrospectively. Before the study, the approval was obtained from the Ethics Committee of the University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (2020-11/877, 25.11.2020).

Patients aged 18 years and over, histopathologically diagnosed with metastatic STS, and unsuitable for operations, such as local curative surgery or metastasectomy, were included in the study. Patients with local recurrence or metastasis which were able to resect and histopathological subtypes requiring different treatment approaches [e.g., rhabdomyosarcoma, uterine leiomyosarcoma, dermatofibrosarcoma protuberans, gastrointestinal stromal tumor (GIST), carcinosarcoma, and Ewing sarcoma] were excluded from the study. Receiving curative surgical treatments before reaching the unresectable stage was not an exclusion criterion.

Patient [gender, age at diagnosis, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)] and tumor characteristics (anatomical location, histological subtype, tumor grade, metastatic sites), treatment (chemotherapies received in the first and subsequent steps, history of pulmonary metastasectomy) modalities, progression, and survival status were recorded by examining manual patient files and or the electronic recording system.

Patients were staged according to the 8th edition of the American Joint Committee on Cancer (AJCC). Progression-free survival (PFS) was defined as the time relapsed from the initiation of therapy to progression in the metastatic stage. Overall survival (OS) was defined as the time relapsed from the onset of metastatic disease to the last follow-up or death.

Among the most used first- and second-line chemotherapy agents, ifosfamide (1.8 g/m^2 days 1-3) plus doxorubicin (75 mg/m^2 day) in combination (IMA), gemcitabine 900 mg/m2 (D1, D8), and docetaxel 75-100 mg/m^2 (D1) were administered intravenously every 21 days. Most patients were evaluated by computed tomography, while those whose primary disease site was extremities were examined by magnetic resonance imaging. Except when required by the patient's clinical condition, imaging was performed every three cycles of chemotherapy and every three months after chemotherapy.

Response to chemotherapy was defined according to response evaluation in solid tumors criteria 1.1 (RECIST 1.1): complete response (CR) was defined as resolution of all metastatic lesions, partial response (PR) as reduction of at least 30% in the sum of the diameters of target lesions, progressive disease (PD) as the appearance of one or more new lesions, or 20% increase in the sum of the longest diameter of target lesions, and stable disease (SD) as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

IBM Statistical Package for Social Sciences (SPSS®, Armonk, NY, USA) v.23 was used for data analysis. The relationship between progression and patient/tumor characteristics and treatment was investigated by univariate analysis. Survival analyses were performed using the Kaplan-Meier method, and subgroups were compared with the log-rank test. A p-value of <0.05 was considered statistically significant.

Results

The study included 179 patients who were monitored in our center and were in the metastatic stage. The median follow-up was 8.4 (IQR, 3.4-14.4) months. While 58 (32.4%) of the patients were de-novo metastatic, 121 (67.6%) of them developed metastases afterward.

Patient and Tumor Features

The median age of 179 patients included in the study was 53.2 (18.8-87.6 years), and 101 (56.4%) patients were male. There were 43 (24.2%) patients over 65 years of age. The most common primary site was the lower extremity (87) (48.6%). The most common histological subtypes were synovial sarcoma (38) (21.2%), pleomorphic sarcoma (37) (20.7%), and liposarcoma (26) (14.5%). The majority were grade 3 (n=131, 73.2%) tumors. 136 (78.0%) patients had lung metastases, and

the lung was the most common site of metastasis. Main patient characteristics and tumor features are shown in Table I.

Treatment Features

One hundred thirty-one (73.2%), 66 (36.8%), and 46 (25.6%) patients received one, two, and three or more lines of chemotherapy, respectively. Lung metastasectomy was performed in 27 (15%) patients.

The most common treatment regimen as first-line therapy was IMA in 74 (41.3%) patients. Secondly, 29 (16.2%) patients were treated with gemcitabine/docetaxel. Other first-line treatment regimens are shown in Table II.

Gemcitabine/docetaxel was used in 28 (42.4%) patients as second-line therapy, while pazopanib was used in 9 (25%) patients in the third-line treatment.

First-line chemotherapy responses were PR in 23 (17.6%) patients, SD in 55 (42%) patients, and PD in 51 (38.9%) patients. Detailed information related to systemic treatment is given in Table II.

Table I. Main Patient and Tumor Characteristics of Study Population (N = 104).

Characteristic	N (%)
Gender	
Female	78 (43.6%)
Male	101 (56.4%)
Age, median (range)	53.2 (18.8-87.6)
Pathological subtype	
Synovial Sarcoma	38 (21.2%)
Pleomorphic Sarcoma	37 (20.7%)
Liposarcoma	26 (14.5%)
Undiferansiye	20 (11.2%)
Leiomyosarcoma	18 (10.1%)
Fibrosarcoma	11 (6.1%)
Angiosarcoma	10 (5.6%)
MPNST	4 (2.2%)
FNCLCC grade	
Grade 1	9 (5.0%)
Grade 2	39 (21.8%)
Grade 3	131 (73.2%)
Localization	
Upper extremity	22 (12.3%)
Lower extremity	87 (48.6%)
Retroperitoneum	25 (14.0%)
Head and neck	8 (4.5%)
Intraabdominal	10 (5.6%)
Trunk	10 (5.6%)
Others	17 (9.4%)
De-novo metastasis	
Yes	58 (32.4%)
No	121(67.6%)
Site of metastasis	
Lung	136 (76%)
Liver	23 (12.8%)
Bone	45 (25.1%)
Soft tissue	11 (6.1%)
Lymph node	5 (2.8%)
Unrezektable local	31 (17.3%)
Others	31 (17.3%)
Number of metastatic sites	
1	101 (56.4%)
2	66 (36.9%)
3	12 (6.7%)
ECOG PS	
0	45 (25.1%)
1	79 (44.1%)
2	39 (21.8%)
3	16 (8.9%)

FNCLCC, Fe´de´ration Nationale des Centres de Lutte Contre le Cancer; MPNST, Malign Peripheral Nerve Sheath Tumor;ECOG PS; Eastern Cooperative Oncology Group Performance Status.

Survival Outcomes

The median overall survival for the entire study population was 9.5 (95% CI, 7.9-11.1) months (Figure 1A). There was no statistically significant OS difference between the subgroups created the line with the variables of patient's gender, age (below or above median), tumor location

Table II. Treatment schemes applied according to the treatment lines.

	N (%)
First-line treatment,	
IMA	74 (56.5%)
Gemcitabine plus Docetaxel	29 (22.1%)
Adriamycin	5 (3.8%)
Paclitaxel	6 (4.6%)
Ifosfamide	1 (0.8%)
IMET	6 (4.6%)
Others	10 (7.6%)
Second-line treatment for advanced disease	
Gemcitabine plus Docetaxel	28 (42.4%)
Pazopanib	23 (34.8%)
IMET	5 (7.6%)
Trabectedin	2 (3.0%)
Eribuline	1 (1.5%)
Others	5 (7.6%)
Third-line treatment for advanced disease	
Gemcitabine plus Docetaxel	8 (22.2%)
Pazopanib	9 (25.0%)
Ifosfamide	1 (2.8%)
Vinorelbine	4 (11.1%)
Others	14 (38.9%)
Fourth-line treatment for advanced disease	
Gemsitabin plus Docetaxel	1 (10.0%)
Pazopanib	2 (20.0%)
Trabectedin	3 (30.0%)
Vinorelbine	4 (40.0%)

IMA, combination of ifosfamide, mesna and doxorubicin; IMET, combination of ifosfamide, mesna and etoposide.

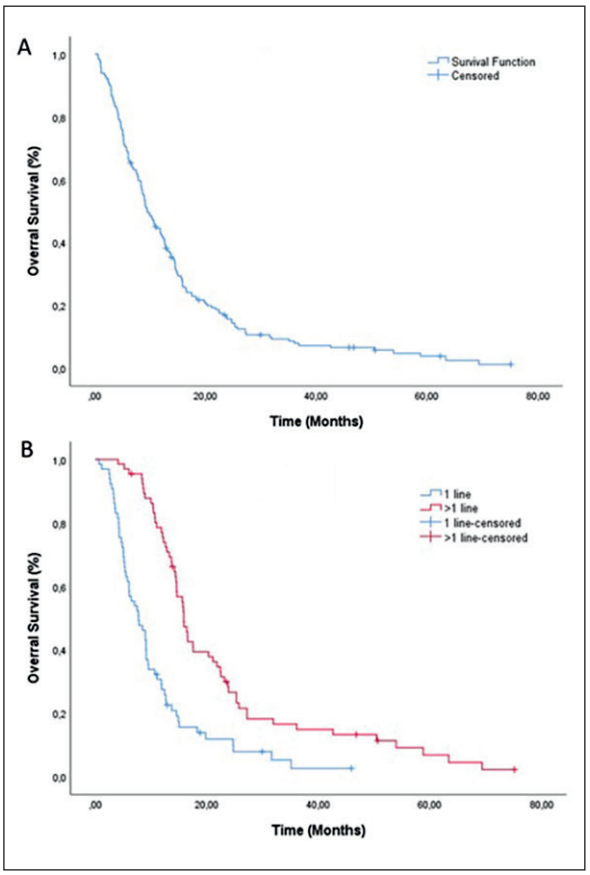

Figure 1. Kaplan-Meier curves of overall survival. **A,** Whole study group (N = 179). **B,** The median OS according to the number of palliative chemotherapy lines.

(extremity and extra-extremity), stage at diagnosis (de-novo metastatic, non-de-novo metastatic), metastasis site (pulmonary and extrapulmonary), number of metastatic sites (1 or 2 or more), and metastasectomy at follow-up (yes, no). The median OS was 13.2 (95% CI 11.1-15.4) months for those with ECOG PS 0-1 and 4.5 (95% CI 3.4-5.5) months for those with ECOG PS 2-3 (p<0.001). The median OS was11 (95% CI 8.5-13.6) months for tumor grade 1-2 and 8.9 (95% CI 7.8-10.1) months for tumor grade 3 (p<0.020). The median OS was 12.6 (95% CI 3.9-5.6) months for those who received palliative chemotherapy and 4.8 (95% CI 10.6-14.6) months for those who did not (p<0.001). According to the number of palliative chemotherapy lines, the median OS was 7.8 (95% CI 5.3-10.3) months for those who received one-line chemotherapy and 15.8 (95% CI 14.8-16.9) (p<0.008) months for those who received two or more lines of chemotherapy (Figure 1B).

ECOG PS 2-3 in Cox regression analysis including factors that could predict overall survival (HR=2.829, 95% CI 1,667-4.800, p<0.001), a tumor grade of 3 (HR=1.748, 95% CI 1.150-2.656, p<0.009), having received palliative chemotherapy (HR=0.294, 95% CI 0.144-0.600, p<0.001), and among those receiving palliative chemotherapy, having received two or more lines of chemotherapy (HR=2.505 95% CI 1.696-3.700, p<0.001) were independent predictive factors of mortality (Table III).

Discussion

This study evaluated the main clinicopathological features and the factors predicting OS in patients with unresectable metastatic stage STS. In this patient group with no treatment options other than systemic treatments and a poor prognosis, good ECOG PS, low tumor grade, having received palliative chemotherapy, and having received more than one line of treatment in palliative chemotherapy were independent positive predictive factors for survival.

Considering our study population's clinicopathological and demographic characteristics, which consisted of mostly male patients, our study was compatible with the literature data regarding median age, primary site, and histological subtype[12,19,20]. In most patients in our study, the lung was the organ with the most common metastasis. Similarly, in many studies, the lung stands out as the first metastasis site in 60-80% of patients[6,7,21]. 131 (73.2%) of our patients had received at least one line of chemotherapy, and since the most frequently used treatment protocol was IMA combination chemotherapy, we consider IMA chemotherapy the primary determinant of survival.

Although the overall survival has improved in metastatic soft tissue sarcomas in the last few decades, the median OS for patients with metastatic disease is around 8 to 20 months[22-24]. In a series of 2,185 patients from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study (EORTC), the median survival time was 51 weeks[18]. In the study of Italiano et al[5], who divided 1,024 patients with a diagnosis of metastatic soft tissue sarcoma into 4 periods by year (P1, 1987 to 1991 (n = 208); P2, 1992 to 1996 (n = 287); P3, 1997 to 2001 (n = 285); and P4, 2002 to 2006 (n = 244)), the median OS was found to be around 14 months. Although the median OS did not differ significantly in the period from P1

Table III. Univariate and multivariate analysis results including factors that may affect overall survival.

Variable, n (%)	Univariate		Multivariatel	
	OS Median Range (95% CI)	p	HR for OS (95% CI)	p
Gender		0.214		0.573
Male	9.1 (7.3-10.9)		0.905 (0.639-1.281)	
Female	11.8 (8.4-15.2)			
Age		0.543		0.090
< median	1.46 (7.8-13.5)		0.728 (0.505-1.051)	
> median	0.76 (7.4-10.3)			
ECOG PS		< 0.001		< 0.001
0-1	13.2 (11.1-15.4)		2.829 (1.667-4.800)	
2-3	4.5 (3.4-5.5)			
Grade		0.020		0.009
1-2	11 (8.5-13.6)		1.748 (1.150-2.656)	
3	8.9 (7.8-10.1)			
Tumor location		0.240		0.775
Extremity	9.1 (8-10.1)		0.944 (0.638-1.398)	
Non-extremity	10.7 (18.8-12.6)			
De-novo metastasis		0.815		0.418
No	10.3 (8.1-12.5)		1.178 (0.793-1.749)	
Yes	8.6 (5.6-11.5)			
Metastasis Site		0.887		0.904
Lung only	9.5 (7.09-11.9)		1.024 (0.698-1.501)	
Lung with others	9.1 (5.7-12.6)			
Metastasis Site Number		0.636		0.875
1	10.6 (8.6-12.7)		1.041 (0.632-1.713)	
≥ 1	8.9 (6.9-10.9)			
Metastasectomia		0.543		0.080
No	10.7 (7.8-15.6)		0.587 (0.324-1.066)	
Yes	8.9 (7.4-10.4)			
Palliative CTx		< 0.001		< 0.001
No	4.8 (3.9-5.6)		0.294 (0.144-0.600)	
Yes	12.6 (10.6-14.6)			
CTx line number		< 0.001		< 0.001
≥ 2	15.9 (14.8-16.9)		2.505 (1.696-3.700)[ε]	
1	7.6 (5.3-10.3)			

OS, overall survival; HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CTx, chemotherapy; ε2 vs. 1; §3 vs. 2; δ4 vs. 3

to P2 (P1, 12.3 months; 95% CI 9.9-14.7 months; P2, 11.4 months; 95% CI, 9-13.9 months), significant improvements were observed in the following periods (P3, 15 months; 95% CI, 11.8-18.2 months; P4, 18 months; 95% CI, 15.3-20.7 months; p=.029), and this analysis has shown that the median OS of patients with metastatic STS has increased by 50% in the last 20 years[5]. In the large-scale study of Gutierrez et al[17], the metastatic subgroup consisted of 1,348 patients, and the median OS of these patients was reported to be eight months and five years (6.6%). In our study, we found the median OS as 9.5 months, which is consistent with the study results stated.

Kawamoto et al[7] evaluated the factors that might be associated with survival in metastatic STS and found that survival improved significantly in those who received chemotherapy in unresectable metastatic disease (19.1 months and 6.3 months, p=0.037) compared to those who did not receive chemotherapy. In the observational study by Savina et al[22], who evaluated 2,225 patients with metastatic STS, 73% of the patients received systemic treatment, and the median number of treatment lines was three. Except for leiomyosarcomas, the benefit of receiving more than three lines of systemic therapy was limited, and the use of combined chemotherapy in the first-line treatment regimen provided a significant OS contri-

bution (95% CI 0.822 (0.724–0.932), p=0.0003) compared to monotherapy[20]. A recent meta-analysis[15] observed a 3-month improvement in OS and a doubled response rate with salvage treatments (chemotherapy, as single or multiple agents or targeted biological agents) for metastatic STS, and a 50% reduction in progression under second-line therapy with salvage therapy. In our study, similar to the large-scale studies mentioned above, we found that receiving palliative chemotherapy and more than one chemotherapy line were independent positive predictive factors for survival. The reason for this effect, which we showed in our study, might be that our patients had ECOG PS that was good enough to continue with two or more lines of treatment, the ECOG PS of our patients was not impaired due to the slow course of the disease, or they progressed after a short-term stable disease after each line of treatment. However, due to the retrospective nature of our study, it is pretty difficult for us to analyze this situation retrospectively. Ferguson et al[25], on the other hand, could not show the survival benefit of chemotherapy in their study in which they evaluated 112 patients diagnosed with metastatic STS. However, this study included histological subtypes that were unlikely to benefit from chemotherapy or undergo different chemotherapy modalities[25]. Our study tried to obtain a highly homogenized group consisting of cases with similar treatment modalities. We think that such a homogeneous group would be more optimal to evaluate the OS benefit.

Many studies have reported that tumor grade is an independent risk factor for STS staging, determining the risk of distant metastasis and survival[26-28]. In the study of the EORTC group, a lower histopathological grade was associated with better survival in patients with metastatic STS[18]. Similarly, Italiano et al[5] reported that low histological grade was a positive independent prognostic factor for OS. In the study of Carbonnaux et al[8], evaluating the factors that might be associated with the prognosis of metastatic STS with a survival of more than five years, it was determined that the tumors of this group of patients were of lower grade. Again, Savina et al[22] reported that grade 3 tumors at the time of diagnosis adversely affected the prognosis. In our study, similar to the studies mentioned above, we found that low tumor grade was an independent positive predictive factor for survival. Although tumor grade is generally seen as an important factor predicting OS, in their study evaluating both de-novo metastatic and non-de-novo metastatic STS, Salah et al[29] reported that tumor grade did not predict OS. However, the inclusion of only patients with a diagnosis of synovial sarcoma and the low number of patients suggests that the argument on grade in this study may not be so robust. Similarly, Ferguson et al[25], inconsistent with the literature data, showed that tumor grade did not predict OS. However, the conclusion that grade was ineffective in survival may have been reached since many of the patients included in this study had unfavorable prognoses.

The EORTC study reported that patients with ECOG PS 0 exhibited better overall survival than those with ECOG PS 1-4, and their median survival was 65 weeks[18]. Lindner et al[12], in their study on 580 patients and with a design quite similar to our study, reported that ECOG PS was a very strong prognostic factor for survival, and patients with ECOG PS 2 and above exhibited very poor survival compared to those with ECOG PS 0 [HR=5.17, 95% CI (2.64-10.1) p<0.001]. Carbonnaux et al[8] stated that 98% of patients with long-term survival had ECOG PS 0-1. In our study, we determined that ECOG PS was an independent positive predictive factor for survival.

Conclusions

The main limitations of our study consist of the retrospective study design, small sample size, and heterogeneity in histopathological subtypes and chemotherapy regimens. However, in conclusion, we recommend the stepwise use of palliative chemotherapy in metastatic STS in patient groups suitable for ECOG PS.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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