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Delayed Initiation of Treatment Is Associated With Metastasis of Soft-tissue Sarcoma

YOSHIHIRO ARAKI, NORIO YAMAMOTO, KATSUHIRO HAYASHI, AKIHIKO TAKEUCHI, SHINJI MIWA, KENTARO IGARASHI, HIGUCHI TAKASHI, ABE KENSAKU, YUTA TANIGUCHI, HIROTAKA YONEZAWA, SEI MORINAGA, YOHEI ASANO and HIROYUKI TSUCHIYA

Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan

Abstract. *Background/Aim: The delayed initiation of treatment is associated with poor clinical outcomes in patients with malignancies. However, few previous studies have investigated prognostic factors, including the delayed initiation of treatment, in soft-tissue sarcoma. Patients and Methods: One hundred and fifty-three patients with soft-tissue sarcoma were enrolled. Univariate and multivariate analyses were performed to identify factors predicting metastasis, including factors that delay the initiation of treatment. Results: The multivariate analysis revealed that high histological grade (p<0.01), tumor located in the trunk (p=0.04), >5-month delay from symptom initiation to consultation of general practitioner (p=0.02), and >29-day delay in referral to a specialized hospital by general practitioners (p=0.03) were independently associated with metastasis of soft tissue sarcoma. Conclusion: Early consultation of a general practitioner and early referral to a specialized hospital might be essential for preventing metastasis of soft-tissue sarcoma.*

Tumor size and histological grade generally affect the survival of patients with malignant tumors, with large-size or high-grade malignancies associated with poorer survival in comparison to small or low-grade malignancies. Other factors that are reported to be associated with survival include tumor site, histological type, and delayed initiation of treatment (1-7).

Delayed initiation of treatment would lead to poor clinical outcomes in patients with malignancies (5-7). However, few studies have so far discussed the factors that are associated with a delay in the initiation of treatment. A delayed initiation of treatment can be ascribed to three periods: The period from the notification of symptoms to the initial consulting of a nearby doctor; the period from the first consultation of a nearby doctor to referral to a hospital specialized in the treatment of malignancies; and the period from referral to the initiation of treatment. Little is known about which delays are significantly associated with poor clinical outcomes.

In patients with malignancies, poor clinical outcomes often occur due to distant metastasis (8, 9). Distant metastasis occurs at an advanced stage of disease, and metastasis might be associated with delay in consulting a doctor or in the initiation of treatment.

While numerous studies have investigated prognostic factors for various types of cancer, few studies have investigated the prognostic factors of sarcoma due to its rarity (10-12). Soft-tissue sarcoma is also a rare malignancy that tends to be mistaken for soft-tissue swelling or a soft-tissue mass due to a lack of awareness of soft-tissue sarcomas (13). In such cases, the patients might delay consulting a nearby doctor; however, little is known about the correlation between delayed consultation and the prognosis of soft-tissue sarcoma.

Increased awareness of this rare malignancy among the general population might help avoid delays in consultation. The knowledge that a delay in consultation might lead to poor clinical outcomes if a soft-tissue mass is actually soft-tissue sarcoma is an important incentive for consulting a physician immediately when a person notices a soft-tissue mass or swelling, as this might contribute to improvement of clinical outcomes.

Unplanned excision is associated with undesirable clinical outcomes in patients with soft-tissue sarcoma, and additional excision is usually necessary for the removal of residual tumor cells. The dissemination of tumor cells during primary surgery may occur and micrometastasis might have already progressed around the excised area (14-19). Thus, a delay in referral to a specialized hospital may lead to poor clinical outcomes in patients with soft-tissue sarcoma.

Correspondence to: Norio Yamamoto (https://orcid.org/0000-0002-7250-625X), MD, Ph.D., Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kanazawa University, 13-1, Takaramachi, Kanazawa-city, Ishikawa, 920-8641, Japan. Tel: +81 762652000, e-mail: norinori@med.kanazawa-u.ac.jp

Key Words: Soft-tissue sarcoma, metastasis, histological grade, tumor site, early consultation, early referral.

Soft-tissue sarcoma is difficult to diagnose accurately due to its rarity and diversity, even by a pathologist at a specialized institution (20). A delayed diagnosis may lead to delayed treatment, which in turn would lead to a poor clinical outcome.

We therefore investigated the factors associated with metastasis in patients with soft-tissue sarcoma, considering three periods of delay before the initiation of treatment: Delay in consultation of a nearby doctor, in referral to a specialized hospital, and delay in the initiation of treatment.

Patients and Methods

One hundred and fifty-three patients were histologically diagnosed with malignant soft tissue tumors at our Institution from January 2010 to December 2017. All of these patients were enrolled in the present study. Using medical records, the following periods were defined: Period A: from the notification of symptoms to the patient's first consultation of a nearby doctor at a non-specialized hospital; Period B: from the first consultation of a nearby doctor to referral to a specialized hospital; and Period C: from referral until the initiation of treatment. The following factors were also investigated: Age, sex, initial symptom, tumor size, histological grade, tumor site, the referral department at a non-specialized hospital, previous procedures (including biopsy, planned or unplanned excision), follow-up period, oncological outcome at the final follow-up examination. The initial symptoms included mass, pain, swelling, and others. The tumor size was defined as the length in the greatest dimension measured on computed tomography or magnetic resonance imaging. The histological grade was classified according to the 2013 WHO classification as high-grade or intermediate malignancy (21). The tumor site was classified as trunk or appendicular skeleton. Non-specialized referral hospitals were classified as orthopedic surgery clinics or clinics of other departments (including dermatology, plastic surgery, general surgery, and other departments).

All patients were divided into two groups according to the presence or absence of metastasis. Five-year overall and disease-free survival were determined by a Kaplan–Meir curve analysis, and were compared between the two groups.

Univariate and multivariate analyses were performed to identify factors predicting metastasis during the follow-up period. Metastasis-free survival was also compared according to each factor.

This retrospective study of patient specimens was approved by the ethical committee of Kanazawa University Hospital [Institutional Review Board Number 2019-061 (3094)] and was performed in compliance with the guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all study participants and/or their parents (in the case of children).

Statistical analysis. Receiver operating characteristic (ROC) curves were used for determining the optimal cut-off values for tumor size, and delay in periods A, B and C. The sum of sensitivity and 1-specificity were defined as the maximum value in accordance with the Youden index, and the area under the curve was >0.5. A log-rank test was performed for the univariate analysis of each factor associated with metastasis. Cox proportional hazards regression analysis was performed as a multivariate analysis of factors predicting metastasis in patients with soft-tissue sarcoma. Values $p<0.05$ were considered to indicate statistical significance in the univariate and multivariate analyses. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria) (22).

Results

The study population included 90 male and 63 female patients, with a median age of 59 years (range=7-88 years). The histological types were as follows: Undifferentiated pleomorphic sarcoma in 31, well-differentiated liposarcoma in 30, myxoid liposarcoma in 14, leiomyosarcoma in 10, myxofibrosarcoma in 10, dedifferentiated liposarcoma in nine, synovial sarcoma in eight, desmoid-type fibromatosis in seven, extrapleural solitary fibroblastic tumor in six, extraskeletal osteosarcoma in six, and other types of soft tissue sarcoma in 22. One hundred and seven cases involved high-grade malignancy, and 46 cases involved intermediate malignancy. The tumor was located on the appendicular skeleton in 112 cases, and the trunk skeleton in 41 cases. The median tumor size was 60 mm (range=14-285 mm). The patients visited the following departments at their previous hospital: Orthopedic Surgery in 111, General Surgery in 10, Medicine in nine, Plastic Surgery in eight, Urology in five, Dermatology in four, Pediatrics in three, and other departments in three. Procedures were performed at a previous hospital in 23 cases; these included biopsy, planned excision and unplanned excision. The median follow-up period was 55 months (range=6-104 months). During the follow-up period, metastasis was observed in 48 cases (31%).

According to the ROC curve analysis, the optimal cut-offs for predicting metastasis were 5 months, 29 days, 24 days, and 46 mm for delay in of periods A, B and C, and tumor size, respectively (area under the ROC curve of 0.62, 0.59, 0.59, and 0.51) (Table I).

The 5-year overall survival rate was 77% for the whole cohort, 100% in patients without metastasis and 46% in patients with metastasis ($p<0.01$) (Figure 1A and B). The 5-year metastasis-free survival rate was 61% overall (Figure 1C).

In the univariate analysis, mass (as a symptom), high histological grade, tumor of the trunk, delay in period A or B, and previous procedures were significantly associated with the progression of metastasis during the follow-up period. In the multivariate analysis, high histological grade [hazard ratio (HR)=9.88, 95% confidence interval (CI)=2.36-41.3, $p<0.01$], tumor located in the trunk (HR=2.01, 95% CI=1.03-3.91, $p=0.04$), >5-month delay in period A (HR=2.08, 95% CI=1.03-3.91, $p=0.02$), and >29-day delay in period B (HR=2.01, 95% CI=1.07-3.77, $p=0.03$) were independently associated with metastasis of soft-tissue sarcoma (Table II).

The 5-year metastasis-free survival rate in patients with intermediate malignancy was 95%, while that in those with high-grade malignancy was 49% ($p<0.01$) (Figure 2A). The

Table I. *Optimal cut-off values for predicting metastasis according to the receiver operating characteristics curve analysis.*

Factor	Optimal cut-off value	AUC	Sensitivity	Specificity
Period A	5 Months	0.62	68.2%	53.4%
Period B	29 Days	0.59	45.7%	77.7%
Period C	24 Days	0.59	47.5%	72.4%
Tumor size	46 mm	0.51	89.6%	22.3%

AUC: Area under the receiver operating characteristics curve. Period A: The period from the notification of symptoms to the initial consulting of a nearby doctor. Period B: The period from the first consultation of a nearby doctor to referral to a specialized hospital. Period C: The period from referral to the initiation of treatment.

5-year metastasis-free survival rate in patients with appendicular soft-tissue sarcoma was 95%, while in those with trunk soft-tissue sarcoma it was 49% (p=0.02) (Figure 2B). The 5-year metastasis-free survival rate in those with delay in period A ≤5 months was 95% *versus* 49% in those with delay >5 months (p=0.02) (Figure 2C). The 5-year metastasis-free survival rate in those with delay in period B ≤29 days was 95% *versus* 49% in those with delay >29 days (p=0.01) (Figure 2D).

Discussion

The effects of delayed initiation of treatment were analyzed in a few studies that investigated prognostic factors for soft-tissue sarcoma (23-26). The interval between the onset of the initial symptoms and the first consultation at a specialized hospital was reported to be a significant predictor of distant metastasis at the time of the diagnosis; however, the previous studies did not divide the interval of delay in detail. The delay from the onset of symptoms to the diagnosis we divided into the following three intervals: from symptom onset to first consultation (period A), from consultation to presentation at a specialized hospital (period B), and from presentation at a specialized hospital until diagnosis (period C). In the present study, a multivariate analysis was performed to identify prognostic factors associated with metastasis of soft tissue sarcoma, including the three intervals. To the best of our knowledge, no previous studies have analyzed the details regarding the delayed initiation of treatment in patients with soft-tissue sarcoma.

An interval between recognition of initial symptoms and the first consultation of a nearby doctor (period A) of more than 5 months was significantly associated with metastasis of soft-tissue sarcoma in our study. An interval between the recognition of initial symptoms and first consultation at a specialized hospital of >6 months was reported by Nakamura et al. to be a significant predictor of metastasis of soft-tissue

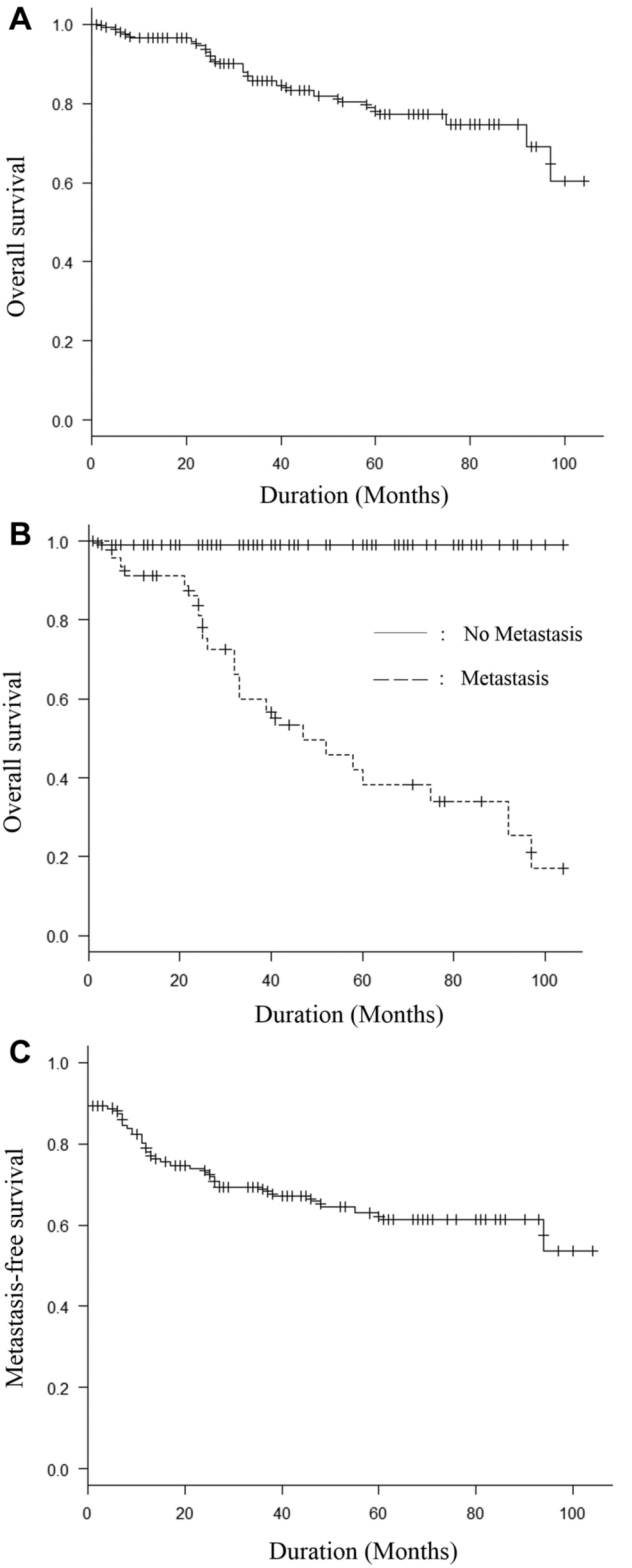

Figure 1. *A: Overall survival of study patients with soft-tissue sarcoma. B: Overall survival of patients with soft-tissue sarcoma according to the presence or absence of metastasis. C: Metastasis-free survival of study patients with soft-tissue sarcoma.*

sarcoma (23); however, based on the outcome of our study, a short interval from recognition of the initial symptom to consultation with a nearby doctor was also essential for preventing metastasis of soft-tissue sarcoma. It may be necessary to promote awareness in the general public, through poster, magazine or online advertisements, of the importance of quickly consulting a doctor when a soft-tissue mass presenting tenderness or increasing size is recognized.

A delay in referral to a specialist of >29 days (period B) was also significantly associated with metastasis of soft-tissue sarcoma in our study. A general practitioner is usually the first physician to come into contact with a patient presenting a soft-tissue mass; however, if they do not consider the possibility of malignancy, the physician may decide to observe the patient conservatively without close examination, or might refer the patient to a dermatologist or plastic surgeon, who are not specialists in musculoskeletal oncology. Based on the outcome of our study, early referral to a specialized hospital is essential for the survival of the patient. Knowledge of the importance of early referral to a specialized hospital when managing patients with a soft-tissue mass might be necessary for general practitioners, unless they continue to examine the patient for soft-tissue masses, considering the possibility of malignancy. Encouraging general practitioners to join small study groups at local hospitals will enable them to share their knowledge with other staff members.

In recent years, 25-50% of excisions of malignant soft-tissue tumors were reported to be unplanned, and to have been performed by a doctor who was not a specialist in musculoskeletal oncology, including general practitioners (14-19). General practitioners in general surgery, dermatology, or plastic surgery departments usually tend to treat patients without close examination. Unplanned excision was defined as the excision of malignant soft-tissue tumors without close examination, including magnetic resonance imaging or biopsy for the histological diagnosis. Residual tumor cells may possibly be disseminated during such procedures and metastasize to distal vital organs, such as the lung or brain. In our study, previous procedures, including unplanned excision, were not significantly associated with metastasis of soft-tissue sarcoma in the multivariate analysis; however, unplanned excision by general practitioners has been associated with poor prognosis, and can possibly result in delayed referral to a specialized hospital (15, 18, 19). Thus, a doctor who is not a musculoskeletal oncology specialist should not perform simple excision or biopsy without close examination. Conversely, they should explain the possibility of malignancy, when a patient presents with a soft-tissue mass, and should refer the patient to a specialized hospital as early as possible.

High-grade malignant soft-tissue tumors or sarcomas at sites of the trunk, such as the pelvis or spine, have been reported to be susceptible to metastasis and confer a poor prognosis (3, 4, 27-29). In our study, high-grade malignant soft-tissue tumors, excluding atypical lipomatous tumor, desmoid-type fibromatosis and other intermediate malignant soft-tissue tumors, were associated with poorer metastasis-free survival in comparison to intermediate malignant soft-tissue tumors, as in previous studies. Soft tissue tumors at the pelvis, spine, or thoracic cavity are difficult to excise completely with a clear margin, and often recur or metastasize, which leads to poor survival. In addition, tumors at these locations are close to the lung and the other vital organs in the abdominal cavity; thus, metastasis might be more likely to occur in comparison to tumors at appendicular sites.

The present study was associated with some limitations. Firstly, this was a retrospective study that was performed at a single institution with a relatively small number of cases that

Table II. *Univariate and multivariate analyses for identifying the factors predicting metastasis of soft-tissue sarcoma.*

Factor	n	Univariate		Multivariate	
		p-Value	HR	95% CI	*p*-Value
Symptom					
Mass	59	0.03			
Pain	20	0.34			
Swelling	57	0.3			
Other	17	0.25			
Tumor size					
>46 mm	121	0.09			
≤46 mm	32				
Tumor grade					
High	107	<0.01	9.88	2.36-41.3	<0.01
Intermediate	46				
Tumor location					
Trunk	41	0.02	2.01	1.03-3.91	0.04
Appendicular	112				
Delay in period A					
>5 Months	71	0.02	2.08	1.09-3.95	0.02
≤5 Months	82				
Delay in period B					
>29 Days	43	<0.01	2.01	1.07-3.77	0.03
≤29 Days	110				
Delay in period C					
>24 Days	78	0.21			
≤24 Days	75				
Referral department					
Orthopedic surgery	112	0.08			
Other	41				
Previous procedures					
Yes	23	<0.01			
No	130				

HR: Hazard ratio; CI: confidence interval. Period A: The period from the notification of symptoms to the initial consulting of a nearby doctor. Period B: The period from the first consultation of a nearby doctor to referral to a specialized hospital. Period C: The period from referral to the initiation of treatment.

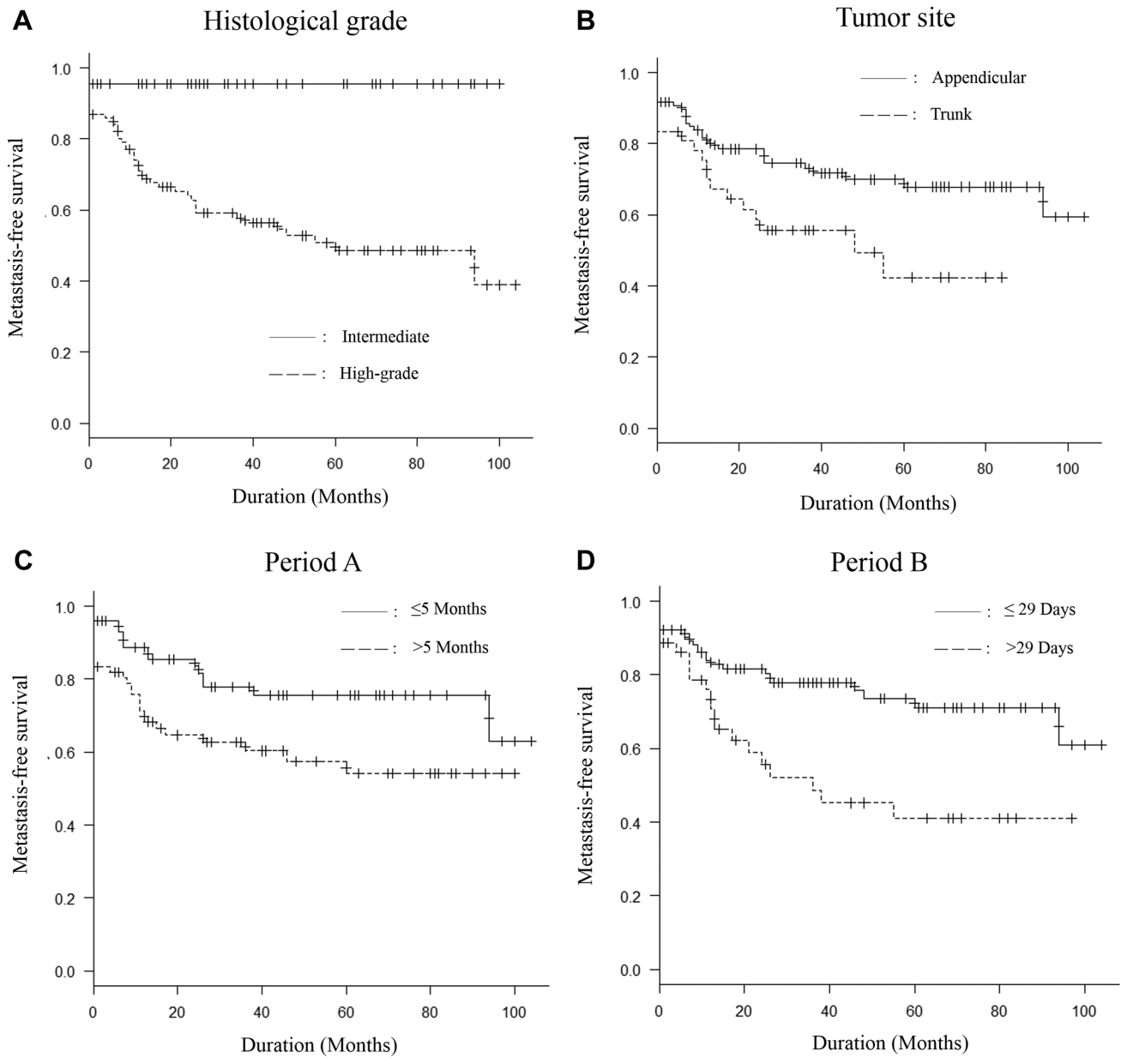

Figure 2. *Metastasis-free survival of study patients with soft-tissue sarcoma according to histological grade (A), tumor site (B), delay in period A, i.e. from symptom onset to first consult (C), and delay in period B i.e. from first consult to specialist consult (D).*

included diverse histological types. Secondly, recall bias by patients might have been present when they reported the timing of the onset of symptoms because of the lack of any validation of the self-reported findings. Thirdly, metastasis was mostly confirmed by imaging modalities alone, not all lesions were subjected to a histological examination. Fourthly, treatment methods were not included in the analysis of prognostic factors because the treatment strategies differed according to the histological type.

In conclusion, we found that a delay in consulting a doctor after the onset of symptoms, and a delay in referral to a specialized hospital were prognostic factors for increased risk of metastasis in patients with soft-tissue sarcoma. Both the knowledge of the importance of early consultation when people notice a soft-tissue mass, and of early referral to a specialized hospital by general practitioners encountering a patient with a soft-tissue mass might be essential for preventing metastasis in patients with soft-tissue sarcoma.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' Contributions

TH, YN, and A Yos conceived and designed the study. NT and IH performed histological examination of all the specimen. A Yos carried out data acquisition. HT, AK, TY, YH, MS, and A. Yoh provided assistance for data acquisition. TH, YN, HK, TA, MS and IK managed the patients for the appropriate treatment and observed them at the follow-up outpatient clinic after treatment completion. TH, YN, NT, and A. Yos contributed to the analysis and interpretation of clinical and pathological data. A. Yos analyzed all the patient's data and wrote the article. All Authors read and approved the final article. All data generated or analyzed during the present study are included in this article.

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References

1 Grimer RJ: Size matters for sarcomas! Ann R Coll Surg Engl *88(6)*: 519-524, 2006. PMID: 17059708. DOI: 10.1308/003588406X130651

2 Nandra R, Forsberg J and Grimer R: If your lump is bigger than a golf ball and growing, think sarcoma. Eur J Surg Oncol *41(10)*: 1400-1405, 2015. PMID: 26163048. DOI: 10.1016/j.ejso.2015.05.017

3 Pasquali S, Pizzamiglio S, Touati N, Litiere S, Marreaud S, Kasper B, Gelderblom H, Stacchiotti S, Judson I, Dei Tos AP, Verderio P, Casali PG, Woll PJ, Gronchi A; EORTC – Soft Tissue and Bone Sarcoma Group: The impact of chemotherapy on survival of patients with extremity and trunk wall soft tissue sarcoma: Revisiting the results of the EORTC-STBSG 62931 randomised trial. Eur J Cancer *109*: 51-60, 2019. PMID: 30690293. DOI: 10.1016/j.ejca.2018.12.009

4 Lazarides AL, Kerr DL, Nussbaum DP, Kreulen RT, Somarelli JA, Blazer DG 3rd, Brigman BE and Eward WC: Soft tissue sarcoma of the extremities: What is the value of treating at high-volume centers? Clin Orthop Relat Res *477(4)*: 718-727, 2019. PMID: 30485258. DOI: 10.1097/01.blo.0000533623.60399.1b

5 Annakkaya AN, Arbak P, Balbay O, Bilgin C, Erbas M and Bulut I: Effect of symptom-to-treatment interval on prognosis in lung cancer. Tumori *93(1)*: 61-67, 2007. PMID: 17455873

6 Ermiah E, Abdalla F, Buhmeida A, Larbesh E, Pyrhönen S and Collan Y: Diagnosis delay in Libyan female breast cancer. BMC Res Notes *5*: 452, 2012. PMID: 22909280. DOI: 10.1186/1756-0500-5-452

7 Goedhart LM, Gerbers JG, Ploeqmakers JJ and Jutte PC: Delay in diagnosis and its effect on clinical outcome in hi-grade sarcoma of bone: A referral oncological center study. Orthop Surg *8(2)*: 122-128, 2016. PMID: 27384720. DOI: 10.1111/os.1223

8 Iqbal N, Shukla NK, Deo SV, Agarwala S, Sharma DN, Sharma MC and Bakhshi S: Prognostic factors affecting survival in metastatic soft tissue sarcoma: an analysis of 110 patients. Clin Transl Oncol *18(3)*: 310-316, 2016. PMID: 26243399. DOI: 10.1007/s12094-015-1369-9

9 Li RH, Zhou Q, Li AB, Zhang HZ and Lin ZQ: A nomogram to predict metastasis of soft tissue sarcoma of the extremities. Medicine *99(21)*: e20165, 2020. PMID: 32481285. DOI: 10.1097/MD.0000000000020165

10 Greither T, Wedler A, Rot S, Keßler J, Kehlen A, Holzhausen HJ, Bache M, Würl P, Taubert H and Kappler M: CMG2 Expression is an independent prognostic factor for soft tissue sarcoma patients. Int J Mol Sci *18(12)*: 2648, 2017. PMID: 29215551. DOI: 10.3390/ijms18122648

11 Liu G, Ke LC and Sun SR: Prognostic value of pretreatment neutrophil-to-lymphocyte ratio in patients with soft tissue sarcoma: A meta-analysis. Medicine *97(36)*: e12176, 2018. PMID: 30200120. DOI: 10.1097/MD.0000000000012176

12 Gannon NP, Stemm MH, King DM and Bedi M: Pathologic necrosis following neoadjuvant radiotherapy or chemoradiotherapy is prognostic of poor survival in soft tissue sarcoma. J Cancer Res Clin Oncol *145(5)*: 1321-1330, 2019. PMID: 30847552. DOI: 10.1007/s00432-019-02885-4

13 Tan MTL, Thompson SR, Schipp D, Bae S and Crowe PJ: Patterns of care of superficial soft tissue sarcomas: It is not always just a lump. Asia Pac J Clin Oncol *14(5)*: e472-e478, 2018. PMID: 29383831. DOI: 10.1111/ajco.12823

14 Pretell-Mazzini J, Brton MD Jr, Conway SA and Temple HT: Unplanned excision of soft-tissue sarcomas: Current concepts for management and prognosis. J Bone Joint Surg Am *97(7)*: 597-603, 2015. PMID: 25834085. DOI: 10.2106/JBJS.N.00649

15 Potter BK, Adams SC, Pitcher JD Jr. and Temple HT: Local recurrence of disease after unplanned excisions of high-grade soft tissue sarcomas. Clin Orthop Relat Res *466(12)*: 3093-100, 2008. PMID: 18818981. DOI: 10.1007/s11999-008-0529-4

16 Nakamura T, Kawai A and Sudo A: Analysis of the patients with soft tissue sarcoma who received additional excision after unplanned excision: Report from the Bone and Soft Tissue Tumor Registry in Japan. Jpn J Clin Oncol *47(11)*: 1055-1059, 2017. PMID: 28973287. DOI: 10.1093/jjco/hyx123

17 Khoo M, Pressney I, Hargunani R and Saifuddin A: Small, superficial, indeterminate soft-tissue lesions as suspected sarcomas: Is primary excision biopsy suitable? Skeletal Radiol *46(7)*: 919-924, 2017. PMID: 28361352. DOI: 10.1007/s00256-017-2635-4

18 Zaidi MY, Ethun CG, Liu Y, Poultsides G, Howard JH, Mogal H, Tseng J, Votanopoulos K, Fields RC and Cardona K: The impact of unplanned excisions of truncal/extremity soft tissue sarcomas: A multi-institutional propensity score analysis from the US Sarcoma Collaborative. J Surg Oncol *120(3)*: 332-339, 2019. PMID: 31172536. DOI: 10.1002/jso.25521

19 Charoenlap C, Imanishi J, Tanaka T, Slavin J, Ngan SY, Chander S, Dowsey MM, Goyal C and Choong PF: Outcomes of unplanned sarcoma excision: Impact of residual disease. Cancer Med *5(6)*: 980-988, 2016. PMID: 26929181. DOI: 10.1002/cam4.615

20 Smith GM, Johnson GD, Grimer RJ and Wilson S: Trends in presentation of bone and soft tissue sarcomas over 25 years: Little evidence of earlier diagnosis. Ann R Coll Surg Engl *93(7)*: 542-547, 2011. PMID: 22004638. DOI: 10.1308/147870811X13137608455055

21 Fletcher CD, Bridge JA, Hogendoorn PC and Mertens F: WHO Classification of Tumours of Soft Tissue and Bone. Fourth Edition. IARC; 2013

22 Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant *48*: 452-458, 2013. PMID: 23208313. DOI: 10.1038/bmt.2012.244

23 Nakamura T, Matsumine A, Matsubara T, Asanuma K, Uchida A and Sudo A: The symptom-to-diagnosis delay in soft tissue sarcoma influence the overall survival and the development of distant metastasis. J Surg Oncol *104(7)*: 771-775, 2011. PMID: 21744348. DOI: 10.1002/jso.22006

24 Urakawa H, Tsukushi S, Arai E, Kozawa E, Futamura N, Ishiguro N and Nishida Y: Association of short duration from initial symptoms to specialist consultation with poor survival in soft-tissue sarcomas. Am J Clin Oncol *38(3)*: 266-271, 2015. PMID: 23648441. DOI: 10.1097/COC.0b013e318295aea2

25 Featherall J, Curtis GL, Lawrenz JM, Jin Y, George J, Scott J, Shah C, Shepard D, Rubin BP, Nystrom LM and Mesko NW: Time to treatment initiation and survival in adult localized, high-grade soft tissue sarcoma. J Surg Oncol *120(7)*: 1241-1251, 2019. PMID: 31587292. DOI: 10.1002/jso.25719

26 Moten AS, Zhao H, Howell K, Nadler A, Reddy SS, von Mehren M, Movva S and Farma JM: Soft tissue sarcoma of the extremity: Characterizing symptom duration and outcomes. Surg Oncol *29*: 190-195, 2019. PMID: 31196487. DOI: 10.1016/j.suronc.2019.05.016

27 Bourcier K, Le Cesne A, Tselikas L, Adam J, Mir O, Honore C and de Baere T: Basic knowledge in soft tissue sarcoma. Cardiovasc Intervent Radiol *42(9)*: 1255-1261, 2019. PMID: 31236647. DOI: 10.1007/s00270-019-02259-w

28 Cates MM and Cates JMM: Surgical resection margin classifications for high-grade pleomorphic soft tissue sarcomas of the extremity or trunk: Definitions of adequate resection margins and recommendations for sampling margins from primary resection specimens. Mod Pathol *32(10)*: 1421-1433, 2019. PMID: 31053757. DOI: 10.1038/s41379-019-0278-9

29 Kainhofer V, Smolle MA, Szkandera J, Liegl-Atzwanger B, Maurer-Ertl W, Gerger A, Riedl J and Leithner A: The width of resection margins influences local recurrence in soft-tissue sarcoma patients. Eur J Surg Oncol *42(6)*: 899-906, 2016. PMID: 27107792. DOI: 10.1016/j.ejso.2016.03.026

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