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Spinal Metastases without Pedicle Signs on Radiograph and their Associated Clinical and Radiological Features

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Background: The pedicle sign is a radiographic indicator of spinal metastases. However, it is not only the pedicle sign that is important in radiographic diagnosis of bone metastases. In the present study, the radiological features of symptomatic spinal metastases in patients without the pedicle sign were retrospectively examined.

Materials and Methods: Among 186 patients with symptomatic spinal metastases who visited our department between January 1, 2011, and December 31, 2017, 64 without the pedicle sign and with available computed tomography (CT) and magnetic resonance imaging (MRI) data in the first visit were enrolled and their data were analyzed. One author evaluated radiographs for findings suggestive of spinal metastases, CT to assess bone destruction, and MRI to evaluate the extent of lesions. Clinical variables were also examined and compared between patients with and without bone changes on radiography.

Results: Bone changes strongly suggesting bone metastasis, other than the pedicle sign, were observed in 31 out of 64 patients: bone cortical disappearance in 20, increased radiolucency of the central area in the vertebral body in 8, an irregular osteoblastic change in 5, and asymmetrical vertebral collapse in 10. An analysis of CT data revealed that intertrabecular, mildly osteolytic, and mildly osteoblastic types were more frequent in patients without any changes suggestive of bone metastases on radiographs.

Conclusion: Radiographic findings other than the pedicle sign are useful for diagnosing bone metastases. The key to a radiographic diagnosis of spinal metastases is to pay attention to changes in the bone cortex of all vertebral components on radiographs in addition to the pedicle.

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Key words: pedicle sign, spinal metastasis, cortical destruction, intertrabecular, radiographic diagnosis

Introduction

Orthopedic practitioners now have more opportunities to treat patients with bone metastases in Japan because of the aging of its population. This disease may also be treated in the early stage because patients often initially visit orthopedic clinics, not general practitioners, in Japan. However, due to its relative rarity and similar symptoms to orthopedic degenerative diseases[1], the diagnosis of bone metastases often takes a few months. Therefore, bone metastasis diagnostic training for orthopedic practitioners is becoming increasingly important.

Orthopedic practitioners generally take radiographs of patients in their first visit to the clinic. Radiography is inferior to other diagnostic imaging modalities, such as computed tomography (CT), for the screening of bone metastases. Nevertheless, it provides important information that is essential for the diagnosis of symptomatic cases[2].

The pedicle sign is a well-known and valuable radiographic indicator of bone metastases[3,4]. A recent investigation revealed the morphological features of the pedicle sign and reported various morphologies[5]. In the present study, we retrospectively investigated the radiological features of symptomatic spinal metastases in patients

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without the pedicle sign.

Materials and Methods

This retrospective study was approved by the relevant Institutional Review Board (No. 30-01-1071) and was conducted in accordance with the Declaration of Helsinki. Informed consent for the publication of personal medical data was obtained from patients by an opt-out procedure, as described in the study protocol. A retrospective review of consecutive patients with bone metastases, including hematopoietic malignancies, was conducted using medical records and images stored at our hospital. The study was conducted at the Orthopedics department of a single university hospital. The first half of this study has already been reported for patients with a positive pedicle sign[5]. This report is the second half of the study, examined patients with negative pedicle signs.

Patients

Patients included in the present study were those with symptomatic spinal metastasis who visited our department between January 1, 2011 and December 31, 2017. Exclusion criteria were the absence of radiographs, CT or magnetic resonance (MR) images during the period from 2 weeks before to 2 weeks after the first visit, and a history of radiation therapy at the target site.

Disease codes were used to search the hospital records of patients who had visited the Orthopedic department for the treatment of bone metastases. The computerization of medical charts began at the hospital in 2011, and the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision[6] was used to code diagnoses. A total of 923 outpatients and inpatients underwent examinations for bone metastases in the Orthopedic department and had an ICD-10 code of C79.5, which corresponds to secondary malignant neoplasms of the bone and bone marrow.

After meticulously reviewing the medical charts of these patients, data from 288 who visited the Orthopedic department for metastases to the cervical, thoracic, and lumbar spines were extracted; 67 who did not have symptoms related to spinal metastases, 23 with no radiographs 2 weeks before or after the first orthopedic visit, and 12 with a history of radiotherapy at the target site were excluded. Among the remaining 186 patients, 94 with the pedicle sign[5] and 28 who did not undergo CT or MR imaging within 2 weeks before and after the first visit were excluded. Finally, 64 patients were ultimately enrolled in the present study and their data were analyzed (**Fig. 1**).

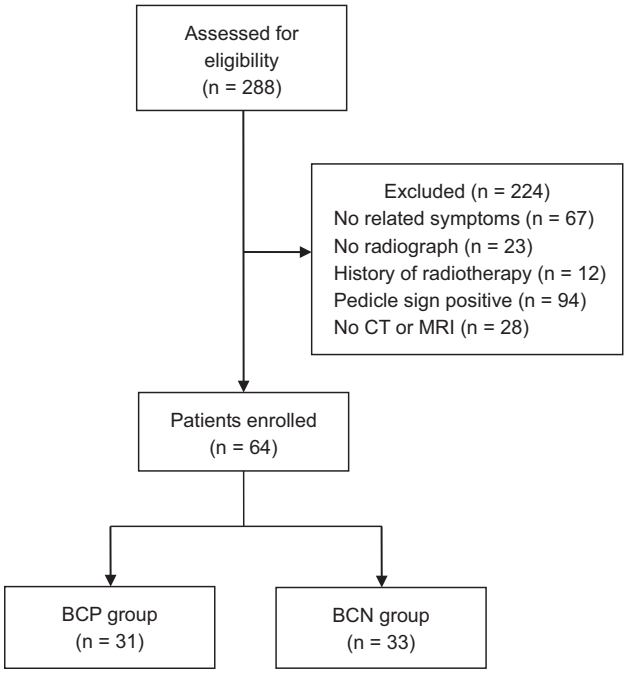

Fig. 1 Flowchart for enrolment.

Study Variables

One author, an orthopedic surgeon with 25 years of bone and soft tissue tumor specialist, evaluated radiographs and CT and MR images. The site evaluated was the vertebra considered to be the primary source of symptoms. Bone changes due to bone metastases other than the pedicle sign were evaluated using anteroposterior and lateral radiographs. When asymmetrical vertebral collapse was observed, bone metastasis was suspected at 5 degrees or more asymmetrical vertebral collapse according to the method of Suzuki et al.[7]. Using CT images, the morphological patterns of bone metastasis were classified into the osteolytic, mildly osteolytic, intertrabecular, mildly osteoblastic, osteoblastic, and mixed types. MRI was used to evaluate tumor occupation within the vertebra (the body, pedicle, and tissues posterior to the pedicle) and extra-skeletal extension.

The following clinical variables were compared between patients with bone changes on radiography (BCP group) and those without (BCN group); age, sex, primary cancer, primary cancer by survival period, the responsible lesion site, visceral or brain metastases, multiple skeletal metastases, pain grade, peripheral neuropathy, the spinal cord compression grade, activities of daily living (ADL) score, Eastern Cooperative Oncology Group performance status (PS), laboratory data, previous chemotherapy, previous bone-modifying agent therapy, and survival time. Primary cancers by survival period were classified as tumors with rapid, moderate, and slow

Table 1 Clinical characteristics of patients by bone change that strongly suggest bone metastasis, other than the pedicle sign (#1)

Characteristics	Bone change (+)	Bone change (–)	*P*
No. of patients (%)	31 (48)	33 (52)	
Mean age, years (range)	65 (17–85)	68 (43–92)	0.44
Sex			0.47
Male/Female	16/15	20/13	
Primary cancer			0.39
Lung, n (%)	12 (39)	12 (36)	
Prostate, n (%)	3 (9)	2 (6)	
Kidney, n (%)	1 (3)	2 (6)	
Breast, n (%)	4 (12)	0 (0)	
Hematopoietic system, n (%)	4 (12)	7 (21)	
Digestive system, n (%)	3 (9)	6 (18)	
Others, n (%)	4 (12)	4 (2)	
Primary cancer by survival period*			0.68
Slow/Medium/Rapid	10/10/11	8/10/15	
Site			0.16
Cervical/Thoracic/Lumbar	2/8/21	1/16/16	

*: Reference 8

growth[8]. Primary cancers by survival period were classified as rapid, moderate, and slow[8]. The slow-growth group included hormone-dependent breast and prostate cancers, thyroid cancer, multiple myeloma, and malignant lymphomas. The moderate-growth group included lung cancers that had been treated with molecularly targeted drugs, hormone-independent breast and prostate cancers, renal cell carcinomas, endometrial and ovarian cancers, sarcomas, and others. The rapid-growth group included lung cancers not treated with molecularly targeted drugs, colorectal cancers, gastric and pancreatic cancers, head and neck cancers, esophageal cancers, other urological cancers, melanomas, hepatocellular carcinomas, gall bladder cancers, cervical cancers, and cancers of unknown origin. Responsible lesion sites were classified as the cervical, thoracic, and lumbar spines. Visceral or brain metastases were classified as nodular or disseminated metastases[8]. The World Health Organization's Pain Relief Ladder[9] was used to grade pain severity from 1 to 3 during a patient's first visit to the Orthopedic department. Pain was also classified as local pain or peripheral neuropathy. Spinal cord compression was graded according to the Frankel classification[10]. ADL categories were defined using the classification scheme developed by Fukuhara et al.[11]. In the present study, these categories included (1) the patient can walk independently, (2) the patient can move with a wheelchair, and (3) the patient cannot move. Regarding laboratory data, elevated CRP (≥0.4 mg/dL), LDH (≥250 IU/L), and hypoalbuminemia (<3.7 g/dL) were categorized as abnormal, while thrombocytopenia (<100,000/μL), hypercalcemia (≥10.3 mg/dL), and hyperbilirubinemia (total bilirubin ≥1.4 mg/dL) were categorized as critical[8].

Statistical Analysis

Clinical or radiographic findings were compared in relation to the bone changes strongly suggesting bone metastasis in each patient. Categorical data were compared using the chi-squared test. Continuous data were compared using the Mann-Whitney U test. To compare survival rates, survival curves were created with the Kaplan-Meier method, and differences between survival curves were tested with a generalized Wilcoxon Test. A two-sided p-value < 0.05 was considered to be significant. All statistical analyses were performed using BellCurve for Excel, version 2.15 2017 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

Patients comprised 36 men and 28 women (average age, 66.4 years; range, 17 to 92 years). The clinical characteristics of the BCP and BCN groups are summarized in **Table 1, 2**. Primary cancer sites included the lung (24), prostate (5), kidney (3), breast (4), digestive system (9), hematopoietic system (11), and others (8). The sites evaluated included 3 cervical, 24 thoracic, and 37 lumbar vertebrae.

In the analysis of radiograph data, bone changes that strongly suggested bone metastasis, other than the pedicle sign, were observed in 31 patients (BCP group) (**Table 3**): cortical bone disappearance in 20, increased radiolu-

Table 2 Clinical characteristics of patients by bone change that strongly suggest bone metastasis, other than the pedicle sign (#2)

Characteristics	Bone change (+)	Bone change (–)	*P*
Visceral or brain metastases			0.72
No/Nodular/Disseminated	17/4/10	15/6/12	
Multiple skeletal metastases			0.75
No/Yes	3/28	4/29	
Pain grade (WHO ladder)			0.25
1/2/3	15/7/6	21/3/9	
Local pain and neuropathy			0.28
Local pain/Neuropathy/Both	25/1/5	21/1/11	
Spinal cord compression (Frankel)			0.07
Grade A–D/Grade E	3/28	9/24	
Activities of daily living score (Fukuhara)			0.89
1/2/3	21/6/4	23/5/5	
ECOG performance status			0.66
0–2/3–4	12/14	24/16	
Laboratory data			0.48
Normal/Abnormal/Critical	6/21/4	3/26/4	
Previous chemotherapy			0.62
Yes/No	16/15	15/18	
Previous BMA[a] therapy			0.07
Yes/No	3/28	0/33	
Median survival time, weeks (95% CI)	23.0 (–3.4–49.4)	38.0 (7.1–68.9)	0.64

[a]bone modifying agent

Table 3 Bone changes that strongly suggest bone metastasis on radiographs, other than the pedicle sign

Bone changes	n (%)*
Cortical bone disappearance	20 (33)
Increased radiolucency of central area in vertebral body	8 (13)
Irregular osteoblastic change	5 (8)
Asymmetrical vertebral collapse (5°≤)	10 (16)

N: number of patients, *: frequency in patients without pedicle sign

cency of the central area in the vertebral body in 8, an irregular osteoblastic change in 5, and asymmetrical vertebral collapse (5 degrees ≤) in 10 (**Fig. 2〜5**). Seven of 8 patients showing increased radiolucency of the central area in the vertebral body overlapped with those with cortical bone disappearance (**Table 4**). The sites of cortical bone disappearance were the anterior cortex of the vertebral body in 5 patients, the lateral cortex in 6, the posterior cortex in 4, the cranial cortex in 4, the caudal cortex in 3, and the spinous process in 1 (**Fig. 6**). The remaining 33 patients had no bone changes that strongly suggested bone metastasis (BCN group). In the patients with the upper thoracic vertebrae lesion, it was not possible to evaluate the lateral image because it overlapped with the shoulder.

An analysis of CT data revealed that intertrabecular, mildly osteolytic, and mildly osteoblastic types were more frequent in the BCN group than in the BCP group (**Table 5**). In the BCN group, the intertrabecular type included lung cancer in 3 cases, malignant lymphoma in 2 cases, pancreatic cancer in 2 cases, multiple myeloma, testicular cancer, colon cancer, and liver cancer in 1 case. The mild osteolytic type included lung cancer in 3 cases, malignant lymphoma in 2 cases, multiple myeloma in 2 cases, renal cancer in 2 cases, gastric cancer, pharyngeal cancer, prostate cancer, and cancer of unknown primary origin in 1 case. The mild osteoblastic type included lung cancer in 3 cases and mesothelioma 1 case. Although cortical bone changes were present in 67% of the BCN group on CT, the changes were minor in most patients (**Table 5**). An analysis of CT data also revealed that increased radiolucency of the central area in the vertebral

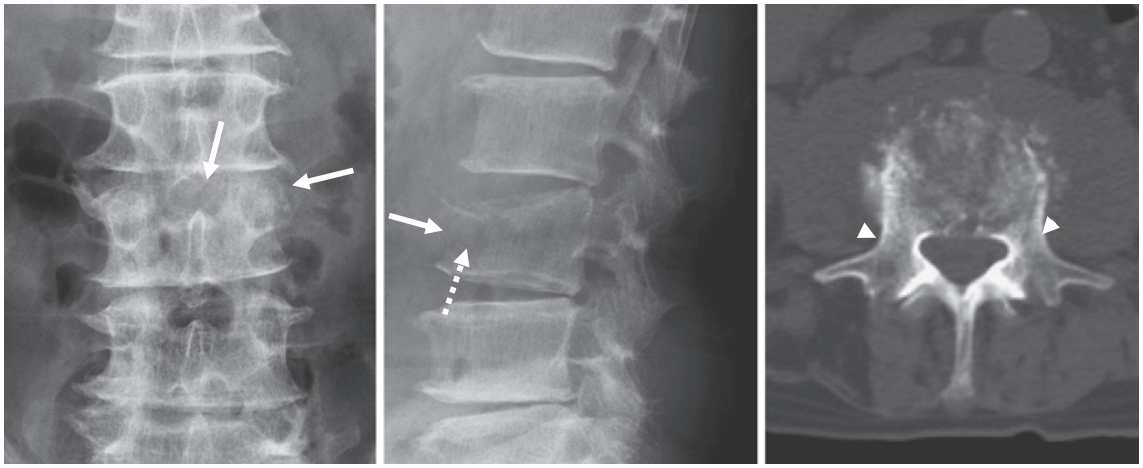

Fig. 2 Radiographic imaging of a 66-year-old man with third lumber vertebra metastasis of lung cancer. Radiographs show the disappearance of the anterior, left lateral, and cranial cortices (arrows) and increased radiolucency of the central area in the vertebral body (dashed arrow). CT shows the extensive destruction of the vertebral body, but no destruction of the pedicles (arrowheads).

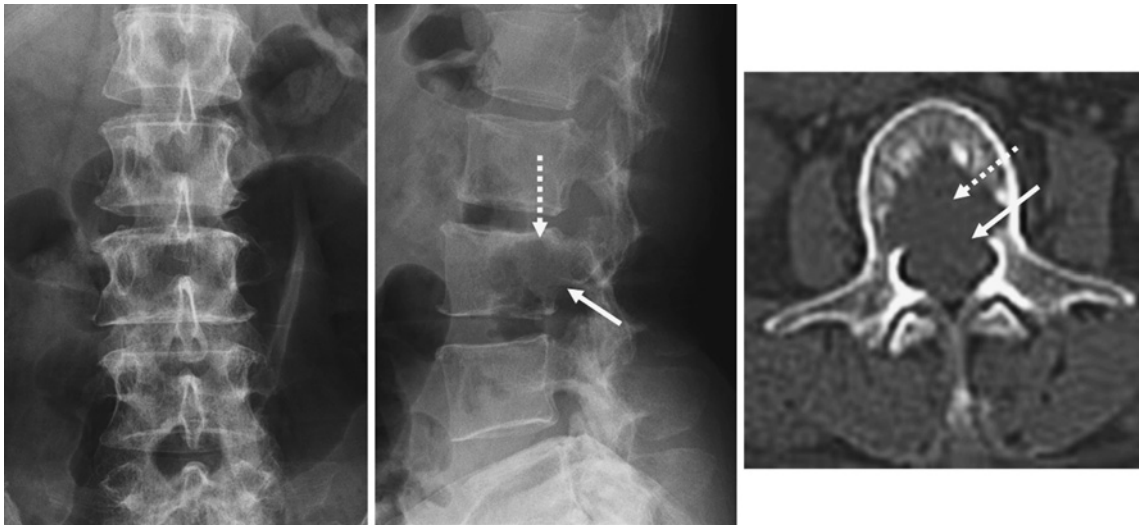

Fig. 3 Radiographic imaging of a 63-year-old woman with third lumber vertebra metastasis of thyroid cancer. Radiographs show the disappearance of the posterior cortex (arrow) and increased radiolucency of the central area in the vertebral body (dashed arrow). CT shows extensive destruction of the posterior part of the vertebral body (arrow) and posterior cortex (dashed arrow).

body on radiography was due to a decrease in the trabecular bone mass in 3 patients. In the other 5 patients, difficulties were associated with confirming whether it was due to a decrease in trabecular or cortical bone because of the extensive destruction of both bone types.

An analysis of the MRI data of the BCN group revealed that lesions were present in the vertebral body in all cases, except two with localized spinous process lesions. In many patients, lesions were present not only in the vertebral body, but also in other components and extraosseous (**Table 5**).

No significant differences were observed in the following clinical factors between the BCP and BCN groups: age, sex, primary cancer, primary cancer by survival period, the responsible lesion site, visceral or brain metastases, multiple skeletal metastases, pain grade, peripheral neuropathy, spinal cord compression grade, ADL, PS, laboratory data, previous chemotherapy, previous bone-modifying agent therapy, or survival time (**Table 1, 2**).

Discussion

The present results indicate that radiographic findings other than the pedicle sign are useful for diagnosing bone metastases, such as cortical bone disappearance, in-

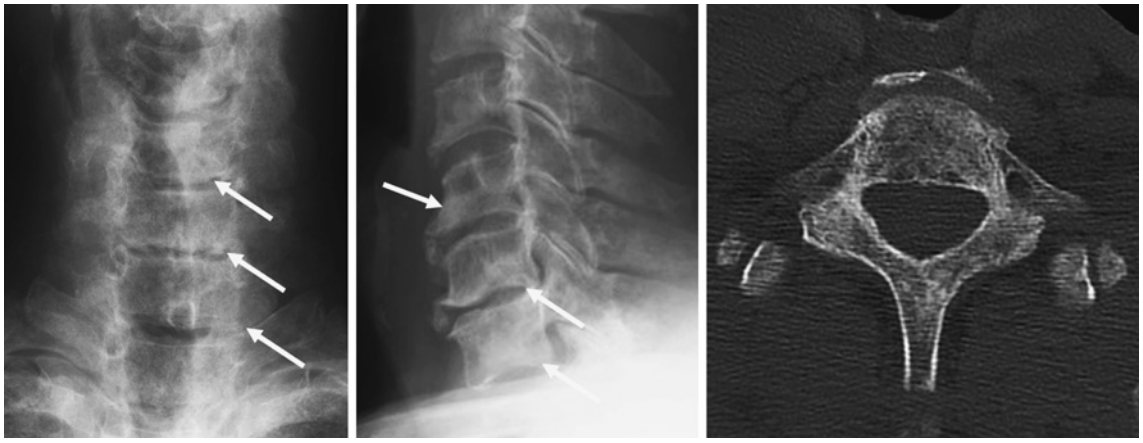

Fig. 4 Radiographic imaging of a 69-year-old man with multiple cervical vertebra metastases of prostate cancer. Radiographs show an abnormal osteoblastic change (arrow). CT shows an osteoblastic change in the whole 7th cervical vertebra.

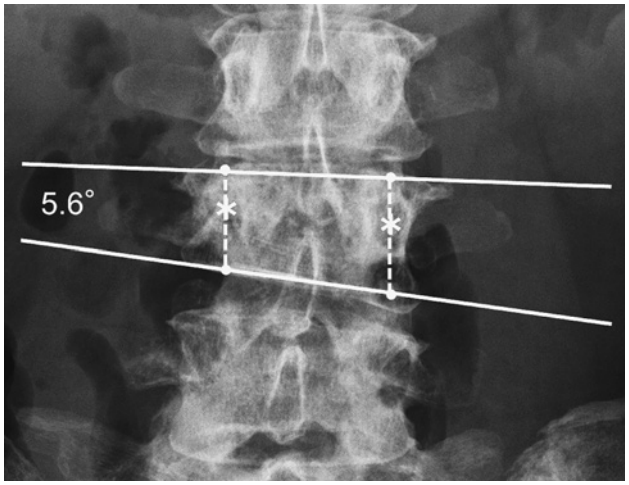

Fig. 5 Radiographic imaging of a 55-year-old woman with 4th lumbar vertebra metastasis of breast cancer. Radiographs show asymmetrical vertebral collapse over 5 degrees.

Table 4 Combination of bone changes that strongly suggest bone metastasis on radiographs, other than the pedicle sign

Positive findings	n (%)*
Cortical +/− Collapse	13 (20)
Cortical + Central +/− Collapse	7 (11)
Collapse	6 (9)
Osteoblastic	4 (6)
Central + Osteoblastic	1 (2)
Total	31 (48)

N: number of patients, *: frequency in patients without pedicle sign, Cortical: cortical bone disappearance, Collapse: asymmetrical vertebral collapse (5°≤), Central: increased radiolucency of central area in vertebral body, Osteoblastic: irregular osteoblastic change

creased radiolucency of the vertebral body, an irregular osteoblastic change, and asymmetrical vertebral collapse. On the other hand, some cases of bone metastases may be difficult to diagnose by radiography, such as the intertrabecular, mild osteolytic, and mild osteoblastic types, even if MR imaging confirms extensive metastases.

The present results also indicated that osteolytic changes on radiographs in symptomatic bone metastasis patients were mainly due to a decrease in cortical bone, with the exception of a decrease in trabecular bone in only a few patients. Trabecular bone must be reduced by between 50 and 75% to be observable on radiographs[12]. The key to a radiographic diagnosis of bone metastases is to pay attention to changes in the cortical bone of all vertebral components, including the vertebral body, superior and inferior articular processes, transverse processes, spinous process, and lamina. The frequency of involvement of each vertebral part based on the CT findings of 95 metastatic vertebrae were as follows: the posterior part of the vertebral body in 94 vertebrae (99%), the anterior part of the vertebral body in 75 (79%), the pedicle in 57 (60%), and the posterior part of the vertebra consisting of spinous and transverse processes and laminae in 21 (22%)[3].

In the present study, MR imaging detected metastatic lesions in the vertebral body in the majority of patients, while two patients with spinous process metastasis did not have lesions in the vertebral body. Algra et al.[3] previously reported that the initial anatomic location of metastases within vertebrae was the posterior portion of the body based on their analysis of CT findings. When bone metastases exceptionally occur in the spinous processes,

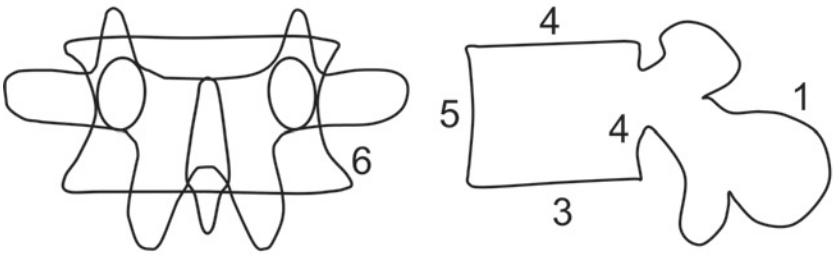

Fig. 6 Sites of disappeared cortical bone other than the pedicle.

Table 5 Imaging characteristics of CT and MR by bone changes on radiographs other than the pedicle sign

Characteristics	Bone change (+)	Bone change (–)	*P*
Morphological pattern on CT			<0.001
Osteolytic, n (%)	18 (58)	5 (15)	
Mildly osteolytic, n (%)	4 (13)	13 (39)	
Intertrabecular, n (%)	2 (6)	11 (33)	
Mildly osteoblastic, n (%)	0 (0)	4 (12)	
Osteoblastic, n (%)	3 (10)	0 (0)	
Mixed, n (%)	4 (13)	0 (0)	
Cortical bone change on CT			
Change in any part of the vertebra, n (%)	29 (94)	22 (67)	0.16
Partial change at the pedicle, n (%)	8 (26)	4 (12)	0.16
Occupation in the vertebra on MRI			0.26
Body, n (%)	30 (97)	32 (97)	0.96
Pedicle, n (%)	22 (71)	24 (73)	0.88
Posterior to pedicle, n (%)	19 (61)	22 (67)	0.65
Extra-skeletal extension on MRI, n (%)	24 (77)	25 (76)	0.18

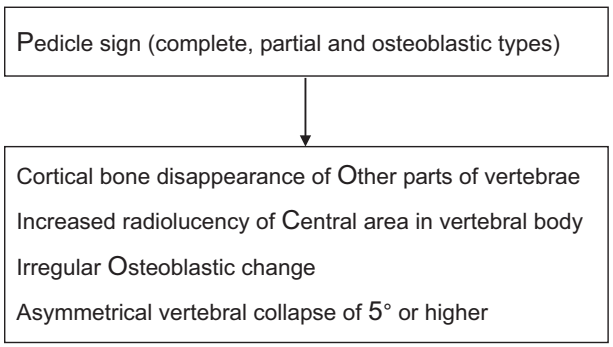

Fig. 7 Radiography diagnostic protocol for painful spinal metastases in daily practice (POCO5)

they could be confined to the posterior part of the vertebra without extending to the vertebral body[13]. An examination of the contours of spinous processes needs to be conducted in a routine radiographic diagnosis.

In the present study, there was no significant correlation between the presence of bone changes on radiography and prognosis. The reason may be that there was no significant difference in the types of primary cancers that have a significant effect on prognosis. The majority of the BCN group, intertrabecular, mild osteolytic, and mild osteoblastic types, consisted of a variety of cancer types including hematopoietic tumors. Intertrabecular-type metastasis was not rare, which was detected in 36.9% of metastatic lesions in examinations of cadavers excluding hematopoietic tumor[14]. This type is difficult to observe on radiographs and bone scans, whereas MR images showed the majority of these lesions[14]. The histological types of primary cancers that are prone to intertrabecular metastasis include small cell carcinoma of the lung, adenocarcinoma of the digestive organs, and hepatocellular carcinoma[14].

Based on the results of the previous study on pedicle signs[5] and the results of this study on cases without pedicle signs, we propose a diagnostic protocol for painful spinal metastases on daily practice (**Fig. 7**). First, the presence or absence of the pedicle sign is evaluated. At that time, it is necessary to recognize that there are complete type, partial type, and osteoblastic type in the pedicle sign[5]. In the absence of pedicle signs, cortical bone

disappearance of other parts of vertebrae, increased radiolucency of central area in vertebral body, irregular osteoblastic change, and asymmetrical vertebral collapse of 5 degrees or higher are assessed. In the absence of these findings, we follow the algorithm proposed in our previous paper for early diagnosis of painful bone metastases[1]. If symptoms cannot be explained as non-severe benign disease, additional examinations such as MRI and CT will be performed immediately, otherwise additional examinations will be performed in the case of non-improvement after 2 weeks conservative therapy.

The present study had some limitations. This was a retrospective and observational study. Furthermore, there was bias in the type of primary cancer because the present study was performed using patients who visited a single hospital. Moreover, image evaluations were conducted by a single doctor. Despite these limitations, the strengths of the present study need to be highlighted. To the best of our knowledge, a comprehensive analysis has not yet been conducted on radiographic findings indicating bone metastasis other than the pedicle sign with reference to CT and MR imaging findings in a large number of patients.

In conclusion, radiographic findings other than the pedicle sign are also useful for diagnosing bone metastases. The key to the radiographic diagnosis of bone metastases is to pay attention to changes in the cortical bone of all vertebral components. The present results and previous findings[5] on the pedicle sign will facilitate the diagnosis of bone metastases with radiography by orthopedic practitioners.

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Conflict of Interest: None declared.

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