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Delayed Initiation of Treatment Is Associated With Metastasis of Malignant Bone Tumor

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Abstract. *Background/Aim: The delayed initiation of treatment is not associated with good clinical outcomes in patients with malignancies. However, few previous studies have examined prognostic factors, including the delayed initiation of treatment, in malignant bone tumors. Patients and Methods: One hundred and one patients with malignant bone tumors 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-grade bone malignancy ($p<0.01$), a >30-day delay in referral to a specialized hospital by a general practitioner ($p=0.03$), and large tumor size (>77 mm) ($p=0.04$), were independently associated with metastasis of malignant bone tumors. Conclusion: When general practitioners notice a patient with a >77 mm bone tumor, early referral to a specialized hospital within one month might be essential for preventing metastasis.*

The size of a tumor and its histological grade generally affect the survival of patients; large-size or high-grade malignancies are associated with poorer survival in comparison to small or low-grade malignancies. Other factors that are reported to be associated with poor survival include tumor location, histological subtype, and delayed initiation of treatment (1-13).

However, few studies have discussed the factors associated with a delay in the initiation of treatment. Delays in the initiation of treatment can be divided into three periods: the period from the notification of symptoms to the initial consultation of a family doctor; the period from the first consultation of a family doctor to referral to a hospital specialized in the treatment of malignancies; and the period from referral to the initiation of treatment, including the period required for histological diagnosis. However, little is known about which periods are significantly associated with poor clinical outcomes in patients with malignancies.

In patients with malignancies, distant metastasis often leads to poor clinical outcomes (14, 15). Distant metastasis occurs at an advanced stage, and might be associated with delays in consulting a doctor or in the initiation of treatment.

While numerous studies have investigated prognostic factors for various types of cancer (1-6), few studies have investigated the prognostic factors of sarcoma due to its rarity (16-19). Bone sarcoma is also a rare malignancy that tends to be mistaken for pain due to excess exercise, osteoarthritis, neurological disorder, or growth pain due to a lack of awareness of bone sarcomas among general practitioners (20, 21). In such cases, the patients might delay consulting a doctor at a specialized institution for orthopedic oncology; however, little is known about the correlation between delayed consultation of an orthopedic oncologist and the prognosis of bone sarcoma (22-26).

Increased awareness of rare malignancies among the general population might help to avoid delays in consultation. The knowledge that a delay in consultation might lead to poor clinical outcomes, is important for urging people to consult a physician immediately when they notice deep skeletal pain, or a bony mass, as this might contribute to the improvement of clinical outcomes (24, 27-29). On the other hand, in some cases, general practitioners may treat patients with periarticular pain with painkillers or intraarticular injection of hyaluronic acid, without performing a close examination. When the practitioners notice continuous, increasing pain, or a large bony mass in a patient who does not show significant

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Key Words: Malignant bone tumor, metastasis, histological tumor grade, tumor size, general practitioner, early referral.

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

Factors	Optimal cut-off value	AUC	Sensitivity	Specificity
Period A	6 Months	0.54	38.5%	78.4%
Period B	30 Days	0.59	37.0%	86.6%
Period C	27 Days	0.58	75.0%	47.8%
Age	56 Years	0.56	55.6%	75.7%
Tumor size	77 mm	0.67	69.2%	63.5%

AUC: Area under the 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.

improvement, despite conservative treatment, the patient is often referred to a specialized hospital. However, a delay in referral to specialized hospital may lead to poor clinical outcomes in patients with bone sarcoma. Moreover, the accurate diagnosis of malignant bone tumors is sometimes difficult due to their rarity and diversity, even when examined by a pathologist in a specialized institution (25, 26). A delayed histological diagnosis may also lead to delayed initiation of treatment.

We therefore examined the factors associated with metastasis in patients with malignant bone tumors, including three periods of delay before the initiation of treatment: delay in the consultation; delay in referral to a specialized hospital; and delay in the initiation of treatment.

Patients and Methods

One hundred one patients histologically diagnosed with malignant bone tumors at our institution from January 2010 to December 2017 were enrolled in the present study. Using medical records, the following periods were determined: the period from the notification of symptoms to the patient's first consultation of a family doctor at a non-specialized hospital (Period A); the period from the first consultation of a family doctor to referral to a specialized hospital (Period B), and the period from referral to the specialized hospital to the initiation of treatment (Period C). The following factors were also investigated: age, sex, symptoms, tumor size, histological grade, tumor site, follow-up period, and the oncological outcomes at the final follow-up examination. The initial symptoms included pain, hard mass and other symptoms. The tumor size was defined as the length of the greatest dimension measured on computed tomography (CT) or magnetic resonance imaging (MRI). The tumor site was classified as the trunk or appendicular skeleton. The histological grade was classified according to the 2013 WHO classification, as high-grade or low-grade to intermediate-grade malignancy (30).

All patients were divided into two groups according to the presence or absence of metastasis. Five-year overall survival (OS) and 5-year distant metastasis-free survival (DMFS) were determined by a Kaplan–Meier curve analysis, and then were compared between the two groups. Univariate and multivariate analyses were performed to identify factors predicting metastasis during the follow-up period. DMFS 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 3249) 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 to determine the optimal cut-off values for Period A, Period B, Period C, age, and tumor size. The sum of sensitivity and 1-specificity was defined as the maximum value in accordance with the Youden index, and the area under the curve (AUC) was >0.5. A log-rank test was performed for the univariate analysis of each factor associated with metastasis. A Cox proportional hazards regression analysis was performed as a multivariate analysis of factors predicting metastasis in patients with malignant bone tumors. *p*-Values of <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) (31).

Results

The study population included 56 male patients and 45 female patients, with a median age of 41 years (range=7-92 years). The histological types were as follows: osteosarcoma (n=32; high-grade, n=30; low-grade, n=2), giant-cell tumor of the bone (n=27), chondrosarcoma [n=12; high-grade (Grade2/3, dedifferentiated), n=8; low-grade (Grade1), n=4], chordoma (n=6), undifferentiated pleomorphic sarcoma of the bone (n=5), Ewing sarcoma (n=4), leiomyosarcoma of the bone (n=3), and other types of malignant bone tumors (n=12). Sixty-one cases involved high-grade malignancy, and 50 cases involved low-grade to intermediate-grade malignancy. The tumor was located on the appendicular skeleton in 70 cases, and the trunk skeleton in 31 cases. The median tumor size was 81 mm (range=21-240 mm). The median follow-up period was 59 months (range=6-109 months). During the follow-up period, metastasis was observed in 27 cases (27%).

According to the ROC curve analysis, the optimal cut-off values of Period A, Period B, Period C, age, and tumor size

for predicting metastasis were 6 months, 30 days, 27 days, 56 years, and 77 mm, respectively (AUC; 0.54, 0.59, 0.58, 0.56, and 0.67) (Table I).

The 5-year OS rate was 90% in the overall study population, 97% in patients without metastasis and 73% in patients with metastasis ($p<0.01$) (Figure 1A and B). The 5-year DMFS rate was 74% (Figure 1C).

In the univariate analysis, age, tumor size, histological grade, and Period B, were significantly associated with the progression of metastasis during the follow-up period. In the multivariate analysis, histological high-grade [hazard ratio (HR)=15.4, 95% confidence interval (CI)=2.01-118, $p<0.01$], Period B >30 days (HR=3.22, 95%CI=1.14-9.09, $p=0.03$), and large tumor size >77 mm (HR=3.18, 95%CI=1.06-9.53, $p=0.04$) were independently associated with metastasis in malignant bone tumors (Table II).

The 5-year DMFS rate in bone sarcoma patients with low-grade to intermediate-grade malignancy was 97%, while that in bone sarcoma patients with high-grade malignancy was 58% ($p<0.01$) (Figure 2A). The 5-year DMFS rate in patients with bone sarcoma with a tumor size of ≤77 mm was 91%, while that in patients with bone sarcoma with a tumor size of >77 mm was 55% ($p<0.01$) (Figure 2B). The 5-year DMFS rate in bone sarcoma patients in whom Period B was ≤30 days was 76%, while that in bone sarcoma patients in whom Period B was >30 days was 52% ($p=0.04$) (Figure 2C).

Discussion

The effects of the delayed initiation of treatment were analyzed in a few studies that investigated prognostic factors for bone sarcoma (22-26). The total delay in referral to a specialized hospital has been previously reported to be 9-120 weeks; however, the study did not define which delay interval was important (26). Moreover, the optimal cut-off point for predicting the clinical outcome was not investigated.

The delay from the onset of symptoms to the treatment can actually be divided into the following three intervals: the interval from the onset of symptoms to consultation of the first doctor (Period A); the interval from consultation of the first doctor to presentation at a specialized hospital (Period B); and the interval between presentation at a specialized hospital and the initiation of treatment (Period C) (32). In the present study, a multivariate analysis was performed to identify prognostic factors associated with metastasis of bone sarcoma; the three intervals were included as factors. To the best of our knowledge, no previous studies have analyzed the details regarding the delayed initiation of treatment in patients with malignant bone tumors.

A >30-day delay in referral to a specialized hospital by the first doctor (Period B) was significantly associated with metastasis of malignant bone tumors in our study (Table II,

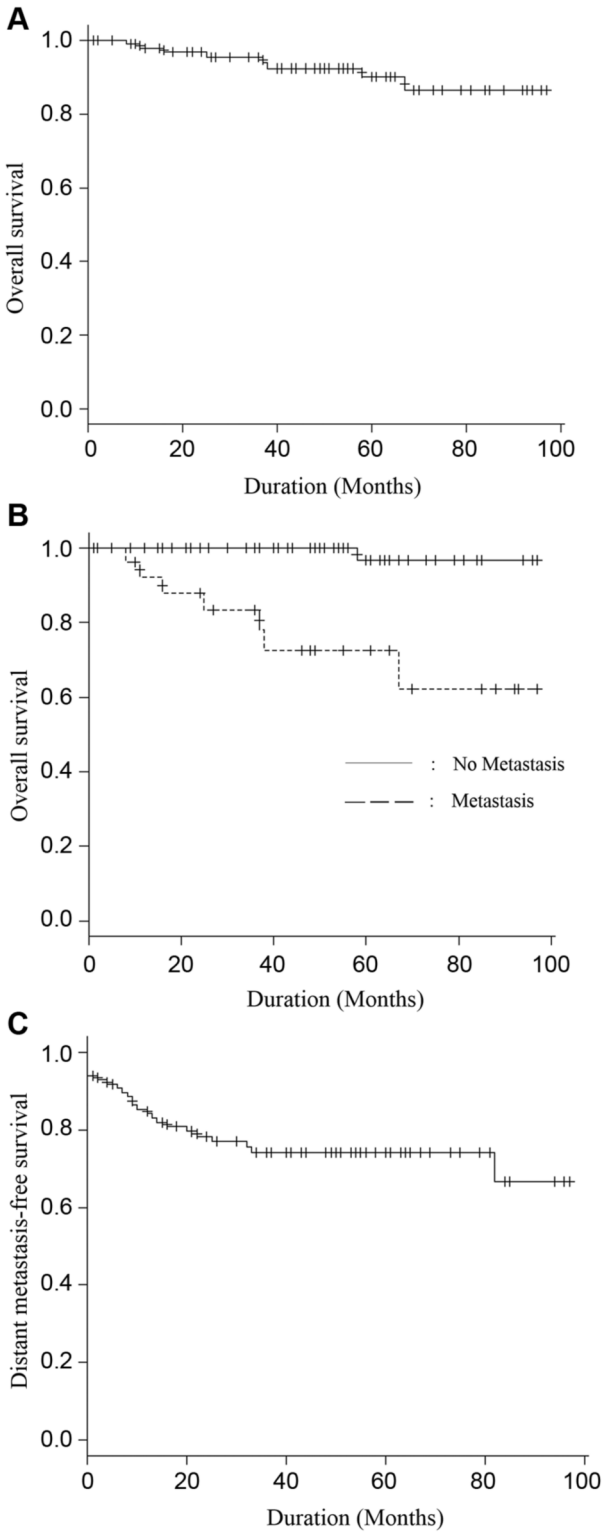

Figure 1. *Overall survival and distant metastasis-free survival of study patients. A: Overall survival of study patients with malignant bone tumors. B: Overall survival of study patients with malignant bone tumors according to the presence or absence of metastasis. C: Distant metastasis-free survival of study patients with malignant bone tumors.*

Table II. *Univariate and multivariate analyses for identifying the factors predicting distant metastasis of malignant bone tumors.*

Factor	n	Univariate	Multivariate		
		p-Value	HR	95%CI	*p*-Value
Age					
>56 years	33	<0.01			
≤56 years	68				
Gender					
Male	56	0.45			
Female	45				
Symptom					
Pain	85	0.99			
Hard mass	7	0.24			
Others	9	0.33			
Tumor size					
>77mm	45	<0.01	3.18	1.06-9.53	0.04
≤77mm	56				
Histological grade					
High-grade	61	<0.01	15.4	2.02-118	<0.01
Low-grade to Intermediate	50				
Tumor site					
Trunk	31	0.54			
Appendicular	70				
Delay in period A					
>6 Months	26	0.09			
≤6 Months	75				
Delay in period B					
>30 Days	19	0.04	3.22	1.14-9.09	0.03
≤30 Days	81				
Delay in period C					
>27 Days	42	0.08			
≤27 Days	59				

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 2C). A general practitioner is usually the first physician to come into contact with a patient presenting with deep skeletal pain; however, if they do not consider the possibility of malignant bone tumors, the physician may consider their symptom to be due to excess exercise, osteoarthritis, neurological disorder, or growth pain and will often decide to observe the patient conservatively with the administration of painkillers, without a close examination (20, 21). Based on the results of our study, early referral to a specialized hospital within one month is essential for the survival of the patient. Knowledge of the importance of early referral to a specialized hospital when managing patients with malignant bone tumors might be necessary for general practitioners, unless they continue to examine the patient for the cause of their symptoms, and consider the possibility of a malignant bone tumor. Encouraging general practitioners

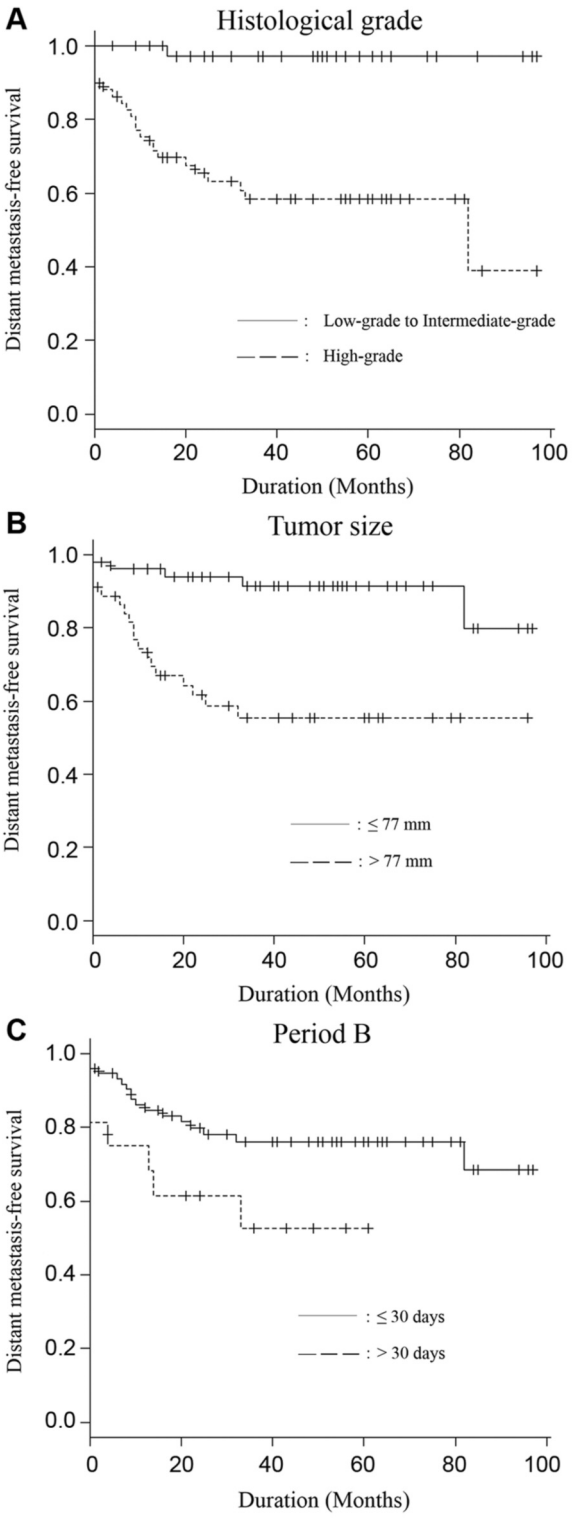

Figure 2. *Distant metastasis-free survival of study patients according to the significant factors. A: Distant metastasis-free survival of study patients with malignant bone tumors according to histological tumor grade. B. Metastasis-free survival of study patients with malignant bone tumors according to tumor size. C. Distant metastasis-free survival of study patients with malignant bone tumors according to delay in Period B.*

to join small study meetings at local hospitals will thus enable them to share their knowledge on malignant bone tumors, and also provide opportunities for doctors to consult about how they should treat bone tumor cases with other staff members.

High-grade malignant bone tumors or bone sarcoma have been reported to be susceptible to metastasis and to be associated with a poor prognosis (10, 11, 15). In agreement with previous studies, the results of our study indicate that high-grade malignant bone tumors – excluding low-grade osteosarcoma, giant cell tumor of the bone, chondrosarcoma (Grade 1), and other low-grade to intermediate-grade malignant bone tumors – were associated with poorer metastasis-free survival in comparison to low-grade to intermediate-grade malignant bone tumors (10, 11, 15, 30, 33) (Figure 2A).

The tumor size has been reported to be significantly associated with survival in soft tissue sarcomas, and a tumor size of approximately 42 mm (a standard-sized golfball) should raise the suspicion of possible soft tissue sarcoma (34, 35). However, little is known about the correlation between the size of bone tumors and survival (18, 19, 22-24). In the previous study, the median size of bone sarcoma at the time of diagnosis was 107 mm (27), while the mean size of malignant bone tumors was 81 mm in the present study, and thus smaller in comparison to the previous studies; however, our data indicated that bone sarcoma size >77 mm was significantly associated with metastasis (Figure 2B). The size was similar to that of a standard-sized baseball (73-75 mm), and we would therefore suggest that this tumor size to be used as a reference to raise the suspicion of bone sarcoma with potential metastasis and to urge patients to consult an orthopedic oncologist as early as possible. It may be also essential to promote awareness of the general public, through magazine, posters, or online advertisements, about the importance of quickly consulting a doctor when a hard bony mass as large as a standard-sized baseball is observed in a patient presenting with deep skeletal pain (27-29, 34, 35).

The present study has some limitations. First, this was a retrospective study that was performed at a single institution with a relatively small number of cases that included diverse histological types. Second, 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. Third, metastasis was mostly confirmed by imaging modalities alone; not all lesions were subjected to a histological examination. Fourth, the treatment methods were not included in the analysis of prognostic factors, because the treatment strategies differed according to the histological type.

In conclusion, a delay in referral to a specialized hospital by a general practitioner was significant prognostic factors for metastasis in patients with malignant bone tumors. The knowledge of the importance of early, within a month, referral to a specialized hospital when a general practitioner encounters a patient with a bone tumor with a size similar or larger than a standard baseball (>77 mm), might be essential for preventing metastasis in patients with malignant bone tumors.

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 specimens. 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.

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