

Prognostic Significance of Histological Subtype in Soft Tissue Sarcoma With Distant Metastasis

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Abstract. *Background/Aim:* Few studies have examined the prognostic significance of histological subtypes in patients with soft tissue sarcoma (STS) and distant metastasis, and we evaluated the relationship between the histological subtypes and clinical outcomes. *Patients and Methods:* This retrospective study evaluated the histological subtypes of 105 patients with STS and distant metastasis. The STS histological subtypes were compared based on the clinical information. *Results:* The Kaplan-Meier curves for overall survival revealed that myxoid liposarcoma had a significantly better prognosis compared to Malignant Peripheral Nerve Sheath Tumor (MPNST) ($p=0.0221$). In the multivariate logistic regression analyses, the independent predictors of a poor prognosis were: i) large size, ii) advanced stage, and iii) non-surgical treatment for metastasis ($p<0.05$). The presence or absence of lung metastasis was not significantly associated with prognosis ($p=0.4452$). *Conclusion:* Myxoid liposarcoma had a better prognosis compared to MPNST in STS patients with distant metastasis. The surgical removal of distant metastatic lesions may improve the patient's prognosis.

Soft tissue sarcoma (STS) is relatively rare, and mainly occurs in middle-aged or older individuals. Despite its low incidence, STS has various histological subtypes, such as liposarcoma and synovial sarcoma, which results in relatively

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small populations of patients with different histological types. Radical resection with adequate margins is important for treating STS, regardless of the histological subtype, in order to prevent local recurrence. However, recent developments in surgical treatment, radiotherapy, and chemotherapy have improved patient outcomes (1), and various studies have identified factors associated with prognosis among STS patients (2-10). There is consensus that distant metastasis, which mainly involves the lungs, has a strong influence on prognosis. However, the small sample sizes for each subtype typically prevent studies from identifying a clear relationship between subtype and prognosis, despite the fact that several reports have examined the prognostic significance of the STS histological subtypes (2-8, 11, 12). Moreover, only few studies have examined this topic among patients with STS and distant metastases. Therefore, the present study aimed to examine the association of clinical outcomes with the histological subtypes and distant metastasis sites in patients with STS and distant metastasis.

Patients and Methods

The study's retrospective protocol was approved by the Institutional Review Board for Clinical Research at Akita University (approval number: 2337), and informed consent was obtained from all patients.

Subjects. We retrospectively identified 118 patients with STS involving the extremities or trunk who also developed distant metastasis (excluding the lymph nodes) and were treated at our two hospitals between 1994 and 2018. The present study focused on histological subtypes of STS with ≥ 5 cases, so we only included a total of 105 patients with STS and distant metastasis (65 male patients and 40 female patients, mean age=63.1 years, range=10-90 years).

The eligible histological subtypes with ≥ 5 cases were as follows: i) dedifferentiated liposarcoma, ii) pleomorphic liposarcoma, iii) myxoid liposarcoma, iv) myxofibrosarcoma, v) undifferentiated pleomorphic sarcoma (UPS), vi) synovial sarcoma, vii) malignant peripheral nerve sheath tumor (MPNST), and leiomyosarcoma. The patients' records were searched to collect information regarding i) age, ii) sex, iii) histological subtype, iv) anatomical location of the tumor, v) size, vi) previous

Table I. Comparison patient characteristics among the histological subtype of soft tissue sarcoma.

	Dedifferentiated liposarcoma	Pleomorphic liposarcoma	Myxoid liposarcoma	MFS	UPS	Synovial sarcoma	MPNST	LMS	p-value
Number	13	5	10	11	31	11	18	6	
Age (years)	73.2±9.7a	54.4±7.0	57.7±13.6	76.2±13.5a	67.5±12.9a	43.6±20.9	57.7±18.5	62.7±20.0	<0.0001
Gender									
Male/female	9/4	3/2	6/4	4/7	24/7	7/4	10/8	2/4	0.2581
Location									
Extremity/axial	8/5	4/1	7/3	7/4	17/14	9/2	5/13	6/0	0.0287
Size (mm)	150±65b	56±21	106±42	81±53	117±65	82±27	100±48	96±89	0.0366
Metastasis at diagnosis									
Present/none	3/10	1/4	3/7	0/11	7/24	3/8	5/13	1/5	0.7536
Past inappropriate excision									
Present/none	0/13	0/5	1/9	0/11	1/30	0/11	1/17	1/5	0.5973
FNCLCC classification									
Grade I/II/III	0/0/13	1/1/3	2/6/2c	3/2/6	1/10/20	0/2/9	0/7/11	3/1/2d	0.0005
AJCC stage									
Stages I/II/III/IV	0/0/10/3	1/1/2/1	2/4/1/3	3/3/5/0	0/10/14/7	0/1/7/3	0/7/6/5	2/1/2/1	0.0798
Lung metastasis									
Present/none	11/2	5/0	4/6	10/1	27/4	9/2	13/5	5/1	0.0519
Follow-up period (months)	31.6±35.4	26.8±30.2	78.7±84.8	61.0±62.3	44.4±59.9	40.0±27.6	25.4±23.9	27.2±30.7	0.1912
Time to the appearance of distant metastasis (months)	15.3±19.4	18.6±29.6	47.4±68.5	24.0±26.9	20.1±35.1	13.3±12.4	13.6±16.7	19.2±27.5	0.3015
AWD period (months)	15.8±22.0	26.5±35.8	21.8±38.1	28.8±34.5	15.1±19.2	23.5±23.5	12.7±15.4	8.0±4.5	0.5533
Outcome at the last follow-up									
NED/AWD/dead	0/2/11	1/0/4	1/3/6	1/1/9	3/4/24	1/1/9	0/1/17	0/3/3	0.3427

Values are expressed as number (%) or mean±standard deviation. MFS: Myxofibrosarcoma; UPS: undifferentiated pleomorphic sarcoma; MPNST: malignant peripheral nerve sheath tumor; LMS: leiomyosarcoma; FNCLCC: French Federation of Cancer Center Sarcoma Group; AJCC: American Joint Committee on Cancer; NED: no evidence of disease; AWD: alive with disease. ^aSarcoma vs. synovial sarcoma ($p<0.01$), ^bDedifferentiated liposarcoma vs. pleomorphic liposarcoma ($p<0.05$), ^cMyxoid liposarcoma vs. dedifferentiated liposarcoma ($p<0.01$), ^dLeiomyosarcoma vs. dedifferentiated liposarcoma ($p<0.05$).

inappropriate excision, vii) metastasis at diagnosis, viii) stage of the primary tumor, ix) treatments for the primary and metastatic tumors, x) follow-up period, and xi) outcomes. The stage of the primary tumor was determined according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system (13). The specimens were also classified using the French Federation of Cancer Center Sarcoma Group (FNCLCC) system, which considers the i) mitotic index, ii) necrosis extension, and iii) histological differentiation (14). We obtained some information regarding the type of local therapy and surgical margins (Enneking criteria) for patients who underwent surgery. In the absence of any events, patients were censored at the last follow-up. We calculated the overall survival (OS) interval from the date of diagnosis to the date of death or the last follow-up. Outcomes and clinical characteristics were compared according to the patients' histological subtypes.

Statistical analysis. Values are reported as a number (%) or mean±standard deviation. Inter-group comparisons were performed using analysis of variance, the χ^2 test, or the Scheffé test for multiple comparisons among the 8 groups. Overall survival was compared using the Kaplan-Meier methods and long-rank test. A Cox proportional hazards model was used to identify the factors that were associated with OS. Differences were considered statistically significant at p -Values of <0.05 .

Results

The mean follow-up period for all patients was 42.3±51.7 months (range=2-284 months). The histological diagnoses were: i) dedifferentiated liposarcoma in 13 cases (12.4%), ii) pleomorphic liposarcoma in 5 cases (4.8%), iii) myxoid liposarcoma in 10 cases (9.5%), iv) myxofibrosarcoma in 11 cases (10.5%), v) UPS in 31 cases (29.5%), vi) synovial sarcoma in 11 cases (10.5%), vii) MPNST in 18 cases (17.1%), and viii) leiomyosarcoma in 6 cases (5.7%). The sites of the primary lesions were the extremities in 63 patients (60%) and axial sites in 42 patients (40%). The mean tumor size for all patients was 105.4±61.8 mm (range=15-370 mm). Previous inappropriate excision had been performed in 4 patients. The FNCLCC classifications were: i) Grade I for 10 patients, ii) Grade II for 29 patients, and iii) Grade III for 66 patients. According to the AJCC staging system, the disease stages were: i) IA for 1 patient, ii) stage IB for 7 patients, iii)

Table II. Comparing treatment methods among the histological subtypes of soft tissue sarcomas.

	Dedifferentiated liposarcoma	Pleomorphic liposarcoma	Myxoid liposarcoma	MFS	UPS	Synovial sarcoma	MPNST	LMS	<i>p</i> -value
Number	13	5	10	11	31	11	18	6	
Surgical treatment for primary tumor									
Present/none	10/3	4/1	8/2	8/3	23/8	10/1	13/5	4/2	0.9579
Surgical margin									
Adequate/inadequate	4/6	4/0	6/2	5/3	16/7	7/3	9/4	4/0	0.3514
Radiation for primary tumor									
Present/none	1/12	2/3	0/10	4/7	6/25	2/9	4/14	2/4	0.3716
Chemotherapy									
Present/none	1/12	3/2	7/3	4/7	12/19	8/3	4/14	4/2	0.0076
Surgical treatment for metastasis									
Present/none	3/10	1/4	4/6	5/6	7/24	3/8	1/17	1/5	0.3412
Radiotherapy for metastasis									
Present/none	0/13	0/5	2/8	0/11	4/27	0/11	8/10	1/5	0.2847
Local recurrence									
Present/none	6/4	0/4	2/6	3/5	7/16	2/8	4/9	1/3	0.4687

Values are expressed as number (%) or means±standard deviations. MFS: Myxofibrosarcoma; UPS: undifferentiated pleomorphic sarcoma; MPNST: malignant peripheral nerve sheath tumor; LMS: leiomyosarcoma.

Table III. The *p*-Value results from the Kaplan-Meier curve comparisons among the histological subtypes of soft tissue sarcoma.

	Pleomorphic liposarcoma	Myxoid liposarcoma	MFS	UPS	Synovial sarcoma	MPNST	LMS
Dedifferentiated liposarcoma (<i>p</i> -Value)	0.9194	0.0911	0.3756	0.2909	0.6368	0.4820	0.5750
Pleomorphic liposarcoma (<i>p</i> -Value)	-	0.2998	0.2533	0.5046	0.6161	0.7670	0.4167
Myxoid liposarcoma (<i>p</i> -Value)	-	-	0.3440	0.2377	0.2131	0.0221	0.5549
MFS (<i>p</i> -Value)	-	-	-	0.7347	0.6761	0.0512	0.7741
UPS (<i>p</i> -Value)	-	-	-	-	0.9532	0.0989	0.8932
Synovial sarcoma (<i>p</i> -Value)	-	-	-	-	-	0.1179	0.8921
MPNST (<i>p</i> -Value)	-	-	-	-	-	-	0.3829

MFS: Myxofibrosarcoma; UPS: undifferentiated pleomorphic sarcoma; MPNST: malignant peripheral nerve sheath tumor; LMS: leiomyosarcoma.

stage IIA for 4 patients, iv) stage II B for 23 patients, v) stage III for 47 patients, and vi)stage IV for 23 patients, with metastasis present at the diagnosis for 23 patients (21.9%). Eighty-four patients (80%) developed pulmonary metastases, and the sites of extra-pulmonary metastases were the bones in 19 patients, axial soft tissue in 12 patients, the brain in 6 patients, the mediastinum in 6 patients, extremity soft tissue in 5 patients, intraperitoneal in 5 patients, the liver in 4 patients, retroperitoneal in 4 patients, and the colon in 1 patient. The mean period until the appearance of distant metastasis for all patients was 20.6±33.1 months (range=0-232 months) (Table I). Surgery for the primary tumor was performed for 80 patients (76.2%), and adequate tumor-free margins were achieved for 55 patients (68.8%). Radiotherapy was performed for 21 patients (20%), which included heavy particle irradiation for 1 patient and radiotherapy plus surgery

for 10 patients (47.6%). Chemotherapy was administered to 43 patients (40.1%), which involved doxorubicin, ifosfamide, dacarbazine, gemcitabine, cisplatin, etoposide, eribulin, trabectedin, and pazopanib. Surgical treatment was performed for the metastasis in 25 patients (23.8%), and radiotherapy was performed for the metastasis in 15 patients (14.3%). Twenty-five patients (23.8%) developed local recurrence. The patient outcomes were no evidence of disease in 7 patients, alive with disease in 15 patients, and 83 patients who died because of their original disease. No patient died because of complications during the perioperative period. The mean period of survival with disease was 17.9±23.9 months (range=1-120 months) (Table II).

Patients with synovial sarcoma were significantly younger compared to those with dedifferentiated liposarcoma, pleomorphic liposarcoma, or UPS. Dedifferentiated liposarcoma

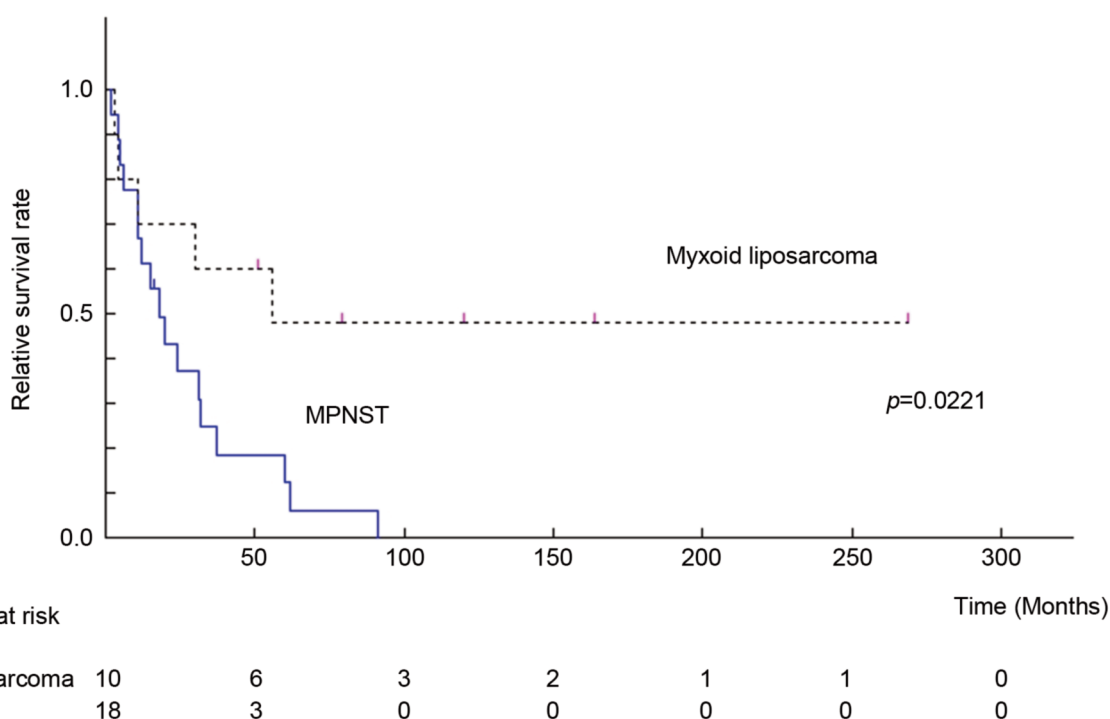


Figure 1. Kaplan-Meier overall survival (OS) curves. Myxoid liposarcoma shows higher OS compared to malignant peripheral nerve sheath tumor (MPNST) ($p=0.0221$).

was significantly larger compared to pleomorphic liposarcoma. Dedifferentiated liposarcoma was significantly more malignant compared to myxoid liposarcoma or leiomyosarcoma, based on histological findings (Table I). The Kaplan-Meier overall survival curves revealed that myxoid liposarcoma had a significantly better prognosis compared to MPNST ($p=0.0221$) (Table III and Figure 1). The univariate and multivariate logistic regression analyses revealed that the prognosis of patients with STS and distant metastasis was associated with i) tumor size, ii) AJCC stage, and iii) surgical treatment for metastasis (all $p<0.05$) (Table IV).

Discussion

Patients with STS and distant metastasis are difficult to cure, regardless of the histological subtype, and have a poor prognosis. However, there is variation in the rate of tumor growth, the number of tumors, the site of development, and the period of survival with disease. To the best of our knowledge, no studies have examined the prognostic differences between the histological subtypes of STS in patients with distant metastasis. Our results revealed that MPNST had a poor prognosis than myxoid liposarcoma in this setting. Several reports have described variable differences in the prognosis between the histological subtypes, regardless of

the presence or absence of distant metastasis. For example, some reports have described no difference in prognosis, while other reports have indicated that a relatively poor prognosis is associated with rhabdomyosarcoma, epithelioid sarcoma, clear cell sarcoma, MPNST, leiomyosarcoma, and malignant fibrous histiocytoma, as well as in dedifferentiated liposarcoma (2, 3, 6-8, 11, 12). Callegaro *et al.* have also reported an overall survival nomogram that can be used to predict the patient's prognosis, based on age, tumor size, histological grade, and histological subtype (2). In that nomogram, vascular sarcoma was associated with the poorest prognosis, while myxoid liposarcoma was associated with the best prognosis. Moreover, MPNST reportedly has a poor prognosis (8) and myxoid liposarcoma has a good prognosis (11, 12), with the outcomes also potentially being affected by the occurrence of distant metastasis. In this context, chemotherapy and radiotherapy are thought to have an elevated influence on the prognosis of patients with distant metastasis. For example, myxoid liposarcoma is more responsive to radiotherapy and chemotherapy compared to other soft tissue sarcoma types (15-18), while MPNST does not respond to chemotherapy, and radiation-induced MPNST is associated with poor prognosis (19, 20). These distinct behaviors of the STS subtypes may differentially affect their outcomes after the appearance of distant metastasis.

Table IV. Univariate and multivariate analyses of potential prognostic factors.

	Univariable			Multivariable		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Age	1.010	0.996-1.024	0.1636			
Female sex	1.018	0.647-1.603	0.9372			
Axial location	1.218	0.779-1.906	0.3878			
Size	1.004	1.000-1.008	0.0311	1.004	1.000-1.008	0.0354
Past inappropriate excision	0.527	0.165-1.684	0.2799			
FNCLCC classification	1.434	1.014-2.027	0.0415	0.887	0.556-1.416	0.6155
AJCC stage	1.963	1.446-2.665	<0.0001	2.146	1.367-3.369	0.0009
Lung metastasis	1.233	0.720-2.112	0.4452			
Surgical treatment for primary tumor	0.297	0.182-0.484	<0.0001	0.774	0.391-1.534	0.4634
Radiation for primary tumor	1.762	1.045-2.972	0.0336	1.744	0.974-3.123	0.0614
Chemotherapy	0.539	0.340-0.855	0.0086	0.723	0.438-1.192	0.2036
Surgical treatment for metastasis	0.383	0.214-0.685	0.0012	0.463	0.242-0.885	0.0199
Radiation for metastasis	0.967	0.523-1.788	0.9142			
Dedifferentiated liposarcoma	1.361	0.719-2.577	0.3463			
Pleomorphic liposarcoma	1.425	0.518-3.917	0.4927			
Myxoid liposarcoma	0.426	0.171-1.060	0.0677			
Myxofibrosarcoma	0.798	0.398-1.601	0.5258			
Undifferentiated pleomorphic sarcoma	0.912	0.558-1.492	0.7145			
Synovial sarcoma	0.935	0.466-1.877	0.8506			
Malignant peripheral nerve sheath tumor	1.779	1.033-3.061	0.0376	1.168	0.649-2.101	0.6049
Leiomyosarcoma	0.864	0.272-2.747	0.8044			

OR: Odds ratio; 95%CI: 95% confidence interval; FNCLCC: French Federation of Cancer Center Sarcoma Group; AJCC: American Joint Committee on Cancer.

Although age, histological grade, stage, tumor diameter, and resection margins are reportedly associated with a poor prognosis for STS, few reports have evaluated factors influencing the prognosis of patients with STS and distant metastasis (9, 21-23). Some of these studies have indicated that surgical resection of the distant metastatic lesions can improve the prognosis, similar to what we observed. Thus, aggressive surgical treatment may be preferable if the distant metastatic lesions are considered resectable. The distant metastases from STS generally occur in the lungs (70-80% of these patients) (9, 23-25), as in our cohort. However, the presence or absence of lung metastasis did not affect the prognosis, and Billingsley *et al.* have also reported no difference in prognosis between lung metastasis and other distant metastases (9).

The present study is limited by the small sample of patients, especially when considering each histological subtype, and only <10 cases of pleomorphic liposarcoma and leiomyosarcoma identified. Furthermore, various factors, including the treatment selection, might have biased our findings, as some patients received chemotherapy and/or radiotherapy. Therefore, further detailed studies are needed to evaluate a larger number of STS patients with distant metastasis.

In conclusion, the present study evaluated the clinical characteristics and outcome of patients with STS and distant

metastasis, which revealed some differences regarding their prognosis according to histological subtype. For example, myxoid liposarcoma had a better prognosis compared to MPNST in this setting. While the surgical removal of distant metastasis may help improve the patient's prognosis, the location of the distant metastasis did not affect the prognosis.

Conflicts of Interest

The Authors report no conflicts of interest.

Authors' Contributions

All Authors were involved in the planning and revising of this research. TH, NH, EM, MY, ME, and SJ collected the clinical data. TH analyzed the raw data and wrote this dissertation. MN, OK, YY, and SY reviewed this manuscript.

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