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Risk Factors of Early Distant Metastasis After Primary Tumor Treatment in Soft Tissue Sarcoma

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Abstract. *Background/Aim: Distant metastasis has a strong influence on prognosis in patients with soft tissue sarcoma (STS). While various risk factors have been reported for distant metastases, risk factors for distant metastases early after treatment of primary tumor have not been investigated. This study aimed to evaluate the factors of early distant metastasis after primary tumor resection in patients with STS. Patients and Methods: We retrospectively identified patients with STS involving the extremities or trunk without any metastasis at the first visit. Data on clinical information and detailed assessment were collected. We evaluated clinical information as a risk factor for distant or lung metastases. Additionally, we evaluated risk factors for metastases in patients with distant metastases as early as 6 months after the initial resection of the primary tumor. Results: A total of 337 patients were included in the study. Multivariate analysis revealed that the size of the primary tumor (p=0.0011 and p=0.0167), consultation in a short period after onset (p=0.0325 and p=0.0402), histological high grade (p=0.0006 and p=0.0002), and inadequate surgical margin (p=0.0151 and p=0.0055) were significant predictors for poor prognosis for all distant and lung metastases, respectively. However, the only risk factor for early metastases within 6 months was young age (p=0.0148). Conclusion: The only risk factor for early distant metastasis after primary tumor resection in patients with STS was young age, even though large tumor diameter and histological high grade were risk factors for distant metastasis.*

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Key Words: Soft tissue sarcoma, distant metastasis, lung, primary tumor.

Soft tissue sarcoma (STS) is a relatively rare malignant tumor of the extremities and trunk, occurring predominantly in middle-aged and older adults. Various studies have identified factors that are associated with prognosis of patients with STS (1-11). Particularly, distant metastasis, primarily involving the lungs, has a strong effect on the prognosis of patients with STS. Recent developments in surgical treatment, radiotherapy, and chemotherapy have improved patient outcomes. However, distant metastases still appear frequently after excision of the primary tumor. In such cases, it is predicted that the prognosis will be worse if distant metastasis appears earlier. While various risk factors have been reported for distant metastases that significantly affect the prognosis of soft tissue sarcoma (12-17), risk factors for the appearance of distant metastases early after treatment of the primary tumor have not been investigated.

Therefore, the present study aimed to examine the factors of early distant metastasis after primary tumor resection in patients with STS.

Patients and Methods

Patients. We retrospectively identified patients with STS involving the extremities or trunk, without any metastasis at the first visit, treated at our two hospitals between 1994 and 2021. Patients' records were searched to collect data including age, sex, histological subtype and malignancy, anatomical tumor location, size, period from onset to consultation, presence or absence of unplanned excision, primary tumor treatment, lung and other metastasis, local recurrence, follow-up period, and outcomes. The specimens of soft tissue sarcoma were classified using the French Federation of Cancer Center Sarcoma Group system (FNCLCC), which includes the mitotic index, necrosis extension, and histological differentiation (15). We additionally collected information on the type of local therapy and surgical margins (Enneking staging system) for patients who underwent surgery (18). In the absence of any events, patients were deidentified at the last follow-up.

We evaluated clinical information as a risk factor for distant or lung metastases in all patients. In addition, we evaluated risk factors for distant or lung metastases in patients with distant metastases as early as 6 months after the initial resection of the primary tumor.

Table I. *Clinical characteristics of the study participants.*

	Patients		
	All	All metastasis	Lung metastasis
Number	337	108	91
Age (years)	62.9±18.6	65.3±16.5	65.0±16.8
Sex (male/female)	175/162	61/47	52/39
Size (mm)	84.1±55.2	98.8±56.6	98.0±54.5
Location (extremity/axial)	242/95	71/37	57/34
Period from onset to consultation (months)	17.0±40.5	9.8±16.7	9.5±16.8
Unplanned excision (yes/no)	48/289	9/99	7/84
Histological subtype			
Liposarcoma	88	20	15
Dedifferentiated/Pleomorphic/Myxoid	34/17/37	9/3/8	9/3/3
Myxofibrosarcoma	77	22	18
Undifferentiated pleomorphic sarcoma	64	24	19
Synovial sarcoma	27	8	8
Malignant peripheral nerve sheath tumor	26	15	14
Leiomyosarcoma	25	12	11
Epithelioid sarcoma	7	3	3
Extraskeletal myxoid chondrosarcoma	5	0	0
Low-grade fibromyxoid sarcoma	4	1	1
Extraskeletal osteosarcoma	3	0	0
Rhabdomyosarcoma	7	2	1
Pleomorphic/Spindle-cell, sclerosing/Embryonal	3/2/2	2/0/0	1/0/0
Angiosarcoma	2	1	1
Clear cell sarcoma	1	0	0
Malignant solitary fibrous tumor	1	0	0
FNCLCC classification (Grade I/II/III)	59/138/140	11/36/61	9/26/56
Surgical treatment for primary tumor (yes/no)	315/22	100/8	84/7
Surgical margin (adequate/inadequate)	247/68	68/32	54/30
Adjuvant therapy for surgical margin (yes/no)	31/284	14/86	13/71
Radiotherapy for primary tumor (yes/no)	59/278	25/83	22/69
Chemotherapy for primary tumor (yes/no)	65/272	24/84	22/69
Distant metastasis (yes/no)	108/229	-	-
Lung metastasis (yes/no)	91/246	91/17	-
Local recurrence (yes/no)	66/249	37/63	33/51
Follow up period (months)	58.6±49.5	49.0±51.7	43.6±50.6
Outcome at the last follow-up (NED/AWD/DOD)	215/42/80	13/30/65	8/25/58

Values are expressed as number or means±standard deviations with ranges. FNCLCC: French Federation of Cancer Center Sarcoma Group; NED: no evidence of disease; AWD: alive with disease; DOD: died of disease.

This study was approved by the Institutional Review Board for Clinical Research at the Akita University (Approval Number: 2830) and was conducted in accordance with the 1975 Declaration of Helsinki and its 1983 revision.

Statistical analysis. All continuous variables are expressed as mean±standard deviation. A Cox proportional hazards model was used to identify the factors that were associated with distant or lung metastases, and multivariate logistic regression analysis was used to identify the factors that were associated with all and lung early metastasis. A p-value of <0.05 was used to define statistical significance.

Results

A total of 337 patients (175 males and 162 females) with STS without any metastasis at the first visit were included in this study. The mean age was 62.9 years (range=0-94 years) and the mean follow-up was 58.6±49.5 months (range=1-299 months). The median period from onset to consultation was 17.0±40.5 months (range=0-420 months). Past inappropriate excision was conducted in 48 patients (14.2%). The histological diagnoses of STS were dedifferentiated liposarcoma (n=34), pleomorphic liposarcoma (n=17), myxoid liposarcoma (n=37), myxofibrosarcoma (n=77), undifferentiated pleomorphic sarcoma (UPS) (n=64), synovial sarcoma (n=27), malignant peripheral nerve sheath tumor (MPNST) (n=26), leiomyosarcoma (n=25), epithelioid sarcoma (n=7), extraskeletal myxoid chondrosarcoma (n=5), low-grade fibromyxoid sarcoma (n=4), extraskeletal osteosarcoma (n=3), pleomorphic rhabdomyosarcoma (n=3), spindle-cell/sclerosing rhabdomyosarcoma (n=2), embryonal rhabdomyosarcoma (n=2), angiosarcoma (n=2), clear cell

Table II. *Univariate and multivariate analysis of factors affecting all metastasis-free survival.*

Variables	Univariate			Multivariate		
	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age	1.009	0.997-1.021	0.1285			
Sex - Female	0.728	0.496-1.068	0.1049			
Size	1.007	1.004-1.010	<0.0001	1.007	1.003-1.011	0.0011
Location - Axial	1.448	0.971-2.159	0.0697			
Period from onset to consultation	0.987	0.975-0.999	0.0303	0.984	0.970-0.999	0.0325
Unplanned excision	0.476	0.240-0.944	0.0337	0.748	0.312-1.792	0.5143
Histological grade (high)	1.872	1.394-2.513	<0.00001	1.771	1.276-2.456	0.0006
Surgical treatment for primary tumor	0.608	0.295-1.254	0.1781			
Radiotherapy for primary tumor	1.690	1.079-2.648	0.0219	0.675	0.362-1.257	0.2153
Chemotherapy for primary tumor	1.418	0.893-2.251	0.1387			
Surgical margin - inadequate	1.935	1.268-2.953	0.0022	1.882	1.130-3.134	0.0151

OR: Odds ratio; 95%CI: 95% confidence interval.

Table III. *Univariate and multivariate analysis of factors affecting lung metastasis-free survival.*

Variables	Univariate			Multivariate		
	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age	1.008	0.995-1.020	0.2371			
Sex - Female	0.718	0.473-1.092	0.1218			
Size	1.006	1.003-1.010	0.0003	1.006	1.001-1.010	0.0167
Location - Axial	1.702	1.109-2.611	0.0149	1.836	1.149-2.932	0.0110
Period from onset to consultation	0.986	0.972-0.999	0.0404	0.982	0.964-0.999	0.0402
Unplanned excision	0.415	0.191-0.901	0.0262	0.503	0.175-1.444	0.2015
Histological grade (high)	2.131	1.526-2.975	<0.0001	2.052	1.410-2.984	0.0002
Surgical treatment for primary tumor	0.577	0.266-1.251	0.1636			
Radiotherapy for primary tumor	1.783	1.101-2.888	0.0186	0.712	0.368-1.377	0.3127
Chemotherapy for primary tumor	1.576	0.966-2.572	0.0684			
Surgical margin - inadequate	2.258	1.440-3.539	0.0004	2.167	1.256-3.739	0.0055

OR: Odds ratio; 95%CI: 95% confidence interval.

sarcoma (n=1), and malignant solitary fibrous tumor (n=1). The sites of these primary lesions were the extremities (71.8%, n=242) and axial sites (28.2%, n=95). The mean tumor size for all patients was 84.1±55.2 mm (range=2-365 mm), and the FNCLCC classifications were Grade I for 59 patients, Grade II for 138 patients, and Grade III for 140 patients (Table I).

Surgical treatment for the primary tumor was performed in 315 patients (93.5%), and adequate tumor-free margins were achieved in 78.4% (n=247) of the cases. Adjuvant therapy for surgical margin was conducted in 31 patients (9.8%) and included absolute ethanol, hot water, and acridine orange (19, 20). Radiotherapy for the primary tumor was performed in 59 patients (17.5%) and included heavy ion radiation (3.4%, n=2), proton beam radiation (5.1%, n=3), and radiotherapy plus surgery (74.6%, n=44). Chemotherapy was administered to 65 patients (19.3%) and included doxorubicin, ifosfamide, dacarbazine, gemcitabine, docetaxel, methotrexate, cisplatin, vincristine, cyclophosphamide, etoposide, actinomycin D, paclitaxel, eribulin, and trabectedin (Table I).

Distant metastases developed in 108 patients (32.0%), and 91 of these patients developed lung metastases. The sites of extra-pulmonary metastases were lymph node (n=21), bones (n=19), soft tissues (n=15), intraperitoneal (n=5), retroperitoneal (n=4), brain (n=4), liver (n=4), thoracic cavity (n=3), mediastinum (n=1), spleen (n=1), and colon (n=1). Sixty-six patients (21.0%) developed local recurrence. The patient outcomes were as follows: no evidence of disease in 215 patients, alive with disease in 42 patients, and 80 patients who died because of their original disease. No patients died due to complications during the perioperative period (Table I).

The multivariate analysis revealed that the size of primary tumor, consultation in a short period after onset, histological high grade, and inadequate surgical margin were significant predictors for poor prognosis for all metastases (p=0.0011,

Table IV. *Multivariate logistic regression analyses of all and lung early metastasis predictors.*

	OR	95%CI	*p*-Value
All metastasis			
Age	0.968	0.944-0.994	0.0148
Sex (female)	0.508	0.225-1.148	0.1037
Size	0.998	0.991-1.005	0.5444
Location (axial)	0.654	0.254-1.684	0.3786
Period from onset to consultation	0.970	0.927-1.015	0.1901
Histological grade (high)	1.590	0.822-3.075	0.1683
Radiotherapy for primary tumor	0.737	0.263-2.067	0.5616
Chemotherapy for primary tumor	0.915	0.364-2.299	0.8496
Surgical margin - inadequate	1.862	0.828-4.188	0.1326
Lung metastasis			
Age	0.960	0.929-0.990	0.0148
Sex (female)	0.699	0.270-1.812	0.4613
Size	0.998	0.990-1.006	0.6444
Location (axial)	0.903	0.328-2.489	0.8439
Period from onset to consultation	0.940	0.868-1.019	0.1328
Histological grade (high)	2.389	0.989-5.773	0.0530
Radiotherapy for primary tumor	0.995	0.311-3.185	0.9928
Chemotherapy for primary tumor	0.679	0.234-1.970	0.4766
Surgical margin - inadequate	1.136	0.425-3.032	0.7994

OR: Odds ratio; CI: confidence interval.

p=0.0325, p=0.0006, and p=0.0151, respectively) (Table II). In addition, the multivariate analysis revealed that the size of primary tumor, axial location, consultation in a short period after onset, histological high grade, and inadequate surgical margin were significant predictors for poor prognosis for lung metastasis (p=0.0167, p=0.0110, p=0.0402, p=0.0002 and p=0.0055, respectively) (Table III). However, in a multivariate analysis of patients with all distant metastases or lung metastasis, the only risk factor for early metastases within 6 months was young age (p=0.0148) (Table IV).

Discussion

This study found that large tumor diameter, histological high grade, short time from onset to consultation, and inadequate surgical margin are risk factors for all distant metastasis and lung metastasis. In addition, the only risk factor for all distant metastasis and lung metastasis early within 6 months after resection of the primary STS was young age.

In STS, some risk factors for distant metastasis or lung metastasis at the time of initial diagnosis or after treatment of the primary tumor have been reported (12-17). Large tumor diameter, histological high grade, and histological type (leiomyosarcoma, malignant peripheral nerve sheath tumor, rhabdomyosarcoma, synovial sarcoma, and hemangio-sarcoma) have been reported as risk factors for distant metastasis at the first visit (12, 13). In addition, these factors have also been reported as risk factors for distant metastasis after primary tumor treatment (14, 17). Large tumor diameter and histological high grade were risk factors for distant metastasis in all reports, and our study also included large tumor diameter and histological high grade as risk factors. However, a risk factor that was examined only in our study was the short period from onset to consultation. We think that if the time between noticing a tumor and going to the hospital is short, it is less likely to metastasize because of initiating treatment quickly. However, the results of this study were the opposite. Tumors with a short period from notice to consultation may have been tumors with a high rate of growth and high malignancy.

Insufficient surgical margin was cited as one of the risk factors in our study. There is a report that did not list it as a risk factor even after evaluating it (14). If the tumor is not sufficiently resected during surgery, postoperative radiation or intraoperative adjuvant therapy may be administered, and the presence or absence of such adjuvant therapy may affect the analysis results. This could not be examined because of the number of cases in this study; hence, more detailed examination is necessary in the future.

In our study, the only risk factor for early all distant or lung metastases after treatment of the primary tumor was young age. Large tumor diameter, histological high grade, and inadequate surgical margins, which are risk factors for distant metastasis itself, were predictably listed as risk factors. The reason for higher risk at young age for early lung metastasis is unclear because there are no reports of such studies. This susceptibility could be due to factors involved in hematogenous metastasis being active at younger age and the momentum of tumors being stronger at younger ages. However, further studies are needed to identify the reason.

This is the first study to examine the factors of early distant metastasis after the primary tumor resection in patients with STS. However, there are some limitations as well. In our study, we examined 337 cases, but some reports that examined the risk of distant metastasis in the past included more than 1,000 cases. Because there are various histological types of STS, a larger number of cases is required in order to investigate the effects of histological types as in past reports. Therefore, further detailed studies are needed with a larger number of included patients.

In conclusion, this study evaluated the factors of early all distant and lung metastasis after the primary tumor resection in patients with STS and revealed that the only risk factor was young age, even though large tumor diameter and histological high grade are risk factors for all distant metastasis and lung metastasis. Future studies should focus on the cause of increased risk for early metastasis in young people.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

All Authors were involved in the planning and revising for this research. Tsuchie H, Nagasawa H, Emori M, Murahasi Y, Mizushima E, and Shimizu J collected the clinical data. Tsuchie H analyzed the raw data. Tsuchie H wrote this dissertation. Miyakoshi N and Yamashita T reviewed this manuscript.

References

1 Callegaro D, Miceli R, Bonvalot S, Ferguson P, Strauss DC, Levy A, Griffin A, Hayes AJ, Stacchiotti S, Pechoux CL, Smith MJ, Fiore M, Dei Tos AP, Smith HG, Mariani L, Wunder JS, Pollock RE, Casali PG and Gronchi A: Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis. Lancet Oncol *17(5)*: 671-680, 2016. PMID: 27068860. DOI: 10.1016/S1470-2045(16)00010-3

2 Smith HG, Memos N, Thomas JM, Smith MJ, Strauss DC and Hayes AJ: Patterns of disease relapse in primary extremity soft-tissue sarcoma. Br J Surg *103(11)*: 1487-1496, 2016. PMID: 27503444. DOI: 10.1002/bjs.10227

3 Italiano A, Le Cesne A, Mendiboure J, Blay JY, Piperno-Neumann S, Chevreau C, Delcambre C, Penel N, Terrier P, Ranchere-Vince D, Lae M, Le Guellec S, Michels JJ, Robin YM, Bellera C and Bonvalot S: Prognostic factors and impact of adjuvant treatments on local and metastatic relapse of soft-tissue sarcoma patients in the competing risks setting. Cancer *120(21)*: 3361-3369, 2014. PMID: 25042799. DOI: 10.1002/cncr.28885

4 Gronchi A, Lo Vullo S, Colombo C, Collini P, Stacchiotti S, Mariani L, Fiore M and Casali PG: Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. Ann Surg *251(3)*: 506-511, 2010. PMID: 20130465. DOI: 10.1097/SLA.0b013e3181cf87fa

5 Gutierrez JC, Perez EA, Franceschi D, Moffat FL Jr, Livingstone AS and Koniaris LG: Outcomes for soft-tissue sarcoma in 8249 cases from a large state cancer registry. J Surg Res *141(1)*: 105-114, 2007. PMID: 17512548. DOI: 10.1016/j.jss.2007.02.026

6 Zagars GK, Ballo MT, Pisters PW, Pollock RE, Patel SR, Benjamin RS and Evans HL: Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. Cancer *97(10)*: 2530-2543, 2003. PMID: 12733153. DOI: 10.1002/cncr.11365

7 Pisters PW, Leung DH, Woodruff J, Shi W and Brennan MF: Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol *14(5)*: 1679-1689, 1996. PMID: 8622088. DOI: 10.1200/JCO.1996.14.5.1679

8 Billingsley KG, Lewis JJ, Leung DH, Casper ES, Woodruff JM and Brennan MF: Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. Cancer *85(2)*: 389-395, 1999. PMID: 10023707.

9 Tsuchie H, Kaya M, Nagasawa H, Emori M, Murahashi Y, Mizushima E, Miyakoshi N, Yamashita T and Shimada Y: Distant metastasis in patients with myxofibrosarcoma. Ups J Med Sci *122(3)*: 190-193, 2017. PMID: 28814152. DOI: 10.1080/03009734.2017.1356404

10 Itoga R, Matsuoka M, Onodera T, Yokota I, Iwasaki K, Matsubara S, Hishimura R, Suzuki Y, Iwata A, Kondo E and Iwasaki N: Brain metastasis in soft tissue sarcoma at initial presentation. Anticancer Res *41(11)*: 5611-5616, 2021. PMID: 34732433. DOI: 10.21873/anticanres.15376

11 Tsuchie H, Emori M, Miyakoshi N, Nagasawa H, Okada K, Murahashi Y, Mizushima E, Shimizu J, Yamashita T and Shimada Y: Prognostic significance of histological subtype in soft tissue sarcoma with distant metastasis. In Vivo *34(4)*: 1975-1980, 2020. PMID: 32606169. DOI: 10.21873/invivo.11994

12 Fan Z, Chi C, Tong Y, Huang Z, Song Y and You S: Score for the risk and overall survival of lung metastasis in patients first diagnosed with soft tissue sarcoma: a novel nomogram-based risk assessment system. Technol Cancer Res Treat *21*: 15330338211066240, 2022. PMID: 35006028. DOI: 10.1177/15330338211066240

13 Krishnan CK, Kim HS, Park JW and Han I: Outcome after surgery for extremity soft tissue sarcoma in patients presenting with metastasis at diagnosis. Am J Clin Oncol *41(7)*: 681-686, 2018. PMID: 27819879. DOI: 10.1097/COC.0000000000000346

14 Zagars GK, Ballo MT, Pisters PW, Pollock RE, Patel SR and Benjamin RS: Prognostic factors for disease-specific survival after first relapse of soft-tissue sarcoma: analysis of 402 patients with disease relapse after initial conservative surgery and radiotherapy. Int J Radiat Oncol Biol Phys *57(3)*: 739-747, 2003. PMID: 14529779. DOI: 10.1016/s0360-3016(03)00714-4

15 Stefanovski PD, Bidoli E, De Paoli A, Buonadonna A, Boz G, Libra M, Morassut S, Rossi C, Carbone A and Frustaci S: Prognostic factors in soft tissue sarcomas: a study of 395 patients. Eur J Surg Oncol *28(2)*: 153-164, 2002. PMID: 11884051. DOI: 10.1053/ejso.2001.1242

16 Pisters PW, Leung DH, Woodruff J, Shi W and Brennan MF: Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol *14(5)*: 1679-1689, 1996. PMID: 8622088. DOI: 10.1200/JCO.1996.14.5.1679

17 Coindre JM, Terrier P, Bui NB, Bonichon F, Collin F, Le Doussal V, Mandard AM, Vilain MO, Jacquemier J, Duplay H, Sastre X, Barlier C, Henry-Amar M, Macé-Lesech J and Contesso G: Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol *14(3)*: 869-877, 1996. PMID: 8622035. DOI: 10.1200/JCO.1996.14.3.869

18 Enneking WF, Spanier SS and Goodman MA: A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res *(153)*: 106-120, 1980. PMID: 7449206.

19 Tsuchie H, Emori M, Miyakoshi N, Nagasawa H, Okada K, Murahashi Y, Mizushima E, Shimizu J, Yamashita T and Shimada Y: Impact of acridine orange in patients with soft tissue sarcoma treated with marginal resection. Anticancer Res *39(11)*: 6365-6372, 2019. PMID: 31704869. DOI: 10.21873/anticanres.13849

20 Tsuchie H, Emori M, Miyakoshi N, Okada K, Nagasawa H, Murahashi Y, Mizushima E, Shimizu J, Yamashita T and Shimada Y: Impact of acridine orange in patients with local recurrent soft tissue sarcoma. In Vivo *34(5)*: 2745-2750, 2020. PMID: 32871809. DOI: 10.21873/invivo.12097

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