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Symptoms Related to Moderate Skeletal-Related Events as Clues for the Diagnosis of Bone Metastasis

Yasuyuki Kitagawa, Toshihiko Ito, Yoshihiro Mizuno, Yoshihiro Sudo, Yong Kim, Ryu Tsunoda and Shinro Takai

Department of Orthopaedic Surgery, Nippon Medical School, Tokyo, Japan

Background: Early diagnosis of bone metastasis is difficult. The aim of the present study was to determine whether symptoms related to skeletal-related events (SREs) can be used for the diagnosis of bone metastasis in the absence of screening tests.

Methods: We reviewed 81 patients with bone metastasis to evaluate their SREs at diagnosis. SREs were arbitrarily classified as moderate or severe. Moderate SREs included radiation to the bone before pathological fracture or paralysis, bone surgery before pathological fracture or paralysis, and hypercalcemia without dialysis. Severe SREs included pathological fracture, spinal cord compression, and hypercalcemia necessitating dialysis.

Results: The complication rates of SREs at the time the bone metastasis was diagnosed were 59.3% and 24.7% for severe and moderate SREs, respectively, and only 16.0% of cases were uncomplicated. The clinical factors that showed a significant relationship with the severity of SREs were age and history of malignancy. However, there was no significant relationship between the complication rate of total SREs and the presence or absence of a malignancy history (83.3% vs. 85.2%, respectively, p=0.83).

Conclusion: The results of the present study suggest that symptoms related to SREs can be used to diagnose bone metastasis in the absence of a screening test. Bone metastasis should be diagnosed as often as possible based on symptoms related to moderate SREs and should be treated as soon as possible before patients develop severe SREs. (J Nippon Med Sch 2019; 86: 159–164)

Key words: skeletal-related events, diagnosis, bone metastasis, pathological fracture, spinal cord compression

Introduction

The progression of bone metastasis causes various complications that reduce patients' abilities to perform activities of daily living and shorten their lifespans[1]. When a patient with malignancy develops bone metastasis, early diagnosis and treatment of the bone metastasis are essential to minimize negative effects on the patient. However, we have reported that early diagnosis of bone metastasis is difficult, and many patients experience complications with severe skeletal-related events (SREs) at the time of diagnosis if screening tests have not been performed[2,3]. This raises the question whether symptoms related to SREs may be the key to diagnose bone metastasis in the absence of screening tests.

Our previous study only evaluated patients with severe SREs (fracture, paralysis, and hypercalcemia), and those with milder SREs were excluded from the evaluation[3]. In the present study, we examined all variations of SREs, which were the primary complaint at the time that bone metastasis was diagnosed. For this, we applied the common definitions of SREs adopted in much of the literature[4,5], not limited to severe SREs, and reviewed the clinical courses of our patients with bone metastasis between 2011 and 2014 using the medical records and images kept at our hospital. The objective of the present study was to determine whether symptoms related to

Correspondence to Yasuyuki Kitagawa, MD, Department of Orthopaedic Surgery, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: kitayasu@nms.ac.jp
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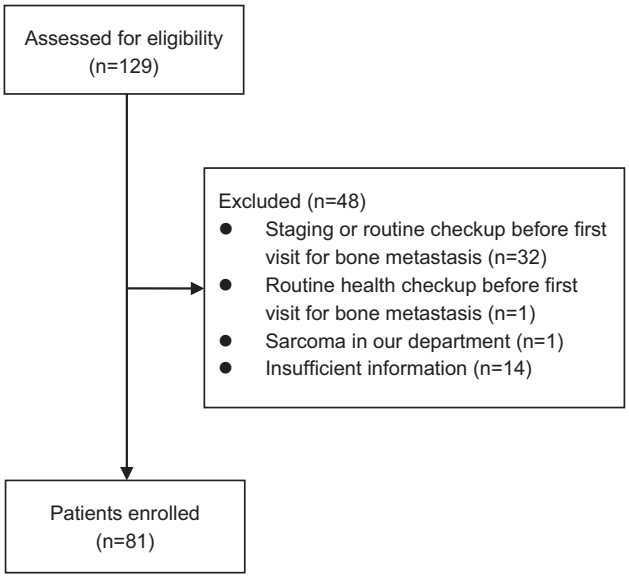

Fig. 1 Flowchart for enrollment.

SREs can be used in the diagnosis of bone metastasis in the absence of a screening test. Such a finding may alter the current methods of diagnosing bone metastasis.

Materials and Methods

This retrospective study was approved by our institutional review board and was conducted in accordance with the Declaration of Helsinki. We followed the retrospective observational research information disclosure procedure (opt-out) of Nippon Medical School to obtain informed consent from the research participants. A retrospective review of consecutive patients with bone metastasis, including hematopoietic malignancies, was undertaken using the medical records and images kept at our hospital regarding the first diagnosis of bone metastasis. This study was conducted at the orthopedics department of a single university hospital.

We conducted a retrospective review of our institutional database to identify all patients with bone metastasis, both outpatients and inpatients, who visited our department for symptoms due to their first bone metastasis between January 2011 and December 2014. We excluded patients diagnosed by staging or routine whole-body checkup after diagnosis of a primary cancer without a previous visit to any clinic for bone metastasis, those diagnosed during a routine health checkup without a previous visit to any clinic for bone metastasis, those who developed bone metastasis from sarcoma and had originally visited our department, and patients for whom sufficient information for review was unavailable.

A total of 129 patients visited our department because of bone metastasis during the study period and were eligible for inclusion in this study. A flowchart outlines the process of patient enrollment (**Fig. 1**). In 32 patients, the first bone metastasis was diagnosed by staging or during a routine whole-body checkup after the diagnosis of a primary cancer without a previous visit to any clinic for bone metastasis. In one patient, the first bone metastasis was diagnosed during a routine health checkup without a previous visit to any clinic for bone metastasis. One patient with sarcoma who was visiting our hospital before the first bone metastasis developed was excluded. Fourteen patients had insufficient information for review. The remaining 81 patients were assessed. The demographic characteristics of the patients are shown in **Table 1**. More than half of the patients with moderate SREs started to use opioids around the time of diagnosis. A second SRE within 3 months after diagnosis occurred in one-quarter of all patients.

We evaluated the SREs at diagnosis, any second SRE within 3 months after the diagnosis, the initiation of opioids within a period 2 weeks before or after diagnosis, hypercalcemia at diagnosis, dialysis due to renal failure after hypercalcemia, and the survival period after the diagnosis of bone metastasis. SREs were arbitrarily classified as moderate or severe. Moderate SREs included radiation to the bone before the occurrence of pathological fracture or paralysis, bone surgery before the occurrence of pathological fracture or paralysis, and hypercalcemia without dialysis. Severe SREs included pathological fractures, spinal cord compression, and hypercalcemia followed by dialysis. We also evaluated several clinical factors including age, sex, primary cancer, location, and the presence or absence of a history of malignancy. The primary cancer was classified into three groups, according to the report by Katagiri et al.[6]: rapid-, moderate-, and slow-growth cancers. The rapid-growth group included lung cancer without molecularly targeted drugs, colorectal cancer, gastric cancer, pancreatic cancer, head and neck cancer, esophageal cancer, other urological cancers, melanoma, hepatocellular carcinoma, gall bladder cancer, cervical cancer, and cancers of unknown origin. The moderate-growth group included lung cancer treated with molecularly targeted drugs, hormone-independent breast and prostate cancer, renal cell carcinoma, endometrial and ovarian cancer, sarcoma, and others. The slow-growth group included hormone-dependent breast and prostate cancer, thyroid cancer, multiple myeloma, and malignant lymphoma. The location was classified as spine or other.

Table 1 Demographic data and comparison of clinical factors of patients by severity of skeletal-related events

Clinical factors	Overall (n=81)	Group			*p*
		Severe SREs (n=49)	Moderate SREs (n=19)	None (n=13)	
Median age (years)	70 [62-77]	71 [64-79]	66 [54-72]	66 [62-72]	0.039[a]
Sex					0.59
Male	41 (50.6)	27 (55.1)	8 (42.1)	6 (46.2)	
Female	40 (49.4)	22 (44.9)	11 (57.9)	7 (53.8)	
Primary cancer					0.088
Slow-growth	18 (22.2)	12 (24.5)	1 (5.2)	5 (38.5)	
Moderate-growth	15 (18.5)	10 (20.4)	2 (10.5)	3 (23.1)	
Rapid-growth	48 (59.2)	27 (55.1)	16 (84.2)	5 (38.5)	
Location					0.79
Spine	56 (69.1)	35 (71.4)	13 (68.4)	8 (61.5)	
Others	25 (30.9)	14 (28.6)	6 (31.6)	5 (38.5)	
History of malignancy					0.0077
Yes	54 (66.7)	27 (55.1)	18 (94.7)	9 (69.2)	
No	27 (33.3)	22 (44.9)	1 (5.3)	4 (30.8)	
Opioids					0.20
Newly started	29 (35.8)	17 (34.7)	10 (52.6)	2 (15.4)	
Already used	4 (49.4)	2 (4.1)	2 (10.5)	0 (0.0)	
None	48 (59.3)	30 (61.2)	7 (36.8)	11 (84.6)	
Second SRE					0.072
Yes	20 (24.7)	11 (22.4)	5 (26.3)	4 (30.8)	
No	61 (75.3)	38 (77.6)	14 (73.7)	9 (69.2)	
Mean survival period after bone metastasis (months)	26.8 {19.9-33.8}	30.8 {21.1-40.5}	21.8 {10.2-33.5}	17.5 {9.03-26.0}	0.56

Values are presented as median [interquartile range], n (%), or mean {95% confidence interval}.
SREs, skeletal-related events.
[a]This *P*-value compares the patients' age with moderate and severe SREs.

To eliminate ambiguity, the definition of pathological fracture did not include impending fractures in this study. Spinal cord compression was defined as motor disturbance or bladder and/or bowel disturbance and not simple sensory disturbance, as simple sensory disturbance was difficult to distinguish from referred pain or numbness from the affected site in some cases in this retrospective review. Hypercalcemia was defined as a serum calcium level above 11 mg/dL[5].

Statistical Analysis

The complication rates of moderate and severe SREs were calculated for all patients and were also calculated according to the presence or absence of a history of malignancy. The relationship between the severity of SREs and age was compared using one-way analysis of variance, followed by the Bonferroni test for post hoc analysis. The relationships between the severity of SREs and several clinical factors including sex, primary cancer, location, presence or absence of a history of malignancy, opioid usage, presence or absence of a second SRE, and survival period after bone metastasis were analyzed with the chi-square test. The survival periods after bone metastasis were analyzed with the Kaplan-Meier test. A two-sided p-value <0.05 was considered significant. All statistical analyses were performed with Excel statistical software package; BellCurve for Excel, version 2.15, 2017 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

The number of patients and percentage of SREs by type are shown in **Figure 2**. The complication rates of severe and moderate SREs were 59.3% and 24.7%, respectively, whereas that of non SRE-complicated cases was only 16.0%. Even among uncomplicated patients (13 patients), 4 patients were considered for radiation therapy for bone metastasis, but they did not receive it owing to their very short life expectancy or poor general condition. When these patients were included in the SRE group, the complication rate of SREs at the diagnosis of bone metastasis was 88.9%. Among the other uncomplicated patients,

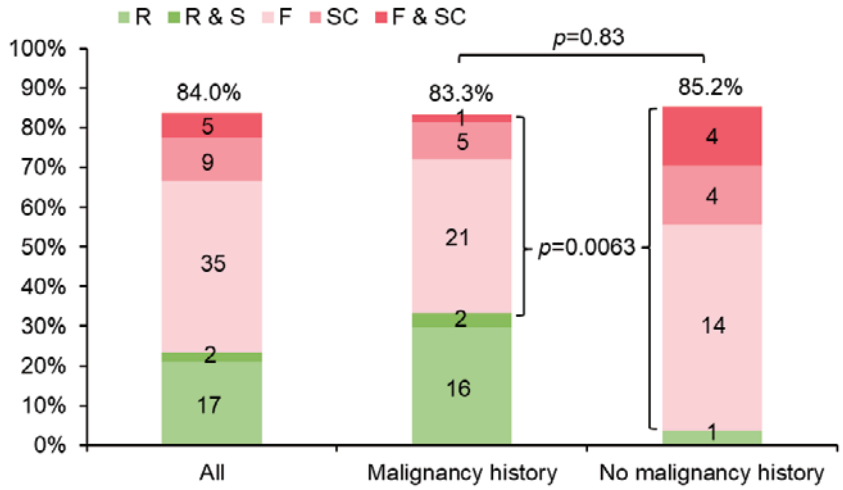

Fig. 2 Number and percentage of skeletal-related events (SREs) by type and presence or absence of a history of malignancy. R, radiation; S, surgery; F, pathological fracture; SC, spinal cord compression.

Table 2 Skeletal-related events in each primary cancer

Primary cancer	Skeletal-related events					
	Severe		Moderate			None
	F	SC	Ca	R	S	
Lung (18)	10	3	1	16	4	0
Gastrointestinal (16)	8	2	0	13	0	1
Prostatic (9)	3	3	0	2	1	4
Hematopoietic (7)	6	1	0	2	2	1
Kidney (7)	4	1	0	3	4	1
Breast (6)	1	1	0	2	2	2
Others (18)	8	3	0	9	1	4

Values are presented as number of patients. F, pathological fracture; SC, spinal cord compression; Ca, hypercalcemia without dialysis; R, radiation; S, surgery.

SREs occurred within 3 months after the diagnosis in 5 patients. Of the remaining 4 patients, 3 had bone metastases from prostate cancer, and pain relief was obtained with conservative treatment such as hormone therapy. The last patient had a bone metastasis to the scapula that did not require aggressive treatment, and the patient died 5 months after diagnosis.

The clinical factors that showed a significant association with the severity of SREs were age and the presence or absence of a history of malignancy (**Table 1**). The breakdown of SREs with and without a history of malignancy is shown in **Figure 2**. Patients without a history of malignancy had a high rate of associated severe SREs. The rate of severe SREs was significantly higher than that in the patients with a history of malignancy (77.8% vs. 50.0%, p=0.0063). However, there was no significant relationship between the association rate of total SREs and the presence or absence of a history of malignancy (83.3% vs. 85.2%, p=0.83). Patients with a history of malignancy received radiotherapy more than those without a history of malignancy. The types of primary cancers for such patients were varied, but the affected bones were usually the spines (13/16 patients).

The SREs for each primary cancer are shown in **Table 2**. The association of SREs at the time of diagnosis of bone metastasis in the absence of screening tests was higher in patients with lung or gastrointestinal cancer. Patients with prostate cancer had a large percentage of SRE-unassociated cases.

Discussion

The most important finding of the present study was that when bone metastasis was first diagnosed without screening tests, 84% to 89% of the patients had some

SREs, which led us to speculate that SRE symptoms could aid in the diagnosis of bone metastasis. There have been some reports on SRE complication rates in various cancers[6,7]. SREs have been reported to be present at the diagnosis of bone metastasis in 22.4%, 22.4%, and 10.0% of breast, lung, and prostate cancers, respectively[7]. However, our research focused on bone metastasis diagnosed without screening tests and, as far as we know, such reports have rarely been documented in the English-language literature[8].

We also found a significant association between the presence or absence of a history of malignancy and the severity of SRE complications at the time of bone metastasis diagnosis. We have previously reported that the diagnosis of bone metastasis was significantly delayed in patients with no history of malignancy compared to that in patients with a history of malignancy[3]. The difficulty in diagnosis appears to be due to the similarity in age and the chronic transition of the symptoms of bone metastasis to manifestations of many general orthopedic diseases, such as degenerative spondylosis. However, we also found no significant difference in the complication rate of total SREs based on the presence or absence of a history of malignancy in the present study, and these complication rates were extremely high. These facts also suggest that symptoms related to SREs are a major factor in the diagnosis of bone metastasis in the absence of screening tests.

Although it would be ideal to diagnose bone metastasis without any SREs, the present study suggests that this is extremely difficult in the absence of screening tests. Therefore, at the moment, it is important to consider symptoms related to SREs as the most important clues in the diagnosis of bone metastasis and to focus on making the diagnosis when the SREs are as mild as possible. This study revealed that more than half the patients diagnosed with moderate SREs had accompanying pain that required opioids. Such pain can be a change in chronic symptoms during the clinical course such as those of degenerative spondylosis. Therefore, we believe that when a patient develops strong pain or mild paralysis, immediate precise examination for bone metastasis and immediate treatment can minimize the effects on the patient.

Hypercalcemia is also an important SRE. Recently, the need for dialysis as a treatment for hypercalcemia due to bone metastasis has decreased with the introduction of bisphosphonate. However, dialysis indications include patients with oliguric renal failure that are difficult to control circulating blood volume with diuretics alone or patients with hypercalcemia who have severe symptoms such as coma despite hydration and bisphosphonate treatment[9].

Regarding the primary site, the association of SREs at the time of diagnosis of bone metastasis in the absence of screening tests was higher in patients with lung or gastrointestinal cancer. There have been no reports on features of SREs at the time of diagnosis of bone metastasis in the absence of screening tests by their primary cancer, to the best of our knowledge. On the results of the study including patients diagnosed by screening tests, SREs were associated with 22.4% of patients with bone metastasis from lung cancer and with 10.0% of those from prostatic cancer SREs at the time of diagnosis of bone metastasis[7]. Even in the subsequent courses, bone metastasis of lung cancer tends to develop SREs earlier from the diagnosis of bone metastasis than that of prostatic cancer[7]. In patients with gastrointestinal cancer, 55% of the patients developed one or more SREs during the course of the disease, which is almost the same frequency as patients with breast, lung, and prostate cancer[7,10].

The present study has some limitations. First, this study was a retrospective observational study. The aim of this study was to describe the SREs of bone metastasis in actual clinical practice. Second, our retrospective study was performed using only the medical records and images kept at our hospital and lacked information on medical records from the first clinics visited by the patient. Those medical records and images might have included more detailed clinical information. Despite these limitations, notable strengths deserve mention. To our knowledge, this is the first study to investigate the frequency of SREs according to severity at the time that bone metastasis was diagnosed without screening tests. We believe that our results shed light on the reality of the diagnosis of bone metastasis and can contribute to earlier diagnosis of bone metastasis.

In conclusion, the results of the present study suggest that SREs are essential in the diagnosis of bone metastasis if screening tests are not used. We must alter our method of diagnosing bone metastasis to rely heavily on symptoms related to moderate SREs. Moderate SREs should be treated as soon as possible before they progress to severe SREs. Future research should focus on diagnosing bone metastasis before SREs occur.

Conflict of Interest: We declare no conflict of interest. No funding was received for this study.

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