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Challenges in the Diagnosis of bone Metastasis in Patients without a History of Malignancy at Their First Clinic Visit

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Background: Many patients with bone metastases whose diagnoses came only after they had suffered aggravated conditions are still frequently encountered. However, there have been few studies regarding the early diagnosis of such metastases. We retrospectively reviewed the clinical courses of cases we experienced between 2004 and 2014 to clarify the practical situation of diagnosis of such bone metastases.
Methods: We undertook a retrospective review of 56 of our patients with bone metastasis who had no history of malignancy at their first visit, who visited our departments between 2004 and 2014. The initial diagnoses at the first visit to any clinic, the period from the first visit to any clinic to diagnosis of bone metastasis, the process to make the diagnosis, the frequency of severe skeletal-related events at diagnosis, and the examination serving as the basis for diagnosis were evaluated.
Results: The diagnosis of bone metastasis was made at the first visit in only 6 of the 56 patients. Pathological fractures, paralysis and/or calcemia were seen in 62.5% of the patients at diagnosis of bone metastasis. The median period from the first visit to any clinic to diagnosis was 7.0 weeks. Typically, the diagnosis of bone metastasis was made only after aggravation. The most frequent examination to serve as the basis of diagnosis was magnetic resonance imaging.
Conclusions: Diagnosis of bone metastasis is challenging in patients without a history of malignancy at their first visit. For early diagnosis, it is important to recognize this challenge and to keep it in mind together with ongoing observation. (J Nippon Med Sch 2018; 85: 271–278)

Key words: diagnosis, challenge, bone metastasis, clinic, MRI

Introduction

The incidence of cancer worldwide increased by 33% between 2005 and 2015, with population aging as the major contributing factor[1]. In Japan, with one of the world's most advanced aging populations, the incidence of cancer is steadily increasing and is about to reach 1 million per year[2]. The presence or absence of bone metastasis is indispensable information for accurate staging and appropriate treatment of the primary malignancy. In addition, when progressing, bone metastasis causes various skeletal-related events, leading to significant losses both in clinical outcomes and costs[3]. Recently, treatments of bone metastasis have been changing dramatically with the development of molecular targeting drugs and bone modifying agents[4]. Still, we encounter many patients whose diagnoses of bone metastases come only after they suffer aggravated conditions after long treatment under other diagnoses. Early diagnosis of bone metastasis is essential to prevent such aggravated conditions.

Patients under treatment or observation for known cancer are routinely evaluated with bone scintigraphy, computed tomography (CT), or blood examination for bone metastasis. On the other hand, patients with bone metastasis without any history of malignancy must be distinguished from among many elderly patients with other common orthopedic diseases. The incidence of bone metastasis from unknown malignancy may be as high as 30%[5], but there have been few studies regarding

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the early diagnosis of such bone metastasis so far. It has not yet been clarified whether is it possible to make a diagnosis of bone metastasis in patients without a history of malignancy at the first visit to a clinic, or if not, how long it may take to make the diagnosis, nor what specific factors are important for making the diagnosis. To clarify these questions, we retrospectively reviewed the clinical courses of our cases regarding diagnosis at the first visit, diagnostic process, and skeletal-related events at diagnosis.

Materials and Methods

This study was approved by our institutional review boards and was conducted in accordance with the Declaration of Helsinki. A retrospective review of patients with bone metastasis without a history of malignancy at their first visit to any clinic was undertaken using medical records and images kept at our hospitals. These patients all visited one of our university hospital departments between January 2004 and December 2014. Patients for whom sufficient information for review was unavailable and/or whose bone metastases were found after a routine health check-up were excluded.

Evaluated clinical findings were age at the first visit, sex, type of primary cancer, symptoms at the first visit, location of bone metastasis, department first visited, diagnosis at the first visit, presence of pathological fractures, paralysis, and/or calcemia (FPC) at diagnosis of bone metastasis, period from onset of symptoms to the first visit (POV), period from the first visit to high suspicion of bone metastasis (PVS), period from the first visit to diagnosis of bone metastasis (PVD), period from the first visit to recognition of FPC (PVFPC), and period from onset of symptoms to recognition of FPC (POFPC). The process to make a diagnosis of bone metastasis and examination to serve as the basis of suspicion or diagnosis of bone metastasis were also evaluated.

The first visit was defined as the first visit to any clinic with symptoms which were found to be due to bone metastasis in this study. The location of bone metastasis is frequently multiple; the location in this study was defined as that of the bone metastasis most related to the main symptoms at the first visit. The department at the first visit was classified as orthopedics and others. The diagnosis at the first visit was classified as "bone metastasis or bone metastasis highly suspected" and others; furthermore, the others were classified into some specific diagnostic categories such as degenerative spine disease, trauma, and inflammation. "Bone metastasis highly suspected" was defined as a diagnosis where a practitioner made planning of further examinations for bone metastasis.

Regarding severe skeletal-related events of bone metastasis, because the materials available to us were limited only to medical records and images at our hospitals, only FPC was evaluated to eliminate ambiguity. In addition, to eliminate ambiguity, the definition of a pathological fracture did not include impending fractures in this study. Paralysis was defined as motor disturbance or bladder and/or bowel disturbance caused by a disorder of the spinal cord, cauda equina, or nerve root, and not simple sensory disturbance, in this study, because simple sensory disturbance was thought to be difficult to be distinguished from referred pain or numbness from the affected site in some cases in this retrospective review.

Regarding the period, the day of diagnosis of bone metastasis was defined as the day of the description of having made a diagnosis of bone metastasis or, if not, the day of starting on the next stage such as treatment based on the diagnosis of bone metastasis. Regarding recognition of FPC, recognition of pathological fractures was defined as a practitioner's confirming of a pathological fracture using image examination, because it is difficult to determine the actual timing of a pathological fracture occurrence. Recognition of paralysis and calcemia were defined as a practitioner's confirming these through physical examination and laboratory data.

The process to make a diagnosis of bone metastasis was classified into 4 groups based on a diagnosis at the first visit and an event which led to the actual diagnosis of bone metastasis: Group A, bone metastasis diagnosed or highly suspected at the first visit; Group B, bone metastasis diagnosed by chance after additional examinations for other suspected diseases at the first visit; Group C, bone metastasis not diagnosed at the first visit and diagnosed only after subsequent aggravation; and Group D, bone metastasis not diagnosed at the first visit and diagnosed only after the primary tumor was found. Regarding examination to serve as the basis of suspicion or diagnosis of bone metastasis, it was examined whether the doctor who made the examination was the doctor of the first-visited clinic.

Relationships between PVD and the various clinical factors were also evaluated. The clinical factors included age, sex, type of primary cancer, location of bone metastasis, department at the first visit, and POV.

The Mann-Whitney test was used to evaluate statistical significance in relationships between PVD and clinical

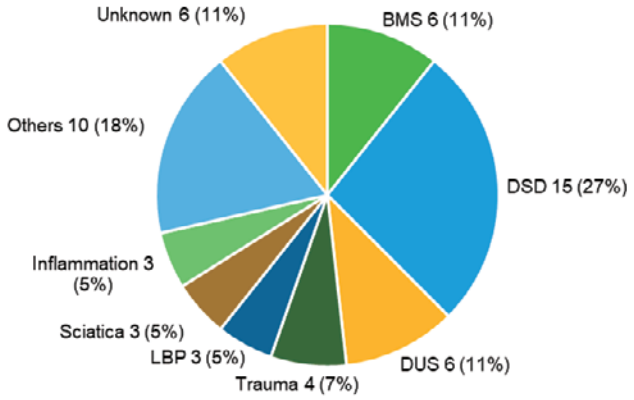

Fig. 1 Diagnoses of bone metastasis from unknown malignancy at the first visit. Number of patients with a diagnosis of "bone metastasis or bone metastasis highly suspected" at the first visit is only 6 of the 56 patients. BMS, bone metastasis or bone metastasis highly suspected; DSD, degenerated spine disease; DUS, diagnosis using symptoms such as "shoulder pain"; LBP, lower back pain.

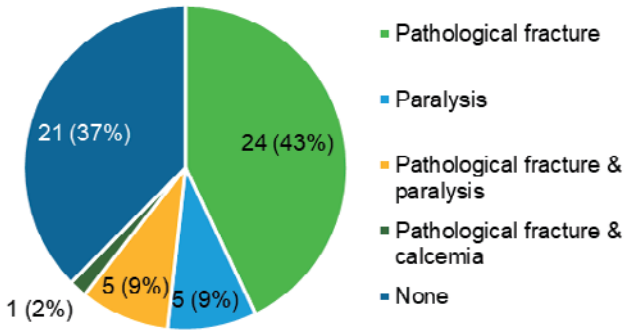

Fig. 2 Severe skeletal-related events up to diagnosis of bone metastasis from unknown malignancy. Severe skeletal-related events such as pathological fractures, paralysis, and calcemia are seen in 35 of the 56 patients (62.5%) at the diagnosis of bone metastasis.

factors. PVDs of the 4 groups of the process to make a diagnosis of bone metastasis were compared using one-way analysis of variance (ANOVA), followed by the Bonferroni test for post-hoc analysis. A two-sided p value of <0.05 was considered significant. All statistical analyses were performed with Excel statistical software package; BellCurve for Excel, ver.2.15, 2017 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

The study population consisted of 34 men and 22 women, with a median age 69 years (range 33–90 years). The types of primary cancers ranged widely: lung cancer in 16 patients, prostate cancer in 9, multiple myeloma in 8, malignant lymphoma in 5, renal cancer in 5, gastrointestinal cancer in 5, others in 3, and unknown in 5. All patients had pain at the first visit except one with only lower extremity discomfort when walking. The location of bone metastasis was mostly the trunk and proximal extremity; lumbar spine in 19 patients, thoracic spine in 9, cervical spine in 5, pelvis in 5, femur in 5, humerus in 5, clavicle in 4, and others in 4. The department at the first visit was orthopedics for 41 patients, including 6 patients at our departments, others for 10 patients, and unknown for 5 patients.

Regarding the diagnosis at the first visit, "bone metastasis or bone metastasis highly suspected" was made in only 6 of the 56 patients (**Fig. 1**). Of the 6 patients with the diagnosis of "bone metastasis or bone metastasis highly suspected" at the first visit, two had a pathological fracture of a long bone, one had a compression fracture of the spine and an impending fracture of a long bone, one had an impending fracture of a long bone, one had osteoblastic change of the spine due to metastasis from the prostate gland, and the other patient had osteolytic change of a long bone due to multiple myeloma. Among other diagnoses, degenerative spine disease was the most frequent (**Fig. 1**).

FPC was seen in 35 of the 56 patients (63.5%) at diagnosis of bone metastasis (**Fig. 2**). Pathological fractures were found in 53.6% of patients.

While the median POV was short (2.0 weeks), and the range was narrow (interquartile range (IQR) 1.0 to 4.0) (n =42), the median PVD was long (7.0 weeks), and the range was wide (IQR 3.0 to 14.3) (n=52) range (**Fig. 3**). Median PVS and POD were 5.5 weeks and 8.0 weeks, respectively. The median value of PVFPC was short (4.0 months), and the range was wide (IQR 0.5 to 9.0) (**Fig. 4**). The median POFPC was 8.0 weeks.

Regarding the process to make a diagnosis of bone metastasis, Group C "bone metastasis not diagnosed at the first visit and diagnosed only after subsequent aggravation" was the most numerous (71%) (**Fig. 5**). Details of aggravation were as follows: pain in 32 patients, pain and paralysis in 8, and paralysis in 1. One-way ANOVA showed a significant difference in PVDs between the groups ($P<0.0043$). Post-hoc analysis showed that Group A (median 0.5 weeks, IQR 0.0–4.25) and Group B (median 2.5 weeks, IQR 0.25–5.5) had a significantly shorter PVD compared to Group D (median 16.0 weeks, IQR 9.5–41.0) (P=0.0059 and 0.019, respectively) (**Fig. 6**).

The most frequent examinations to serve as the basis of suspicion were X-ray (19 patients, 47.5%) and mag-

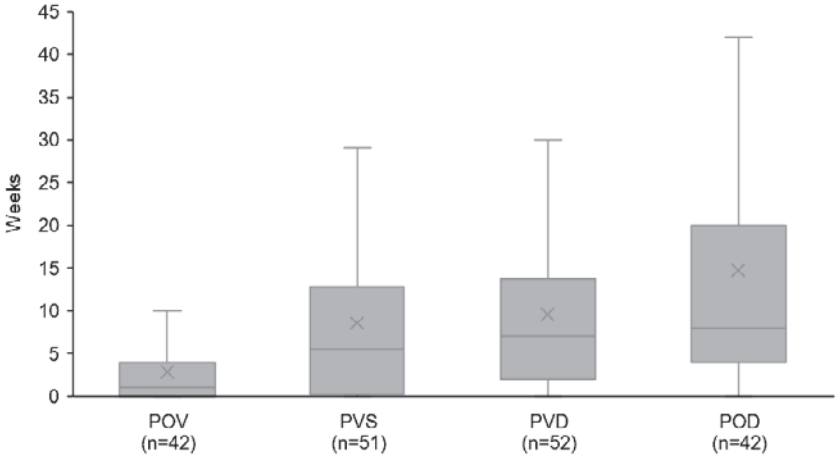

Fig. 3 Periods to diagnosis of bone metastasis. The median period from the first visit to diagnosis is 7.0 weeks. POV, period from onset of symptoms to first visit; PVS, period from first visit to suspicion of bone metastasis; PVD, period from first visit to diagnosis of bone metastasis; POD, period from onset of symptoms to diagnosis of bone metastasis.

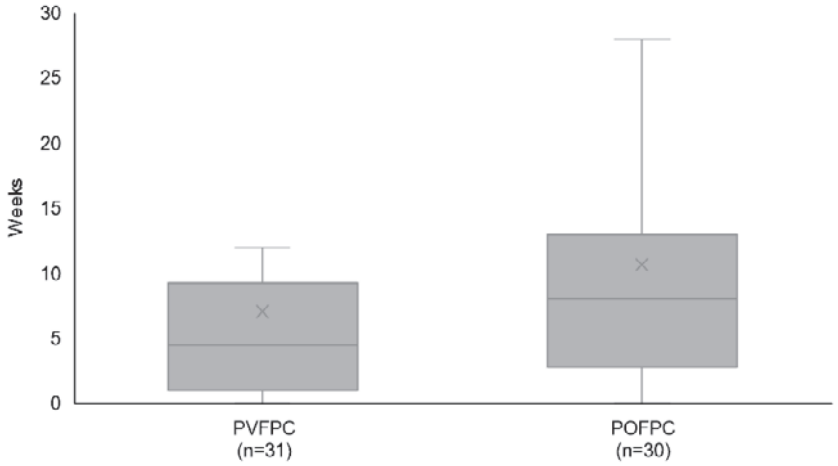

Fig. 4 Periods to occurrence of severe skeletal-related events such as pathological fractures, paralysis, and calcemia (FPC) of bone metastasis. Period from first visit to recognition of FPC is relatively short. PVFPC, period from first visit to recognition of FPC; POFPC, period from onset of symptoms to recognition of FPC.

netic resonance imaging (MRI) (17 patients, 42.5%) (**Fig. 7**). Among these examinations, only 16 cases (40.0%) were made by the first doctor. The most frequent examination to serve as the basis of diagnosis was MRI (26 patients, 63.4%). The number of cases where the first doctor made these examinations was even smaller (12 patients, 29.3%).

The clinical factors including age, sex, type of primary cancer, location of bone metastasis, department at the first visit, and POV did not show a significant association with PVD (**Table 1**).

Discussion

In the present study, we investigated the diagnosis of bone metastasis in patients without a history of malignancy at their first visit. Our study found that such bone metastasis is extremely difficult to detect at the first visit, and making the diagnosis generally takes a relatively long period. There have been few similar reports on initial diagnosis and the period to diagnosis of bone metastasis from unknown malignancy in the English language literature, to the extent we could find. Ichinohe et al. reported a mean period between the onset and diagnosis of 53.3 days, as a result of their study of 110 patients with bone metastasis including 40 with bone metastasis

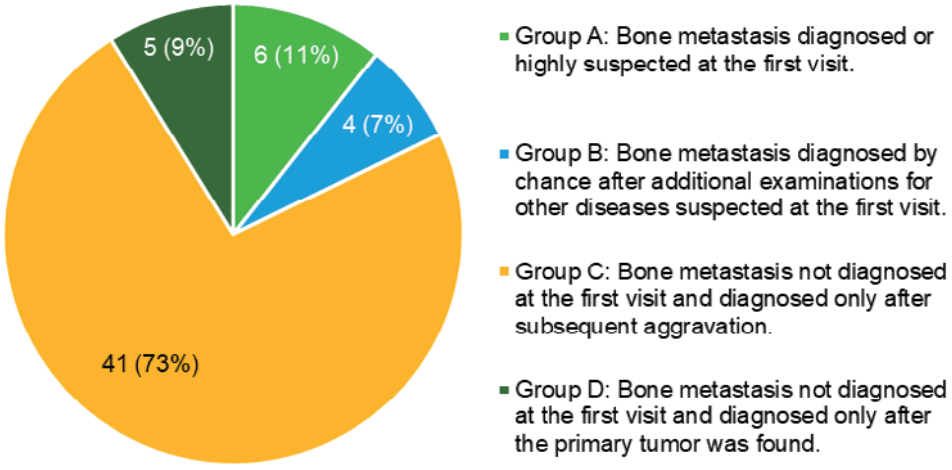

Fig. 5 Process to make a diagnosis of bone metastasis. Process of Group C "bone metastasis not diagnosed at the first visit and only diagnosed after aggravation" is the most frequent.

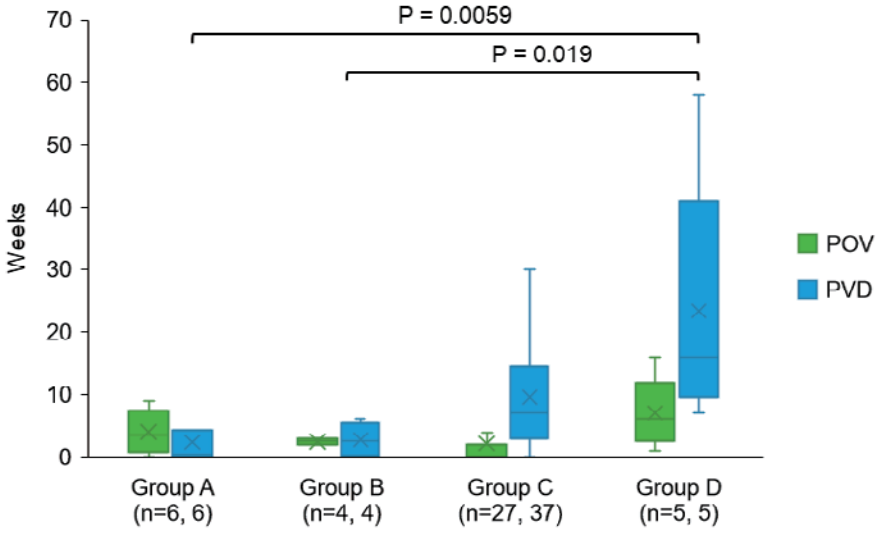

Fig. 6 Period to diagnosis of processes to make a diagnosis of bone metastasis. Median PVD of Group A, B, C, and D is 0.5, 2.5, 7.0 and 16.0, respectively. PVD is significantly shorter for Group A and Group B compared with Group D (P=0.0059 and 0.019, respectively). POV, period from onset of symptoms to the first visit; PVD, period from the first visit to diagnosis; (n=X, Y), (n=POV, PVD).

from unknown malignancy[6].

We also found that FPC was associated with over half of the patients studied at the diagnosis of bone metastasis. Regarding skeletal-related events including spinal cord compression, pathological fractures, radiation to bone, and bone surgery, these have been reported to be present at the diagnosis of bone metastasis in 22.4, 22.4, and 10.0% of patients with breast cancer, lung cancer, and prostate cancer, respectively[7], but these results were not limited only to bone metastasis in patients of unknown malignancy at their first visit.

One of the possible causes of difficulty in the diagnosis of bone metastasis in patients without a history of malignancy at their first visit is its commonality with age and similar manifestation to other common orthopedic degenerative diseases. A typical early manifestation of bone metastasis is pain, which is usually insidious in onset and gradually increases in intensity over weeks or months in the spinal column or proximal limb girdle[8]. Degenerative spine disease was common as the initial diagnosis rather than bone metastasis in the present study, as well.

Another possible cause of difficulty in the diagnosis of bone metastasis from unknown malignancy is the low

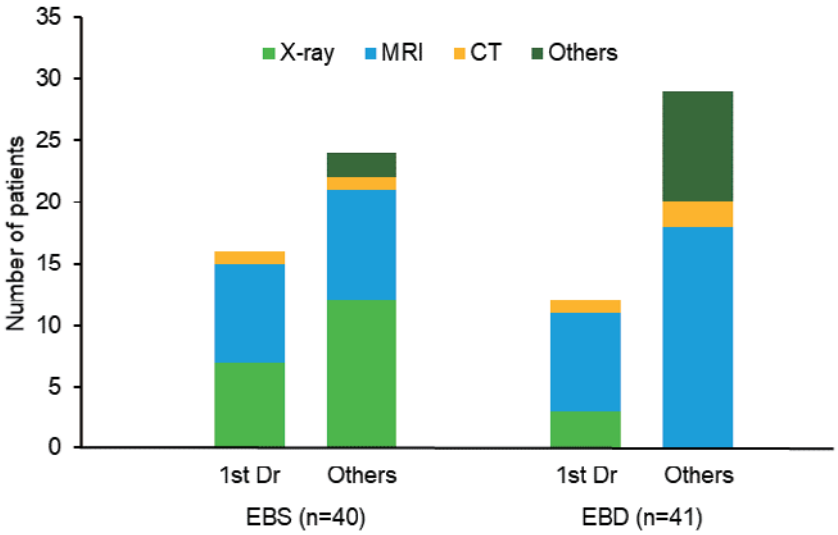

Fig. 7 Performed examinations to serve as the basis of suspicion and diagnosis of bone metastasis. The most frequent examinations to serve as the basis of suspicion are X-ray (19 patients, 47.5%) and magnetic resonance imaging (MRI) (17 patients, 42.5%). The most frequent examination to serve as the basis of diagnosis is MRI (26 patients, 63.4%). Examinations to serve as the basis of suspicion or diagnosis of bone metastasis are often performed by doctors other than the doctors at the first-visited clinic (60.0% and 70.7%). EBS, examination to serve as the basis of suspicion of bone metastasis; EBD, examination to serve as the basis of diagnosis of bone metastasis.

Table 1 Relationships between PVD and clinical factors.

Clinical factor		Mean PVD (IQR)	P-value
Age (n=52)	≤ 69 (n=27)	9.6 (3.5–10.0)	0.78
	≥ 70 (n=25)	11.0 (2.0–16.0)	
Sex (n=52)	Male (n=32)	10.0 (1.8–11.3)	0.24
	Female (n=20)	10.8 (4.0–14.0)	
Location of bone metastasis (n=52)	Trunk (n=41)	9.5 (4.0–14.0)	0.80
	Extremity (n=11)	13.3 (1.0–17.0)	
Department at first visit (n=51)	Orthopedics (n=42)	9.0 (3.3–11.8)	0.15
	Others (n=9)	17.3 (7.0–20.0)	
POV (n=42)	≤ 2w (n=23)	7.9 (2.0–8.0)	0.21
	≥ 3w (n=19)	13.2 (3.5–16.0)	

PVD, period from first visit to diagnosis of bone metastasis; IQR, interquartile range; POV, period from onset of symptoms to first visit.

sensitivity of plain radiography for bone metastasis. Negative findings of plain radiography do not always mean free-of-bone metastasis[9]. To detect apparent lytic findings of bone metastasis on plain radiographs, trabecular bone needs to be destroyed by more than half[10]. A recent study showed that each imaging modality's sensitivity and specificity for bone metastasis were respectively, 33.0% and 96.1%, for plain radiography, 75.6% and 89.2% for CT, 90.5% and 81.1% for MRI, 74.1% and 62.5% for bone scintigraphy, and 92.3% and 63.2% for positron-emission tomography (PET)/CT[11].

In Japan, no official system of general practitioners has yet been established, and thus most patients with pain in extremities or the spinal column directly visit an orthopedic practitioner in an independent clinic or a hospital-based clinic[12]. These orthopedic practitioners usually perform a plain X-ray examination at the first visit. After the first visit, some patients continue to regularly visit the same clinic for conservative treatments such as medication, physical therapy, or nerve blocks. When bone metastasis is suspected, however, the patient is usually referred to a regional core hospital.

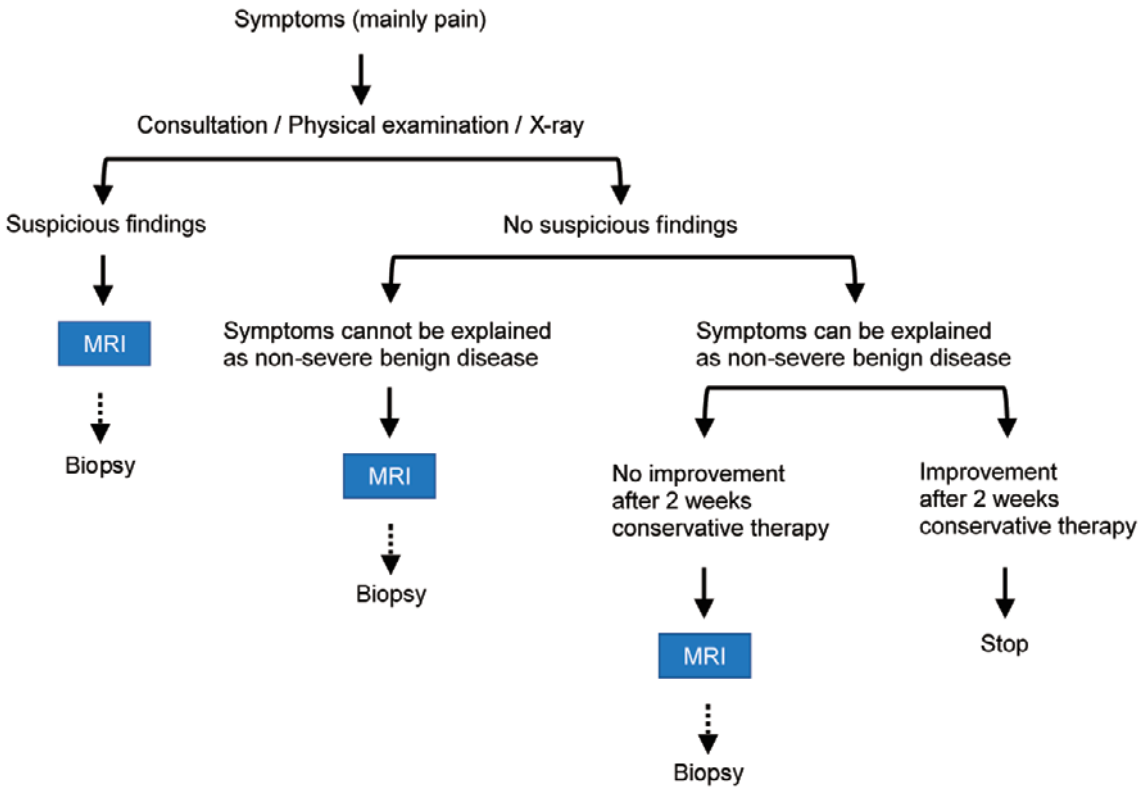

Fig. 8 Diagnostic algorithm for bone metastasis from unknown origin. MRI, magnetic resonance imaging.

Our study showed that MRI is the most frequent examination to serve as the basis of the diagnosis of bone metastasis from unknown malignancy. When plain radiography does not reveal apparent findings for symptoms, but a practitioner suspects severe common orthopedic degenerative disease or bone metastasis based on other clinical factors, MRI would be the next investigation modality in many instances because of its high sensitivity, broad utility, and availability. MRI has a high diagnostic ability not only for bone metastasis, but also for common orthopedic degenerative diseases such as osteoporotic occult fractures, osteonecrosis, and spinal canal stenosis. MRI is also widely available in Japan: the number of MRI units was 51.7 per million inhabitants in 2014 in Japan, which was the largest in the world[13].

So, what do we need for the early diagnosis of bone metastasis in patients without a history of malignancy at their first visit?

Figure 8 presents a diagnostic algorithm for bone metastases based on the findings of this study. If symptoms worsen even after conservative therapy for benign disease, additional examinations are considered to be required. Additional examinations should be considered from about 2 weeks after the first visit in order to prevent associated severe skeletal-related events. The first necessary additional examination is MRI in most cases, which becomes the main diagnostic tool. However, if MRI cannot be used for any reason, CT and others will be substituted. It is understood that this algorithm may be limited only to ideal geographical areas with the availability of MRI and conditions such as a national health insurance system to cover costs.

Furthermore, a part of the algorithm, "no improvement after 2 weeks conservative therapy," is a very subjective clinical factor, and one which is to be determined by the practitioner. Basically, in order to diagnose bone metastasis early, it is necessary to be aware of the challenges for early diagnosis and carefully take note of the transition of pain. It is difficult to diagnose bone metastasis at any stage in the absence of skeletal-related events, but it is important to diagnose it as much as possible before such events become severe. We must seriously face the important facts revealed in this research and take measures through educational activities to alert orthopedic practitioners and the medical community in general.

The present study had some limitations. First, this study was a retrospective observational study which had no control group. The aim of this study was to describe the current situation of the clinical diagnosis of bone metastasis in patients without a history of malignancy at their first visit in clinical practice. Second, our retrospective study was performed using only medical records

and images kept at our hospitals, and lacking those from other first-visited clinics. The medical records and images from the first-visit clinics might have provided more detailed and useful clinical information. Third, the unique primary care system of Japan may have influenced the results, thus the results might not apply to other countries with officially established general practitioner systems. Despite these limitations, notable strengths deserve mention. To our knowledge, this is the first study to investigate the early diagnosis of bone metastasis in patients without a history of malignancy at their first visit and which could reveal concrete challenges in such diagnosis. We believe that our results can contribute to the improvement of the early diagnosis of bone metastasis in patients without a history of malignancy at their first visit.

In conclusion, the diagnosis of bone metastasis is challenging in patients without a history of malignancy at their first visit. For early diagnosis, it is important to recognize this challenge and to keep it in mind together with ongoing observation.

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