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Diagnosis of Bone Metastasis in Patients Without a History of Cancer

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Background: Diagnosing bone metastasis in patients without a history of cancer remains challenging. Diagnostic evaluation may be prolonged owing to difficulties in distinguishing between bone metastasis and common orthopedic diseases. We hypothesized that bone metastasis due to occult cancer would be more difficult to diagnose than bone metastasis in patients with a history of cancer. Few studies exist on the difficulty of diagnosing bone metastasis in patients without a history of cancer. Therefore, we reviewed the clinical course of patients with bone metastasis between January 2011 and December 2014.

Methods: We reviewed patients with bone metastasis to determine the diagnostic rate at first visit, period from symptom-onset to first visit, period from first visit to diagnosis, and presence of severe skeletal-related events at diagnosis, and compared these between 27 patients without a history of cancer (Group A) and 54 patients with a history of cancer (Group B).

Results: The diagnostic rate at first visit was significantly lower (11.5% vs. 52.4%, p=0.00069), the period from first visit to diagnosis was significantly longer (median, 7 weeks vs. 3 weeks, p=0.018), and the presence of severe skeletal-related events at diagnosis was significantly higher (81.4% vs. 50.0%, p=0.05) in patients without a history of cancer compared with those with a history of cancer.

Conclusions: The results of this study indicate that it is difficult to diagnose bone metastasis in patients without a history of cancer. This must be considered in the early diagnosis of bone metastasis to prevent severe skeletal-related events. (J Nippon Med Sch 2019; 86: 22–26)

Key words: bone metastasis, clinic, delay, diagnosis, history

Introduction

Treatment of bone metastasis has dramatically changed with the development of molecular-targeting drugs and bone-modifying agents[1]. Nevertheless, we still experience difficulties in diagnosing bone metastasis in patients without a history of cancer. These patients account for 25 to 30% of all cases of bone metastasis[2]. The diagnostic evaluation may be prolonged owing to the difficulty in distinguishing between bone metastasis and common orthopedic diseases[3,4].

Few studies have examined the difficulty of diagnosing bone metastasis in patients without a history of cancer, as well as the time to diagnosis and the adverse effects of a delay in diagnosis. Therefore, we retrospectively reviewed the clinical course of bone metastasis by comparing patients with and without a history of cancer. The hypothesis of this research was that making a diagnosis of bone metastasis in patients without a history of cancer would be more difficult than in patients with a history of cancer.

Materials and Methods

This retrospective study was approved by our institutional review board and was conducted in accordance with the Declaration of Helsinki. A retrospective review of consecutive patients with bone metastasis, including hematopoietic malignancies, was undertaken using medical records and images kept at our hospital for data on the diagnosis of first bone metastasis. This study was conducted at the orthopedic department of a single university hospital.

Patients

We retrospectively reviewed our institutional database by searching for all outpatients and inpatients with bone

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metastasis who visited our department for symptoms due to first bone metastasis between January 2011 and December 2014. Patients were classified as those with or without a history of cancer. Patients excluded from this study were: those diagnosed by staging or routine complete check-up after diagnosis of primary cancer without a previous visit to any clinic for bone metastasis; those diagnosed via routine health check-up without a previous visit to any clinic for bone metastasis; those who developed bone metastasis from sarcoma previously managed by our department; and those with insufficient information for review.

Methods

We evaluated the diagnostic rate at first visit, the period from onset of symptoms to first visit, the period from first visit to diagnosis of bone metastasis, and the presence of severe skeletal-related events, including pathological fracture, paralysis, and/or hypercalcemia at diagnosis of bone metastasis, and compared these between the two groups. The first visit was defined as the first visit to any clinic with symptoms of bone metastasis in this study. The initial diagnosis at first visit was classified as "bone metastasis or bone metastasis highly suspected," and others. "Bone metastasis highly suspected" was diagnosed when a practitioner planned further examination based on suspicion of bone metastasis. The diagnostic rate at the first visit was defined as the number of patients with "bone metastasis or bone metastasis highly suspected" divided by the total number of patients in each group. The day of diagnosis of bone metastasis was defined as the day of either having made a diagnosis or the day of treatment initiation. Evaluation of severe skeletal-related events of bone metastasis only included pathological fracture, paralysis, and hypercalcemia to eliminate ambiguity, because the materials available were limited to medical records and images at our hospital. In addition, impending fracture was not included in the definition of pathological fracture in this study to eliminate ambiguity. Paralysis was defined as motor disturbance or bladder or bowel disturbance caused by a disorder of the spinal cord, cauda equina, or nerve root, and not simple sensory disturbance, because the latter was thought to be difficult to distinguish from referred pain or numbness from the affected site in some cases in this retrospective review. Bone metastasis frequently occurs in multiple locations; thus, the location of bone metastasis in this study was defined as that most related to the main symptoms at first visit. The department at first visit was classified as orthopedics or others. Patients were classified into Group A, those without a history of cancer, and Group B, those with a history of cancer.

Statistical Analysis

Continuous data were analyzed using the Mann-Whitney test, and data grouped into distinct categories were analyzed with the chi-square test. A two-sided p-value of <0.05 was considered significant.

Results

A total of 129 patients visited our department for bone metastasis during the study period and were eligible for inclusion in this study. The flowchart outlines the process of grouping (**Fig. 1**). In 32 patients, first bone metastasis was diagnosed by staging or routine whole-body check-up after the diagnosis of a primary cancer. In one patient, first bone metastasis was diagnosed by a routine health check-up. One patient with a sarcoma who visited our hospital before first bone metastasis developed was excluded. Fourteen patients had insufficient information for review. The missing data for the period from onset to first visit was significant due to insufficient description of symptoms in the medical records. The remaining 81 patients were classified into Group A, those without a history of cancer (n=27), and Group B, those with a history of cancer (n=54). Demographic characteristics of the patients in the two groups are shown in **Table 1**.

Table 2 summarizes the results for diagnostic rate at first visit, period from onset to first visit, period from first visit to diagnosis of bone metastasis, and frequency of associated severe skeletal-related events at diagnosis. At the first visit, "bone metastasis" or "bone metastasis highly suspected" was diagnosed in only 3 of 27 Group A patients. These 3 patients had pathological fractures in long bones at first visit. The diagnostic rate was significantly lower in Group A than in Group B. Diagnoses other than bone metastasis at first visit are summarized in **Figure 2**. While there was no significant difference in the period from onset of symptoms to first visit between the two groups, the period from first visit to diagnosis was significantly longer in Group A than in Group B.

Pathological fracture, paralysis, and/or hypercalcemia were seen in 81.4% of patients in Group A at diagnosis of bone metastasis. This was significantly higher than in Group B. **Table 3** summarizes severe skeletal-related events of bone metastasis at diagnosis of bone metastasis in both groups.

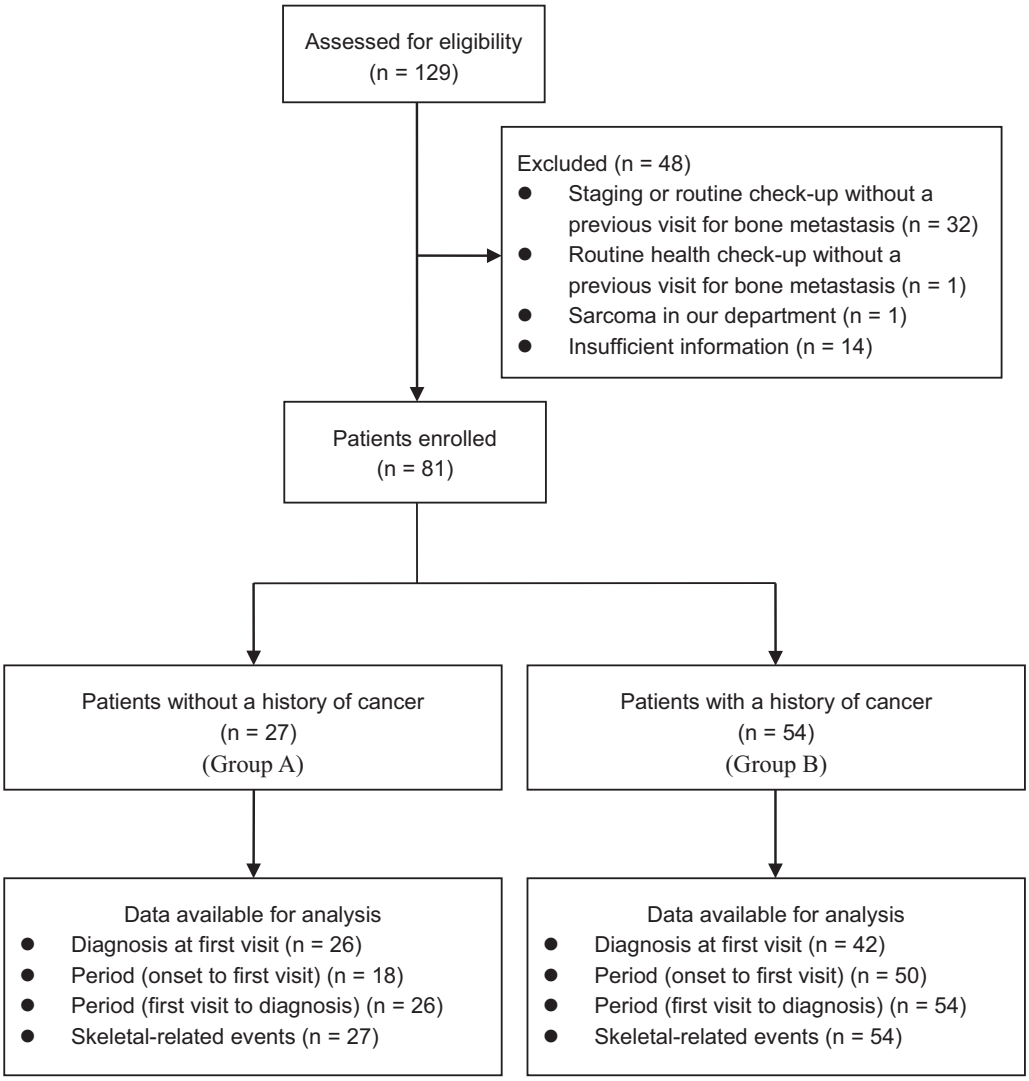

Fig. 1 Flowchart for enrolment.

Table 1 Demographic characteristics

	Patients without a history of cancer (n=27) (Group A)	Patients with a history of cancer (n=54) (Group B)	p
Age at first visit	70.0±10.8[a]	69.9±9.9[a]	0.79[b]
Sex (female/male)	12/15	24/30	1.00[b]
Bone metastasis location (trunk/extremity)	19/8	45/9	0.06[b]
First doctor (orthopedic/others)	19/8	23/20[c]	0.16[b]
Primary cancer	Lung (10), multiple myeloma (5), prostate (4), others (8)	Lung (8), breast (6), colon (6), stomach (6), prostate (5), kidney (5), others (18)	-

a) The values are given as the mean and standard deviation.
b) The p-values were determined with the chi-square test or Mann-Whitney test.
c) n=43

Discussion

The most important finding of this study was that the diagnosis of bone metastasis in patients without a history of cancer is significantly more difficult to make compared with that in patients with a history of cancer, based on evaluation of the diagnostic rate, the time to diagnosis, and the rate of severe skeletal-related events. The first conclusion of this study was that making a diagnosis of

Table 2 Summary of results

	Patients without a history of cancer (Group A)	Patients with a history of cancer (Group B)	p
Diagnostic rate at first visit	11.5% (3/26)	52.4% (22/42)	0.00069[a]
Period from onset to first visit[b]	1 week (1-4) (n=18)	1 week (0-6) (n=50)	0.64[c]
Period from first visit to diagnosis[b]	7 weeks (2-16) (n=26)	3 weeks (1-6) (n=54)	0.018[c]
Skeletal-related events at diagnosis	81.4% (22/27)	50.0% (27/54)	0.005[a]

a) The p-values were determined with the chi-square test.
b) The values are given as the median and interquartile range.
c) The p-values were determined with the Mann-Whitney test.

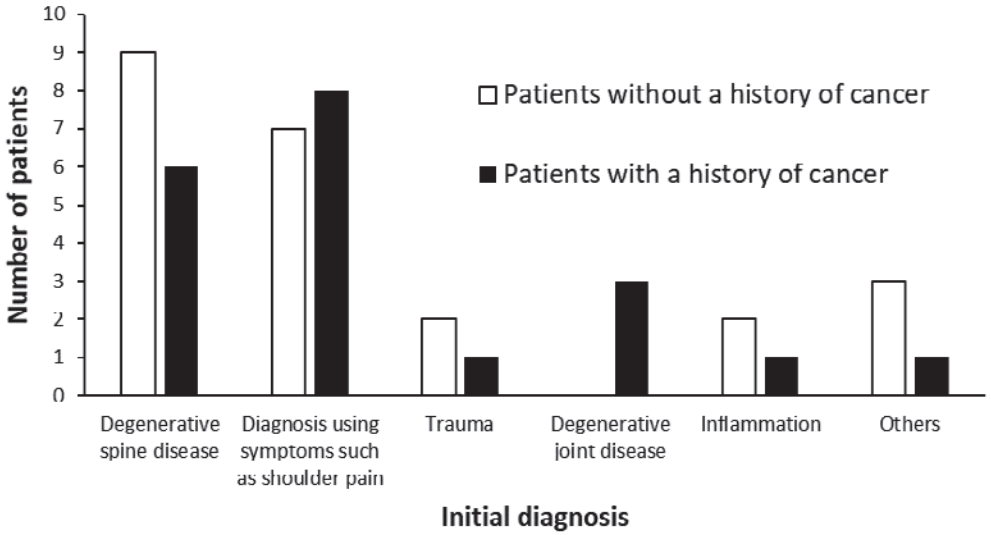

Fig. 2 Diagnoses other than bone metastasis at first visit.

Table 3 Summary of severe complications

Severe complications	Patients without a history of cancer (n=27) (Group A)	Patients with a history of cancer (n=54) (Group B)	p[a]
Pathological fracture	13	21	0.43
Paralysis	4	5	0.45
Pathological fracture and paralysis	4	1	0.02
Pathological fracture and hypercalcemia	1	0	0.16
None	5	27	0.006

a) The p-values were determined with the chi-square test.

bone metastasis in patients without a history of cancer at first visit would be almost impossible without a pathological fracture of a long bone or other findings. Second, the median period from first visit to diagnosis of bone metastasis ranged from 2–4 months or more. Third, up to 80% of patients may have severe skeletal-related events at the diagnosis of bone metastasis.

Few similar reports on initial diagnosis and time to diagnosis of bone metastasis due to occult malignancy have appeared in the searchable English language literature. One study on patients presenting with low back pain at a walk-in clinic of a public hospital reported that 9 patients without a history of cancer at the index visit had occult malignancy as the cause, and the average diagnostic delay in these 9 patients was 51 days, with a delay of about 3 months in 3 cases[5].

Skeletal-related events are reportedly present at diagnosis of bone metastasis in 22.4%, 22.4%, and 10.0% of patients with breast, lung, and prostate cancer, respectively[6]. Those ratios are much lower than those we expe-

rienced in patients with a history of cancer in the present study (50.0%). This may reflect sampling bias, as the present study was limited to patients who visited orthopedic departments. The high rate of association suggests that severe skeletal-related events may be the main indicator of bone metastasis in patients without a history of cancer.

Diagnosis of bone metastasis due to occult malignancy is thought to be difficult to make due to the similar age of onset and early symptoms in common with orthopedic degenerative disease, and the generally low frequency of bone metastasis compared to that of other common diseases. The prevalence of occult malignancy in patients with low back pain who visit walk-in hospital clinics is as low as 0.4–0.7%[7].

To differentiate bone metastasis due to occult malignancy from common orthopedic degenerative disease, it may be useful to refer to clinical guidelines for management of low back pain[8]. Clinical findings include major red flags for malignancy: previous history of cancer, age 50 years or over, failure to improve with conservative therapy, unexplained weight loss, and insidious onset[9]. However, only a previous history of cancer has a high positive likelihood ratio (15.8 to 31.7) and other factors have a low positive likelihood ratio (1.9 to 3.2)[7].

The present study had some limitations. First, this was a retrospective observational study. The aim was to identify features associated with early clinical diagnosis of bone metastasis due to occult malignancy in actual clinical practice. Second, our retrospective study was performed using medical records and images at our hospitals and lacked those from predecessor clinics. The medical records and images from predecessor clinics might have provided more detailed clinical information. Third, the study was based on a single hospital assessment of 81 patients. Despite these limitations, notable strengths deserve to be mentioned. To our knowledge, this is the first study to investigate the early diagnosis of bone metastasis due to occult malignancy at the first visit by comparing these patients with controls. Moreover, this study revealed factors associated with difficulty in making a diagnosis.

The results of the present study indicate that it is very difficult to diagnose bone metastasis in patients without a history of cancer. Accordingly, this must be considered in the early diagnosis of bone metastasis to prevent skeletal-related events. It is important to pay attention to the possibility that bone metastases may be present in follow-up observation even if there have been no findings that led to the diagnosis of bone metastasis at first visit. According to the progress of symptoms, it may be necessary to perform additional examinations such as re-examination of plain radiography or other imaging at an early stage before occurrence of any severe skeletal-related events. We believe that our results can contribute to the improvement of the early diagnosis of bone metastasis due to occult malignancy.

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