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Association of Pedicle Sign Type with Clinical and Radiological Features in Patients with Symptomatic Spinal Metastases

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Background: Because of population aging in Japan, the number of cancer diagnoses is increasing rapidly. The pedicle sign is a valuable radiographic indicator of metastases, as the pedicle is the most commonly affected vertebral structure in radiographic assessment. However, few studies have carefully examined the morphological features of pedicle signs. To improve the capacity of medical professionals to diagnose symptomatic spinal metastases, we retrospectively examined the morphological characteristics of pedicle signs and their associations with clinical and radiological features.

Methods: 186 patients with symptomatic spinal metastases who visited our department during the period from January 1, 2011 through December 31, 2017 were enrolled. The pedicle sign was defined as a missing or obscured pedicle on an anteroposterior radiograph. Radiographs were evaluated for pedicles and other vertebrae structures. Clinical and other radiological features were compared in relation to the type of pedicle sign identified.

Results: Pedicle signs were classified as completely disappeared (complete, 26 patients), partially disappeared (partial, 40 patients), or obscured by the osteoblastic background (blastic, 28 patients). Disappearance of both the bone cortex and pedicle was observed in almost half of the patients with complete or partial pedicle signs. The complete pedicle sign was associated with significantly longer survival.

Conclusion: Diagnosis of bone metastases requires understanding of pedicle sign types.

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Key words: pedicle sign, spinal metastases, classification, survival rate

Introduction

The number of cancer patients in Japan is increasing rapidly because of population aging[1]. In addition, survival of cancer patients has been extended by the development of new drugs to treat the disease[2]. Because orthopedic surgeons now have more opportunities to treat patients with bone metastases, training regarding bone metastases is increasingly important for the general orthopedic surgeon. Bone metastasis can be diagnosed by screening or after symptoms appear. In the latter case, delayed diagnosis often results in serious complications, such as pathological fracture or spinal cord paralysis[3,4].

Bone metastasis is difficult to diagnose on the basis of interviews and physical findings alone[5]. For example, the symptoms of degenerative spine disease, a common orthopedic disease, are not easy to distinguish from the initial symptoms of bone metastasis. In Japan, patients often initially visit orthopedic clinics, rather than general practitioners, and orthopedic practitioners frequently take radiographs. For screening for bone metastases, radiography is inferior to magnetic resonance imaging (MRI), computed tomography (CT), and bone scintigraphy. However, radiography has been reported to provide the information necessary to make some diagnoses related to symptomatic bone metastases[6]. The practice of performing radiography as part of a first orthopedic visit in Japan can be beneficial for early diagnosis of bone metastases. To take advantage of these potential benefits, orthopedic practitioners must have the knowledge necessary to diagnose bone metastases radiographically.

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The pedicle sign, first reported in 1958 by Jacobson et al[7], is an obscuration of a pedicle in an anteroposterior image of the spine. It is also called the 'winking owl' sign or 'absent pedicle' sign. The pedicle sign is a valuable radiographic indicator of metastasis, because abnormalities related to the pedicle are frequently observed[8]. Fully understanding the pedicle sign is considered a first step in the early diagnosis of bone metastasis. However, few morphological studies have evaluated this sign. In this study, to improve diagnosis of symptomatic bone metastasis, the morphological characteristics of pedicle signs, and the associations of pedicle signs with clinical and other radiological features, were retrospectively examined in patients with symptomatic spinal metastases.

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 principles of the Declaration of Helsinki. Informed consent for 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 done by using medical records and images kept at our hospital. This study was conducted in the orthopedics department of a single university hospital.

Patients

Patients were included in the study if they had visited our department for treatment of symptomatic spinal metastasis during the period from January 1, 2011 through December 31, 2017. Exclusion criteria were absence of radiographs during the period from 2 weeks before to 2 weeks after the first visit and history of radiation therapy at the target site. Disease codes were used to search hospital records for patients who had visited the orthopedic department for treatment of bone metastases. Computerization of medical charts began at the hospital in 2011, and the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)[9] 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 patients who visited the orthopedic department for metastases to the cervical, thoracic, or lumbar spine were extracted; 67 patients 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. Data from the remaining 186 patients were further analyzed.

Study Variables

The clinical variables evaluated included age, sex, responsible lesion site, primary cancer, previous chemotherapy, previous bone-modifying agent therapy, activities of daily living (ADL) score, Eastern Cooperative Oncology Group performance status (PS), pain severity, pain type, spinal cord compression grade, visceral or brain metastases, multiple skeletal metastases, laboratory data, and survival time. Growth of primary cancers was classified as rapid, moderate, and slow[10]. 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.

Using the classification scheme developed by Fukuhara et al[11], we defined ADL categories, namely, (1) the patient can walk independently, (2) the patient can move with a wheelchair, and (3) the patient cannot move. The World Health Organization Pain Relief Ladder was used to grade pain severity from 1 to 3 during the patient's first visit to the orthopedic department[12]. Pain was also classified as local pain or neuropathy. Spinal cord compression was graded according to the Frankel classification[13]. Visceral and brain metastases were classified as nodular metastases or disseminated metastases, in accordance with the study of Katagiri et al[10]. Regarding laboratory data, elevated CRP ($\geq$0.4 mg/dL) and LDH ($\geq$250 IU/L) and hypoalbuminemia (<3.7 g/dL) were categorized as abnormal, and thrombocytopenia (<100,000/μL), hypercalcemia ($\geq$10.3 mg/dL), and hyperbilirubinemia (total bilirubin $\geq$1.4 mg/dL) were categorized as critical, in accordance with the study of Katagiri et al[10].

One author (Y.K.), an orthopedic surgeon with 24 years of specialist experience, evaluated radiographs and CT and MR images. The site evaluated was the vertebra con-

Table 1 Clinical characteristics of patients

Characteristic	Pedicle sign (+)	Pedicle sign (–)	*P* value
No. of patients (%)	94 (50)	92 (50)	
Mean age, years (range)	69 (44-93)	68 (17-92)	0.85
Sex			0.18
Male, n (%)	64 (68)	54 (59)	
Female, n (%)	30 (32)	38 (41)	
Site			<0.001
Cervical spine, n (%)	17 (18)	5 (5)	
Thoracic spine, n (%)	43 (46)	30 (33)	
Lumbar spine, n (%)	34 (36)	57 (62)	
Primary cancer			0.0024
Lung, n (%)	16 (17)	27 (29)	
Prostate, n (%)	26 (28)	9 (10)	
Kidney, n (%)	8 (9)	5 (5)	
Breast, n (%)	6 (6)	6 (7)	
Hematopoietic system, n (%)	3 (3)	15 (16)	
Digestive system, n (%)	20 (21)	19 (21)	
Others, n (%)	15 (16)	11 (12)	

sidered to be the primary source of symptoms. The pedicle sign was defined as a missing or obscured pedicle on an anteroposterior radiograph. Since visualization of the pedicle depends on radiographic conditions, visualization of pedicles contralateral to, above, or below the pedicle to be evaluated were referred to for the evaluation. A complete pedicle sign was defined as a pedicle that completely disappeared because of osteolysis. A partial pedicle sign was defined as a pedicle that partially disappeared or was obscured because of osteolysis. A blastic pedicle sign was defined as a pedicle that disappeared or was obscured because of marked osteoblastic change in the vertebral body. Patients with a pedicle sign were extracted via image evaluation. Using CT images performed 2 weeks before or after radiography, we classified pedicles as complete, partial, and blastic. Bone cortical destruction other than the pedicle, including vertebral body collapse and the morphological pattern of bone metastasis (osteolytic, osteoblastic, mixed, and intertrabecular), were evaluated by using anteroposterior and lateral radiographic views. An MRI performed 2 weeks before or after radiography was used to evaluate tumor incorporation within the vertebra (the body, pedicle, and tissues posterior to the pedicle) and extraskeletal extension in all patients.

Statistical Analysis

Clinical and radiographic findings were compared in relation to the type of pedicle sign identified for each patient. Categorical data were compared with the chi-square test. Continuous data from two groups were compared by using the Mann-Whitney U test, and data from three groups were compared with one-way analysis of variance, followed by the Bonferroni post hoc test. To compare survival rates, survival curves were created with the Kaplan-Meier method, and differences between survival curves were tested with the Generalized Wilcoxon Test. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed with BellCurve for Excel, version 2.15 2017 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

The patients comprised 118 men and 68 women (average age, 68.7 years; range, 17 to 93 years), and the sites evaluated included 22 cervical, 73 thoracic, and 91 lumbar vertebrae sites. The sites of the primary cancer were the lung (43), prostate (35), kidney (13), breast (12), digestive system (39), hematopoietic system (18), and other (26).

A pedicle sign was observed in 94 patients, and the clinical characteristics of these patients are summarized in **Table 1**. The pedicle signs identified in 26, 40, and 28 patients were classified as complete (**Fig. 1**), partial (**Fig. 2**), and blastic (**Fig. 3**), respectively. The clinical characteristics of patients, in relation to type of pedicle sign, are shown in **Table 2** and **Table 3**.

Although pedicle sign type was not significantly associated with speed of tumor growth, there were more prostate cancers in the blastic pedicle group than in the

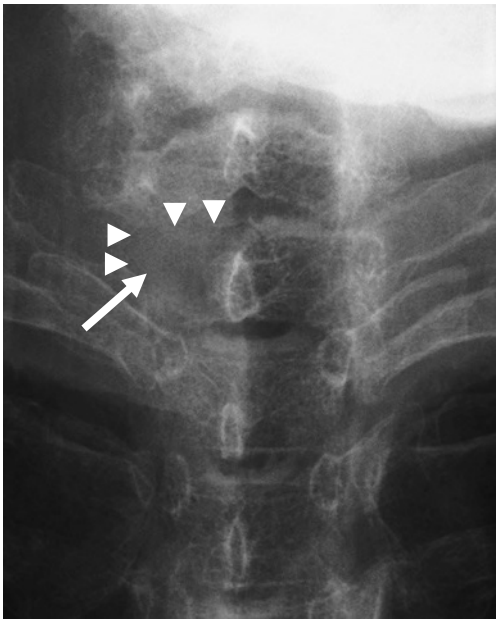

Fig. 1 Radiograph showing a complete pedicle sign in a 73-year-old woman with a multiple myeloma lesion in the first thoracic vertebra. The shadow of the right pedicle on an anteroposterior radiograph has disappeared completely (arrow). The vertebral cortices at the upper right and lateral sides have also disappeared (arrowheads).

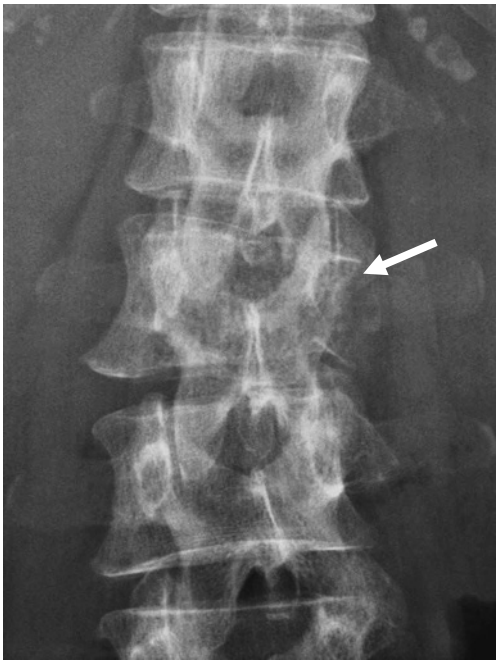

Fig. 2 Radiograph showing a partial pedicle sign in a 65-year-old woman with metastasis of lung cancer to the second lumbar vertebra. The bone cortex of the left pedicle on an anteroposterior radiograph has partially disappeared and is thin (arrow). Asymmetric vertebral body collapse is also evident.

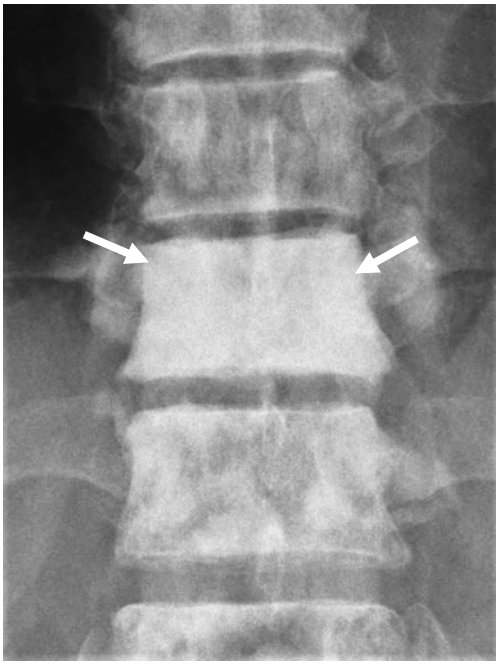

Fig. 3 Radiograph showing a blastic pedicle sign in a 70-year-old man with metastasis of prostate cancer to the 10th thoracic vertebral. Bilateral pedicles on an anteroposterior radiograph are obscured by marked osteoblastic change in the vertebral body (arrow).

other groups. Patients with complete pedicles were less likely, and those with blastic pedicles were significantly more likely, to have received previous chemotherapy. A blastic pedicle sign was significantly positively associated with previous bone-modifying agent therapy, and with the presence of neuropathy without local pain as compared with the other two types. Presence of a complete pedicle sign was associated with significantly longer survival, as compared with the other two groups.

ADL score, PS, pain grade, spinal cord compression grade, visceral and brain metastases, multiple skeletal metastases, and values for laboratory variables did not significantly differ in relation to type of pedicle sign. Radiological characteristics, in relation to type of pedicle sign, are shown in **Table 4**. CT images showed some cortical destruction of the pedicle. Almost half of the patients with complete and partial pedicle signs exhibited disappearance of the bone cortex in addition to the pedicle (**Fig. 1**). Body collapse, tumor incorporation within vertebra, and extraskeletal extension were not associated with pedicle sign type.

Discussion

The present findings indicate that pedicle signs are variable, which has not been extensively examined. We have

Table 2 Clinical characteristics of patients, by pedicle sign type (1)

Clinical characteristics	Pedicle sign			*P* value
	Complete	Partial	Blastic	
No. of patients (%)	26 (28)	40 (43)	28 (30)	
Mean age, years (range)	70 (45-93)	68 (44-87)	71 (50-89)	0.98
Sex				0.067
Male, n (%)	13 (50)	30 (75)	21 (75)	
Female, n (%)	13 (50)	10 (25)	7 (25)	
Site				0.28
Cervical spine, n (%)	7 (27)	6 (15)	4 (14)	
Thoracic spine, n (%)	11 (42)	22 (55)	10 (36)	
Lumbar spine, n (%)	8 (31)	12 (30)	14 (50)	
Primary cancer				<0.001
Lung, n (%)	7 (27)	7 (18)	2 (7)	
Prostate, n (%)	3 (12)	5 (13)	18 (64)	
Breast, n (%)	4 (15)	1 (3)	1 (4)	
Kidney, n (%)	1 (4)	6 (15)	1 (4)	
Hematopoietic system, n (%)	2 (8)	1 (3)	0 (0)	
Digestive system, n (%)	7 (27)	12 (30)	2 (7)	
Others, n (%)	2 (8)	8 (20)	4 (14)	
Primary cancer by growth speed				0.053
Slow growth, n (%)	5 (19)	7 (18)	11 (39)	
Moderate growth, n (%)	10 (39)	18 (45)	14 (50)	
Rapid growth, n (%)	11 (42)	15 (38)	3 (11)	

Table 3 Clinical characteristics of patients, by type of pedicle sign (2)

Clinical characteristics	Pedicle sign			*P* value
	Complete	Partial	Blastic	
Previous chemotherapy				0.01
No, n (%)	17 (65)	16 (39)	7 (25)	
Yes, n (%)	9 (35)	24 (60)	21 (75)	
Previous BMA[a] therapy				<0.001
No, n (%)	25 (96)	39 (98)	18 (64)	
Yes, n (%)	1 (4)	1 (3)	10 (37)	
Local pain and neuropathy				0.039
Both, n (%)	17 (65)	23 (58)	16 (57)	
Local pain only, n (%)	8 (31)	15 (38)	5 (18)	
Neuropathy only, n (%)	1 (4)	2 (5)	7 (25)	
Mean survival time, weeks (95% CI)	162 (111-214)	85 (48-123)	85 (36-135)	0.012

[a]bone-modifying agent

shown that even a finding of partial pedicle disappearance is useful for diagnosing spinal metastasis. A better understanding of these diagnostic steps thus might improve diagnosis and treatment of spinal metastases.

Trabecular bone mass must be reduced by 50% to 75% to be observable on radiographs[14], so diagnosis of spinal metastases is more challenging than for metastases in long bones; diagnosis is particularly difficult in patients with osteoporosis. The pedicle is composed of cortical bone, and disappearance of the pedicle on a radiograph is a powerful diagnostic basis for identifying spinal metastases. For similar reasons, radiographic findings from the superior and inferior articular processes, transverse processes, spinous process, lamina, and thin bone cortex of the vertebral body are also important.

The present results indicate that about half of the complete and partial pedicle signs were associated with partial disappearance of the bone cortex, in addition to the pedicle. The posterior vertebral body is typically the initial anatomic site of metastases in vertebrae, and metastases to the spine rarely start at the pedicle[8]. Diseases with radiographic findings that must be differentiated

Table 4 Radiological characteristics, by pedicle sign type

Radiological characteristics	Pedicle sign			*P* value
	Complete	Partial	Blastic	
Morphological pattern				<0.001
Osteolytic, n (%)	24 (92)	30 (75)	0 (0)	
Osteoblastic, n (%)	0 (0)	1 (3)	24 (86)	
Mixed, n (%)	2 (8)	9 (23)	4 (14)	
Other cortical destruction				<0.001
Yes, n (%)	13 (50)	19 (48)	2 (7)	
No, n (%)	13 (50)	21 (53)	26 (93)	
Vertebral body collapse				0.071
Yes, n (%)	17 (65)	17 (43)	10 (64)	
No, n (%)	9 (35)	23 (58)	3 (36)	
Pedicle destruction (CT)[a]				<0.001
Complete destruction, n (%)	11 (42)	0 (0)	0 (0)	
Partial destruction, n (%)	15 (58)	38 (100)	3 (12)	
Blastic change, n (%)	0 (0)	0 (0)	23 (89)	
Extent in vertebra (MRI)[b]				0.26
Pedicle only, n (%)	0 (0)	0 (0)	0 (0)	
Pedicle + body, n (%)	0 (0)	4 (12)	1 (4)	
Pedicle + PP, n (%)	0 (0)	1 (3)	0 (0)	
Pedicle + body + PP, n (%)	24 (100)	28 (85)	22 (96)	
Extraskeletal extension (MRI)[b]				0.18
Yes, n (%)	24 (100)	31 (94)	20 (87)	
No, n (%)	0 (0)	2 (6)	3 (13)	

[a]CT: n = 26, 38, 26 (complete, partial, blastic), [b]MRI: n = 24, 33, 23 (complete, partial, blastic), PP: posterior to pedicle

from the pedicle sign include infection and congenital aplasia/hypoplasia[15,16].

In patients with a blastic pedicle sign the presence of osteoblastic change alone raises suspicion of spinal metastasis, regardless of the appearance of the pedicle, and usually suggests osteoblastic metastasis or an osteoblastic change that occurred after treatment of an osteolytic metastasis. Diagnosis of conditions associated with a blastic pedicle sign must differentiate between osteoarthritis of a facet joint, healing of compression fracture, bone island, SAPHO syndrome, lymphoma, Paget's disease, Ewing's sarcoma, osteosarcoma, myeloma, myeloid metaplasia, mastocytosis, and various infectious lesions, such as tuberculosis and sarcoidosis[17].

Pedicle signs were noted in about half of the present patients, but frequency varied in relation to the interval from onset of bone metastasis to radiographic evaluation. In a previous study, the frequency of the pedicle sign depended on whether radiographs were taken at a patient's first visit to a clinical research hospital[6]. The frequency of pedicle signs identified on radiographs varied between 22% and 95% in previous reports[7,8,18,19].

This is the first study to report that a complete pedicle sign is associated with a significantly better prognosis, as compared with the other two types. Katagiri et al[10] identified six prognostic factors that were significantly associated with survival: speed of growth of the primary lesion, presence of visceral or cerebral metastases, abnormal laboratory findings, poor PS, previous chemotherapy, and presence of multiple skeletal metastases. In the present study, however, only previous chemotherapy varied significantly in relation to type of pedicle sign. Recent history of chemotherapy was an effective prognostic indicator for cancer patients[2]. However, the reason why a complete pedicle sign, but not the other pedicle sign types, was significantly associated with previous chemotherapy remains unclear.

In general, bone strength is less impaired by osteoblastic bone metastases than by osteolytic metastases. However, the present results indicate that the blastic pedicle sign is associated with skeletal events in patients visiting orthopedic clinics. Bone metastasis, whether associated with a complete, partial, or blastic pedicle sign, must be carefully examined and treated quickly.

The present study had limitations. First, it was a retrospective, observational study. Second, there was bias in type of primary cancer because the study enrolled patients at a single center. Third, image evaluation was per-

formed by a single doctor. Despite these limitations, the strengths of the study should be highlighted. To our knowledge, this is the first study to investigate the various pedicle signs observed and to identify an association between pedicle sign type and outcome. Further, this study identified methods that can be used for initial diagnosis of symptomatic spinal metastases, which is currently considered difficult.

In conclusion, pedicle signs can be classified as complete, partial, and blastic, which must be understood when diagnosing bone metastases. Outcomes appear to be better for the complete pedicle sign than for the partial and blastic pedicle signs.

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Conflict of Interest: None declared.

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