Types of pedicle signs indicating symptomatic spinal metastases
and their associated clinical and radiological features

Running head: Types of pedicle signs

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Abstract

Background: Cancer diagnoses are increasing rapidly due to the aging population of Japan. Pedicle sign is a valuable radiographic indicator of metastases as the pedicle is the most commonly affected part of the vertebra upon radiographic assessment. However, few detailed studies examining the morphological features of pedicle signs have been performed. To improve the capacity of medical professionals to diagnose symptomatic spinal metastases, we retrospectively examined the morphological characteristics of pedicle signs and their relationship with clinical and radiological features.

Methods: In total, 186 patients with symptomatic spinal metastases who visited our department between January 1, 2011, and December 31, 2017, were enrolled in the study. Pedicle sign was defined as a pedicle that had disappeared or had become obscured on an anteroposterior radiographic image. Radiographic images were evaluated for pedicles and other structures of the vertebrae. Clinical and other radiological features were compared among the types of pedicle signs identified.

Results: Pedicle signs were classified according to whether they had completely disappeared (complete type, 26 patients), partially disappeared (partial type, 40 patients), or were obscured by the osteoblastic background (blastic type, 28 patients). The disappearance of the bone cortex in addition to the pedicle was observed in almost half of the patients with complete and partial types of pedicle signs. Complete types were associated with significantly longer survival rates.

Conclusion: Understanding of the various types of pedicle sign is required to properly diagnose bone metastases.
Key words: pedicle sign, spinal metastases, classification, survival rate

Introduction

The number of cancer patients is increasing rapidly due to the aging population of Japan\(^1\). In addition, the survival of cancer patients has been extended with the recent development of new drugs to treat the disease\(^2\). As a result, orthopedic surgeons today have more opportunities to treat patients with bone metastases than ever before. Therefore, for the general orthopedic surgeon, training regarding bone metastases is increasingly important. Bone metastasis may be diagnosed either via screening or after symptoms appear. In the latter case, a delayed diagnosis often results in serious complications such as pathological fractures or spinal cord paralysis\(^3,4\).

Diagnosis of bone metastasis based only on interviews and physical findings is difficult\(^5\). For example, symptoms of degenerative spine disease, one of the most common orthopedic diseases, are not easily distinguishable from the initial symptoms of bone metastasis. In Japan, patients often visit orthopedic clinics initially, rather than general practitioners, where orthopedic practitioners frequently take radiographs. Radiography for screening for bone metastases is inferior to magnetic resonance imaging (MRI), computed tomography (CT), or bone scintigraphy. However, radiography has been reported to provide information necessary to perform certain 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 the early diagnosis of bone metastases. To take advantage of the potential benefits, it is essential that orthopedic practitioners have the knowledge necessary to radiographically diagnose bone metastases.
The pedicle sign was first reported in 1958 by Jacobson et al.\(^7\) It is defined as an obscuration of the pedicle image taken using an anteroposterior view of the spine and is also called the ‘winking owl’ sign or the ‘absent pedicle’ sign. The pedicle sign is a valuable radiographic indicator of metastases, 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, contrary to its high level of name recognition, few morphological studies have been performed regarding the pedicle sign. In this study, to improve our capacity to diagnose symptomatic bone metastases, the morphological characteristics of pedicle signs, and the relationship between pedicle signs and clinical and other radiological features were retrospectively examined in patients with symptomatic spinal metastases.

**Materials and Methods**

This retrospective study was approved by our institutional review board (No. 30-01-1071) and was conducted in accordance with the Declaration of Helsinki. Informed consent from patients for the publication of their personal medical data was obtained by the opt-out procedure, as described in the study protocol. A retrospective review of consecutive patients with bone metastases, including hematopoietic malignancies, was undertaken using medical records and images kept at our hospital. This study was conducted within the orthopedics department of a single university hospital.

**Patients**

The patients included in the study were those who had a symptomatic spinal metastasis who visited our department throughout the time period beginning January 1,
2011, and ending December 31, 2017. Exclusion criteria included the provision that no radiographs were taken for two weeks before or after the first visit, and that there was a history of radiation therapy at the target site. Hospital records were searched for patients who had visited the orthopedic department regarding bone metastases using disease name registrations. 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) was used to register diagnoses. A total of 923 patients were initially selected, whose diagnoses were classified as C79.5, which corresponds with secondary malignant neoplasms of the bone and bone marrow in the ICD-10, and who underwent examinations for bone metastases in the orthopedic department as outpatients or inpatients. By meticulously reviewing the medical charts of all of these patients, 288 patients were extracted who visited the orthopedic department for metastases to the cervical, thoracic, and lumbar spine. In total, 67 patients who did not have symptoms due to spinal metastases, 23 patients who had not been radiographically imaged two weeks before or after the first orthopedic visit, and 12 patients who had radiation history at the target site were excluded. The remaining 186 patients identified were enrolled in the study and their records were further evaluated.

Methods

Clinical information evaluated included age, sex, responsible lesion site, primary cancer, previous chemotherapy, previous bone modifying agent therapy, activities of daily living (ADL) score, the Eastern Cooperative Oncology Group performance status (PS), pain grade, pain type, spinal cord compression grade, visceral or brain metastases, multiple skeletal metastases, laboratory data, and survival time. Primary cancers were classified as tumors that grew rapidly, moderately, and slowly. The group
characterized by slow-growth 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 that were 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, ADL categories were defined. For the present study, these included (1) the patient can walk independently, (2) the patient can move with a wheelchair, and (3) the patient cannot move. Pain was graded from 1 to 3 in the patient’s first visit to the orthopedic department using the World Health Organization’s Pain Relief Ladder. Pain was also classified as either local pain or neuropathy. Spinal cord compression was graded according to the Frankel classification. Visceral or brain metastases were classified as nodular metastases or disseminated metastases based on reports by Katagiri et al. Regarding laboratory data, elevated CRP (≥ 0.4 mg/dL), LDH (≥ 250 IU/L), or hypoalbuminemia (< 3.7 g/dL) were categorized as abnormal, and thrombocytopenia (< 100,000/µL), hypercalcemia (≥ 10.3 mg/dL), or hyperbilirubinemia (total bilirubin ≥ 1.4 mg/dL) were categorized as critical according to reports by Katagiri et al.

One researcher, an orthopedic surgeon (Y.K.) with 24 years of specialist experience, evaluated radiographic, CT, and MR images. The site evaluated was the vertebra considered to be the main source of symptoms. Pedicle sign was defined as a
pedicle that had disappeared or was obscured on an anteroposterior view of radiography. Since the visualization of the pedicle depends on various radiographic conditions, the visualization of the pedicles on the contralateral, above, or below the pedicle to be evaluated were referred to for the evaluation. Complete type was defined as a pedicle that had completely disappeared due to osteolysis. Partial type was defined as a pedicle that had partially disappeared or was obscured due to osteolysis. Blastic type was defined as a pedicle that had disappeared or was obscured due to a remarkable osteoblastic change in the vertebral body. Patients with pedicle sign were extracted via image evaluation. Using CT images performed two weeks before or after radiography, pedicles were classified into complete destructive, partial destructive, and blastic categories. 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 using anteroposterior and lateral radiographic views. Using an MRI performed two weeks before or after radiography, tumor incorporation within the vertebra (the body, the pedicle, or the posterior parts from the pedicle) and extra-skeletal extension were evaluated for all patients included.

**Statistical analysis**

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

**Results**

Patients included in the study, which consisted of 118 men and 68 women, were an average of 68.7 years old (17 to 93 years old). Sites evaluated included 22 cervical, 73 thoracic, and 91 lumbar vertebrae. Primary cancer sites included 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 information for these individuals has been summarized in Table 1. Pedicle signs identified from 26, 40, and 28 patients were classified as completely disappeared (complete type, Figure 1), partially disappeared (partial type, Figure 2), and obscured by osteoblastic background (blastic type, Figure 3), respectively. Clinical characteristics corresponding to the type of pedicle sign identified have been shown in Table 2 and Table 3.

Though there were no significant differences among the three types in terms of the speed of tumor growth, there was an increased number of prostate cancers associated with the blastic type of pedicle sign relative to the other two types. The complete type was significantly less associated with previous chemotherapy than the other two types, while the blastic type was significantly more associated with previous chemotherapy. The blastic type was also significantly associated with bone modifying agent therapy. There were significantly more patients who experienced neuropathy without local pain with the blastic type of pedicle sign when compared to the other two
types. Finally, the complete type was associated with a significantly longer survival rate than the blastic and partial types of pedicle signs.

The three types of pedicle signs did not differ significantly with regard to ADL score, PS, pain grade, spinal cord compression grade, visceral or brain metastases, multiple skeletal metastases, and laboratory data. Radiological characteristics associated with types of pedicle signs have been shown in Table 4. CT images showed a certain degree of cortical destruction of the pedicle. The disappearance of bone cortex in addition to the pedicle was found in almost half of the patients with complete type and partial type pedicle signs (Figure 1). The three types of pedicle signs were not associated with significantly different frequencies of body collapse, tumor incorporation within vertebra, or extra-skeletal extension.

**Discussion**

Importantly, these findings indicate that pedicle signs are variable, which is an observation that has not been examined extensively. We have shown that even when the disappearance of the pedicle is incomplete, such a finding is useful for the diagnosis of spinal metastasis. A full understanding of these diagnostic steps has the potential to improve the diagnosis and treatment of spinal metastases.

For trabecular bone loss to be observable using radiographic imaging, the trabecular bone must be reduced by 50–75%, so the diagnosis of spinal metastases is difficult compared to metastases associated with long bones. Diagnosis is particularly difficult in patients with osteoporosis. The pedicle is composed of cortical bone, and the 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.

Results from this study revealed that about half of the complete and partial types of pedicle signs are associated with the partial disappearance of the bone cortex in addition to the pedicle. The posterior part of the vertebral body is typically the initial anatomic location of metastases within the vertebrae, and metastases to the spine are rarely initiated from the pedicle. Diseases with radiographic findings that should be differentiated from the pedicle sign include infection and congenital aplasia/hypoplasia.

Regarding the blastic type of pedicle sign, an osteoblastic change itself raises suspicion of spinal metastasis regardless of the appearance of the pedicle image. It usually suggests an osteoblastic metastasis or an osteoblastic change that occurred after treatment of an osteolytic metastasis. The diagnosis of the blastic type of pedicle sign must differentiate between osteoarthritis of facet joint, healing process of compression fracture, bone island, SAPHO syndrome, lymphoma, Paget's disease, Ewing's sarcoma, osteosarcoma, myeloma, myeloid metaplasia, mastocytosis, and various infective lesions such as tuberculosis and sarcoidosis.

Results here reveal that pedicle signs were found in about half of the patients examined, but their frequency may vary depending on how long the evaluated radiographs were taken after the onset of bone metastases. The frequency of the appearance of pedicle signs depends on whether radiographs were taken at a patient’s first clinical research hospital visit. The frequency of pedicle signs identified using radiography that have been reported previously varies between 22 and 95%.

This study was the first to reveal that the complete type of pedicle sign is
associated with a significantly better prognosis than the other two types. Katagiri et al\textsuperscript{10} identified six prognostic factors that significantly determine survival: the speed of growth of the primary lesion, visceral or cerebral metastases, abnormal laboratory data, poor PS, previous chemotherapy, and multiple skeletal metastases. Among these, only “previous chemotherapy” varied significantly among the three types of pedicle sign examined in the present study. Recent chemotherapy has been shown to be a very effective prognostic indicator for cancer patients\textsuperscript{2}. However, the reason the complete type of pedicle sign was significantly less associated with previous chemotherapy than the other types remains unclear.

In general, osteoblastic type bone metastases appear to impair bone strength less than osteolytic types. However, based on the results of the present study, blastic types are also often associated with skeletal related events when the patients visit orthopedic clinics. It is necessary to carefully examine, and initiate treatment as soon as possible after diagnosis of any type of bone metastasis, be it complete type, partial type, or blastic type.

The present study did have some limitations. First, this was a retrospective and observational study. Second, there is a bias in the type of primary cancer because the study was performed using patients who visited a single hospital. Third, image evaluation was performed 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 variety of the pedicle signs observed and also the first to identify a relationship between pedicle sign type and prognosis. Further, this study identified methods that can be used for the initial diagnosis of symptomatic spinal metastases, which is currently considered difficult.
In conclusion, there are various types of pedicle signs, such as the complete type, partial type, and blastic type, and it is necessary to understand this to properly diagnose bone metastases. In addition, our findings indicate that the complete type may be associated with a better prognosis than the partial or blastic types.
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Conflict of Interest: None declared.
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**Figure legends**

Figure 1. Radiographic imaging of a complete type of pedicle sign in a 73-year-old woman with the first thoracic vertebral lesion of multiple myeloma. The shadow of the right pedicle on an anteroposterior radiograph has disappeared completely (arrow). The vertebral cortexes at the upper right and lateral sides have also disappeared (arrow heads).

Figure 2. Radiographic image of a partial type of pedicle sign from a 65-year-old woman with the second lumbar vertebral metastasis of lung cancer. The bone cortex of the left pedicle on an anteroposterior radiograph is thinned and partially disappeared (arrow). An asymmetric vertebral body collapse is also associated.

Figure 3. Radiographic image of a blastic type of pedicle sign in a 70-year-old male with 10th thoracic vertebral metastasis of prostate cancer. Bilateral pedicles on an anteroposterior radiograph are obscured due to a remarkable osteoblastic change in the vertebral body (arrow).
Figure 1
Figure 2
Figure 3
### Table 1. Clinical characteristics of patients included in the study.

| 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)          |                |
| Location                       |                  |                  | < 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)          |                |
Table 2. Clinical characteristics of patients with varying types of pedicle signs. (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)|
| Sex                      |              |           |           |
| Male, n (%)              | 13 (50)      | 30 (75)   | 21 (75)   |
| Female, n (%)            | 13 (50)      | 10 (25)   | 7 (25)    |
| Location                 |              |           |           |
| 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 with varying types of pedicle signs. (2)

| Clinical characteristics | Pedicle sign | P value |
|--------------------------|--------------|---------|
|                          | Complete     | Partial | Blastic |
| Previous chemotherapy    |              |         |         |
| No, n (%)                | 17 (65)      | 16 (39) | 7 (25)  |
| Yes, n (%)               | 9 (35)       | 24 (60) | 21 (75) |
| Previous BMA\(^a\) therapy |            |         |         |
| No, n (%)                | 25 (96)      | 39 (98) | 18 (64) |
| Yes, n (%)               | 1 (4)        | 1 (3)   | 10 (37) |
| Local pain and neuropathy|              |         |         |
| 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) |

\(^a\)bone modifying agent
Table 4. Radiological characteristics associated with each type of pedicle sign.

| Radiological characteristics                  | Pedicle sign |       |       |
|-----------------------------------------------|--------------|-------|-------|
|                                               | 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)<sup>a</sup>          |              |       | < 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 the vertebra (MRI)<sup>b</sup>     |              |       | 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)|
| Extra-skeletal extension (MRI)<sup>b</sup>   |              |       | 0.18  |
| Yes, n (%)                                    | 24 (100)     | 31 (94)| 20 (87)|
| No, n (%)                                     | 0 (0)        | 2 (6) | 3 (13)|

<sup>a</sup>CT: n = 26, 38, 26 (complete, partial, blastic), <sup>b</sup>MRI: n = 24, 33, 23 (complete, partial,
blastic, PP: the posterior parts from the pedicle