Metastatic bone tumors: Analysis of factors affecting prognosis and efficacy of CT and ^{18}F-FDG PET-CT in identifying primary lesions

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Abstract. We analyzed the prognostic factors in patients with metastatic bone tumors and evaluated the efficacy of different modalities in identifying the primary lesions. A total of 145 patients with bone metastases who attended the orthopaedic outpatient clinic were included in this study. The most frequent site of bone metastases was the spine. The primary tumor type was differently distributed between patients with a known primary tumor at the first visit and those with an unknown primary lesion. The number of breast cancer cases was statistically significantly lower in the primary-unknown group. However, the number of myeloma cases was significantly higher in the primary-unknown group. Survival was significantly lower in the skeletal-related events (SREs) compared to that in the non-SREs group. Furthermore, survival was significantly worse in patients with a performance status (PS) of ≥2 compared to those with a PS of ≤1 and neurological complications occurred statistically more often in the group with worse PS (≥2). Survival rates were significantly lower in the non-spinal compared to those in the spinal metastatic group. Since the majority of breast cancer patients presented with metastasis in the spine, a breast cancer origin was a positive prognostic factor in patients with spinal metastases. Although there were no significant differences between computed tomography (CT) and ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography (PET)-CT in detecting primary lesions, CT may be the first choice due to its feasibility. In conclusion, lung cancer, SREs and worse PS were adverse prognostic factors for patients with bone metastasis. In addition, CT scans may be more useful for determining the primary lesion of a bone metastasis compared to ^{18}F-FDG PET-CT in a timelier manner.

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Introduction

The recent advances in cancer treatment have improved patient survival. Cancers that have metastasized to the bones are considered to be at an advanced stage. Metastatic bone tumors often promote skeletal-related events (SREs), which include pathological fractures, neurological complications caused by compression of the spinal cord or cauda equina, or hypercalcemia, as well as the need for radiotherapy or surgery of the bone metastasis (1,2). Although the prognosis of patients with certain types of cancer has improved with the recent advances in chemotherapy and radiotherapy, patients with metastatic bone tumors require treatment of the primary lesion as well as anti-SRE assessment, in order to improve their quality of life and prognosis.

Metastatic bone tumors are treated by multidisciplinary teams, in which orthopaedic surgeons play an important role in the diagnosis and treatment of the bone metastasis, as well as in the detection of the primary cancer lesion. A delay in the diagnosis increases the risk of SREs and negatively affects the prognosis. In this regard, we investigated the background of patients with bone metastasis and the factors associated with prognosis. We investigated 145 cases of metastatic bone tumors with respect to the primary lesion, affected bone site and frequency of SREs and evaluated the effectiveness of a single computed tomography (CT) scan of the chest/abdomen/pelvis against that of ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography (PET)-CT scan in detecting the primary lesion of a metastatic bone tumor.

Materials and methods

Patients. In this retrospective study, we reviewed the medical records and imaging results of 145 patients with metastatic bone

tumors who were referred to the Department of Orthopaedic Surgery, Kagoshima University, between 2006 and 2011. The patients included 81 men and 64 women, with a mean age of 65 years (range, 29-87 years) and a mean follow-up of 9 months. A bone scan was performed on 97 patients.

The study protocol was approved by the Ethics Committee on Clinical Research at the Kagoshima University Hospital and all the patients provided written informed consent prior to inclusion.

Evaluation of imaging modalities and patient survival. Two well-trained radiologists reviewed all the bone scan results and compared them with radiographs, CT or magnetic resonance imaging (MRI) scans. The results of the imaging modalities were assessed taking into account clinical symptoms and any positive findings that indicated bone metastasis. To identify the primary lesion, a single chest/abdominal/pelvic CT, ^{18}F-FDG PET-CT and Tl scan were performed on each patient. Following an initial detection of the primary lesion, roentgenogram, MRI, biopsy and formal clinical follow-up were performed to obtain a definitive diagnosis. We examined the frequency of each primary tumor, bone metastatic site and incidence of SREs; we also estimated the survival rate and the detection rate of the original lesion using clinical examinations and evaluated the factors affecting survival. The survival rate was analyzed according to the Kaplan-Meier method. The clinical examinations that were performed to locate the original tumor were also evaluated.

Statistical analysis. Statistical analysis was performed using the Student's t-test or the Chi-square test and analyzed using Microsoft Office Excel software (Microsoft, Redmond, WA, USA). Kaplan-Meier analysis was performed using Kaplan 97 software. $P<0.05$ was considered to indicate statistically significant differences.

Results

Primary lesion and bone metastatic site. We examined the origin of all metastatic bone tumors (145 cases). The most frequent origin of bone metastasis was lung cancer (34 cases, 23%), followed by breast cancer (19 cases, 13%), kidney cancer (10 cases, 7%), liver cancer (10 cases, 7%), thyroid cancer (9 cases, 6%), prostate cancer (9 cases, 6%), colorectal cancer (8 cases, 6%), malignant lymphoma (7 cases, 5%), multiple myeloma (6 cases, 4%), gastric cancer (6 cases, 4%), and bladder cancer (4 cases, 3%) , as previously reported (3-5). The primary tumor could not be identified in 5 cases (3%; Fig. 1A). The Kaplan-Meier analysis demonstrated that the 1-, 2- and 3-year survival rate was 49, 34 and 18%, respectively, among all patients with bone metastasis (Fig. 2).

The most frequent bone metastatic site was the spine (143 cases), including the cervical vertebrae (28 sites), thoracic vertebrae (45 sites), lumbar vertebrae (53 sites) and sacrum (17 sites). Other sites of metastasis included the femur (28 cases), pelvis (27 cases), humerus (16 cases) and ribs (15 cases) (Fig. 1B). Our findings revealed that the most frequent spinal metastatic site was the lumbar spine, followed by the thoracic and cervical spine. It was previously reported that the most frequent metastatic site was the thoracic spine, followed by the lumbar and cervical spine (6-9). To explain this discrepancy, we compared the primary malignant tumor between the lumbar and thoracic metastatic groups. We identified no statistically significant difference in the primary lesion between these two groups.

The primary tumor site distribution was compared between patients with a known primary lesion and those with unknown primary lesion at the first visit. In the primary-known group (n=84), the primary tumors were breast (18 cases, 21%), lung (11 cases, 13%), liver (9 cases, 11%), thyroid (7 cases, 8%) and kidney cancer (6 cases, 7%). In the primary-unknown group (n=61), the primary tumors were lung cancer (23 cases, 38%), myeloma (5 cases, 8%), kidney and prostate cancer and malignant lymphoma (4 cases each, 7%) (Table I). During the follow-up period, the primary lesion was not identified in 5 cases. The number of breast cancer cases was statistically significantly lower in the primary-unknown group. However, the number of myeloma was significantly higher in the primary-unknown group.

Factors affecting the prognosis of bone metastasis. We first investigated the association between prognosis and SREs and observed that survival was significantly lower in the SREs compared to that in the non-SREs group (Fig. 3A). In addition, PS was found to be an important factor for the selection of the appropriate chemotherapeutic regimen and, therefore, we investigated the association between patient prognosis and PS (10,11) and survival was found to be significantly lower in the PS≥2 compared to that in the PS≤1 group (Fig. 3B). Since the most frequent bone metastatic site was the spine, we investigated the association between spinal metastasis and patient prognosis. The Kaplan-Meier analysis revealed that the 1- and 3-year survival rates for patients with spinal metastases was 56 and 23%, respectively. Furthermore, the 1- and 3-year survival rates for patients with non-spinal metastases were 37 and 8%, respectively. Therefore, survival rates were significantly lower in the non-spinal compared to those in the spinal metastatic group (Fig. 3C). To determine which factors were associated with a favorable prognosis in patients with spinal metastasis, we investigated the association between prognosis and neurological complications caused by compression of the spinal cord or cauda equina. The Kaplan-Meier analysis revealed that neurological complications did not exert a significant effect on survival for any of the patients with bone metastasis (Fig. 3D). We next investigated the primary lesion in the non-spinal and spinal metastatic groups and found that the number of breast cancer patients was higher in the spinal metastatic group (Table II).

Association between SREs and prognosis or PS. We demonstrated that the survival rate was significantly lower in the PS≥2 compared to that in the PS≤1 group (Fig. 3B). We investigated the association between SREs and PS. The incidence of SREs among all the bone metastatic cases was 107 (74%). Hypercalcemia (serum calcium levels, 10.4-12.6 mg/dl; normal range, 8.5-10.3 mg/dl) occurred in 8 cases (5.5%) and was accompanied by renal dysfunction in 4 of the 8 cases (Table IIIA). Symptoms caused by compression of the spinal cord or cauda equina were observed in 36 cases (24.8%), including symptoms of the cervical (11 cases), thoracic (15 cases) and lumbar segments (10 cases) (Table IIIA and B).

Table I. Comparison of the primary tumor site between groups with known and unknown origin at initial visit.

Origin known at initial visit	Cases (%)	Origin unknown → diagnosed	Cases (%)
Breast	18[a] (21)	Lung	23 (38)
Lung	11 (13)	Myeloma	5[b] (8)
Liver	9 (11)	Kidney	4 (7)
Thyroid	7 (8)	Prostate	4 (7)
Kidney	6 (7)	Lymphoma	4 (7)
Prostate	5 (6)	Gastric	3 (5)
Colorectal	5 (6)	Colorectal	3 (5)
Lymphoma	3 (4)	Thyroid	2 (3)
Esophagus	3 (4)	Pancreas	2 (3)
Gastric	3 (4)	Bladder	2 (3)
Uterus	3 (4)	Breast	1[a] (2)
Tongue	2 (2)	Others	8 (12)
Bladder	2 (2)		
Myeloma	1[b] (1)		
Others	6 (7)		
Total	84 (100)	Total	61 (100)

[a]P<0.01, [b]P<0.05.

Table II. Comparison of the primary tumor site between groups with and without spinal metastasis.

Spinal metastasis (+)	Cases	Spinal metastasis (-)	Cases
Lung	22	Lung	12
Breast	17[a]	Kidney	5
Liver	8	Thyroid	4
Prostate	7	Liver	4
Colorectal	6	Bladder	4
Thyroid	5	Lymphoma	3
Kidney	5	Esophagus	2
Myeloma	5	Gastric	2
Gastric	4	Breast	2[a]
Lymphoma	4	Prostate	2
Pancreas	3	Colorectal	2
Tongue	2	Others	4
Others	11		
Total	99	Total	46

[a]P<0.05.

Pathological fractures were detected in 23 cases (15.9%), including fractures of the extremities (femur, 9 cases; and humerus, 5 cases); thoracic vertebrae, 3 cases; and lumbar vertebrae, 2 cases (Table IIIC). Surgery for SREs was performed in 26 cases (18%), including internal fixation (10 cases), resection plus reconstruction (9 cases), spinal decompression (2 cases), spinal fusion (4 cases) and total en bloc spondylectomy (1 case)

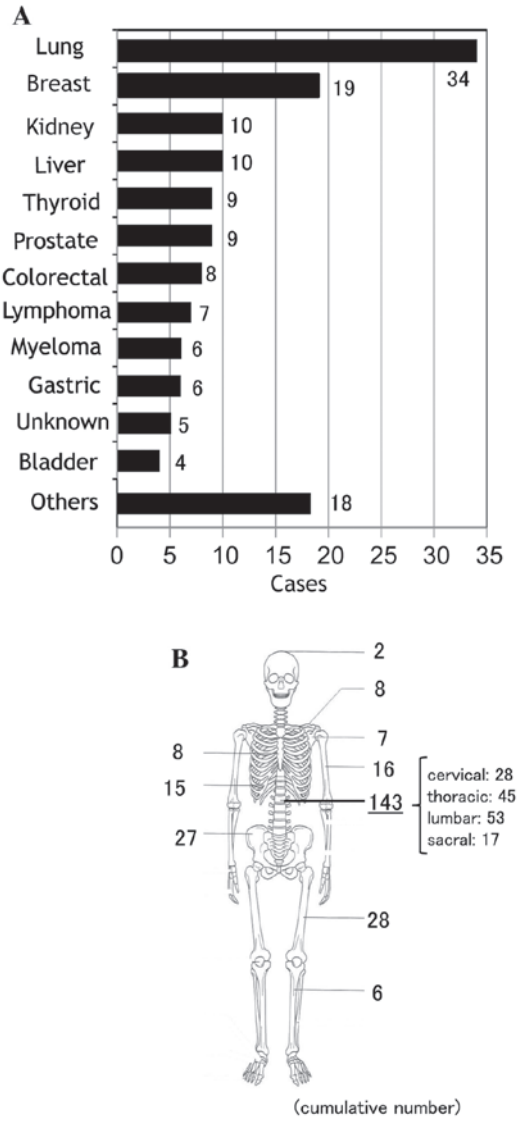

Figure 1. Number of bone metastases. (A) Number of cases with bone metastases per primary lesion. (B) Number of patients per bone metastatic site.

(Table IIID). Radiotherapy for bone metastasis was performed in 75 cases (51.7%).

In the group with better PS scores (≤1, n=32), pathological fractures were detected in 3 cases (9.4%), neurological complications were observed in 3 cases (9.4%), hypercalcemia occurred in 2 cases (6.3%), surgery for SREs was performed in 4 cases (12.5%) and radiotherapy was performed in 14 cases (43.8%). In the group with poor PS scores (≥2, n=113), pathological fractures were detected in 20 cases (17.7%), neurological complications caused by compression of the spinal cord or cauda equina were observed in 33 cases (29.2%), hypercalcemia occurred in 6 cases (5.3%), surgery for SREs was performed in 24 cases (21.2%) and radiotherapy was performed in 70 cases (61.9%). Among the 5 SREs, only neurological complications were found to be significantly increased in the group with a PS score of ≥2 compared to that with a PS score of ≤1 (Table IIIE).

Identification of the primary lesion using imaging studies. The primary tumor site was identified using diagnostic imaging in

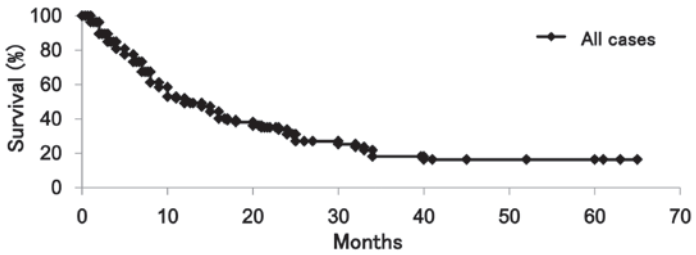

Figure 2. Overall survival rate. The Kaplan-Meier analysis revealed that the 1-, 2- and 3-year survival rates were 49, 34 and 18%, respectively, among all patients with bone metastasis.

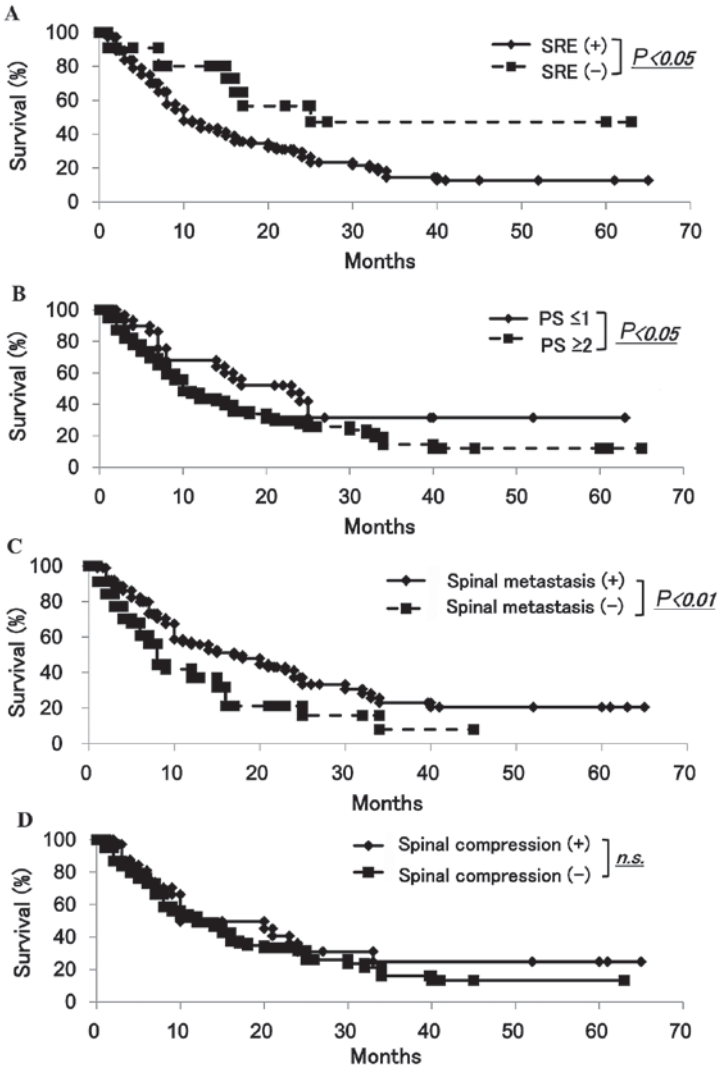

Figure 3. Comparison of survival rates. The Kaplan-Meier analysis revealed that (A) survival was significantly lower in the skeletal-related events (SREs) compared to that in the non-SREs group; (B) survival was significantly lower in the performance status (PS)≥2 compared to that in the PS≤1 group; (C) survival rates were significantly lower in the non-spinal compared to those in the spinal metastatic group; and (D) neurological complications did not exert a significant effect on survival for any bone metastatic patients; n.s., not signifigant.

49 cases, which included CT (32 cases) and ^{18}F-FDG PET-CT (17 cases) (Table IVA). Whole-body bone scans and Tl scans could not identify the primary lesion. CT was performed on 55 patients (90%) in whom the primary tumor was not identified during the first visit to the hospital. The time interval from the first visit until the CT scan was performed was 3.6 days. ^{18}F-FDG PET-CT was performed on 39 patients (64%) with unidentified primary tumors. The time interval from the first visit until the ^{18}F-FDG PET-CT was performed was 7.2 days. CT scans helped identify the following primary cancers: lung (16 cases), kidney (3 cases), thyroid (2 cases), pancreatic (2 cases) and bladder cancer (2 cases), myeloma (2 cases) and others (5 cases). ^{18}F-FDG PET-CT scans identified the following primary cancers: lung (6 cases), prostate (4 cases),

Table III. Analysis of SREs.

A, Number of cases per SRE

Cases	Fracture	Hyper-calcemia	Spinal compression	Radiation therapy for bone metastasis	Surgery for bone metastasis	Total cases with SREs
No. (%)	23 (15.9)	8 (5.5)	36 (24.8)	75 (51.7)	26 (17.9)	107 (73.8)

B, Distribution of spinal metastases in patients with symptoms caused by compression of spinal cord or cauda equina

Cases	Cervical spine	Thoracic spine	Lumbar spine	Total
No. (%)	11 (30.5)	15 (41.7)	10 (27.8)	36 (100)

C, Pathological fractures

Cases	Femur	Humerus	Thoracic spine	Lumbar spine	Others	Total
No. (%)	9 (39.1)	5 (21.7)	3 (13.0)	2 (8.7)	4 (17.5)	23 (100)

D, Type of surgery for pathological fractures

Cases	Resection plus reconstruction	Internal fixation	Spinal fusion	Spinal decompression	Total en bloc spondylectomy	Total
No. (%)	9 (34.6)	10 (38.5)	4 (15.4)	2 (7.7)	1 (3.8)	26 (100)

E, Incidence of SREs in groups with better (≤1) and worse (≥2) PS

Cases, no. (%)	Fracture	Hypercalcemia	Spinal compression	Radiation therapy for bone metastasis	Surgery for bone metastasis
PS≤1 (n=32)	3 (9.4)	2 (6.3)	3 (9.4)[a]	14 (43.8)	4 (12.5)
PS≥2 (n=113)	20 (17.7)	6 (5.3)	33 (29.2)[a]	70 (61.9)	24 (21.2)

SRE, skeletal-related event; PS, performance status. [a]$P<0.05$.

colorectum (2 cases) and others (5 cases) (Table IVB). A CT scan alone was able to identify primary tumors of the bladder (2 cases), myeloma (2 cases) and thyroid cancer (1 case) that could not be identified using ^{18}F-FDG PET-CT imaging. However, a ^{18}F-FDG PET-CT scan alone was able to identify primary lung cancer (1 case), myeloma (1 case) and colorectal cancer (1 case) (Table IVB). Although there were no significant differences between CT and ^{18}F-FDG PET-CT scans in the detection of primary lesions, CT scans were found to be more useful in determining the primary lesion of a bone metastasis in a timelier manner.

Discussion

Over the last few years, the number of cancer patients has increased. The majority of patients who are diagnosed with bone metastasis are referred to an orthopaedic surgeon to evaluate the bone metastasis and its progression, locate the primary lesion and decide upon treatment options.

We demonstrated that metastasis to the spine was the most frequent, followed by the femur and pelvic bone, as previously reported (6). Of the total bone metastases, the ratio of spinal metastasis was 54.7% (141/258 lesions). Our findings revealed that the number of bone metastases to the spine was lower compared to what was previously reported; in addition, the incidence of lumbar metastasis was relatively high compared to previous reports (6-9,12). Overall survival depends mainly on the type of the primary tumor. We did not identify a statistically significant difference regarding the type of primary tumor between the lumbar and thoracic metastatic groups. The relatively low number of spinal metastases may be the cause of this discrepancy. However, further studies are required to elucidate this issue.

It has been reported that the median overall survival of patients with spinal metastases is 7 months. In addition, only 10-20% of patients with spinal metastases remained alive at 2 years after diagnosis (12). We found that the 1-year survival rate was 49% and the 3-year survival rate was 18% among

Table IV. Comparison of imaging modalities for the identification of the primary lesion in patients with bone metastasis.

A, Time interval for detection of the primary lesion with different imaging modalities

Imaging modality	Detection of primary lesion/total number of patients	Interval between first visit and examination (days)
CT scan	32/55	3.6
PET-CT	17/39	7.2
Bone scan	0/43	6.3
Tl scan	0/13	5.5

B, Number of cases with different primary lesions detected with CT or PET-CT

	Method of identification of primary lesion			
Primary lesion	CT	PET	CT alone	PET alone
Lung	16	6	0	1
Kidney	3	1	0	0
Thyroid	2	0	1	0
Bladder	2	0	2	0
Pancreas	2	0	0	0
Myeloma	2	1	2	1
Gastric	1	1	0	0
Liver	1	1	0	0
Colorectal	1	2	0	1
Lymphoma	1	0	0	0
GIST	1	0	0	0
Prostate	0	4	0	0
Breast	0	1	0	0
Total	32	17	5	3

PET-CT, positron emission tomography-computed tomography.

all patients with bone metastasis. Our results indicated a relatively good prognosis compared to those of a previous study (12). In addition, the survival rates were significantly lower in patients in the non-spinal compared with those in the spinal metastatic group, which included all the patients with bone metastasis. Furthermore, our findings revealed that the number of breast cancer patients was higher in the spinal compared to that in the non-spinal metastatic group. Survival was significantly increased in breast cancer patients with bone metastasis compared to those with other primary lesions with bone metastasis (data not shown). These findings suggest that differences in the origin of the cancer may affect prognosis, depending on whether bone metastasis occurs in the spine or elsewhere.

We demonstrated that SREs exert a significant negative effect on survival. Although neurological complications did not appear to exert a statistically significant effect on survival in patients with spinal metastasis, the number of patients with neurological complications was statistically different between the PS≤1 and PS≥2 groups. These findings suggest that the incidence of neurological complications was increased in the group with PS≥2 and negatively affected survival. In addition, Katagiri *et al* (11) reported that PS scores of 3 or 4 were a significant poor prognostic factor. Our findings suggest that a PS score of 2 may also exert a negative effect on prognosis in patients with bone metastasis.

We observed that the primary lesion distribution differed depending on whether the primary tumor was known or unknown at the initial visit. In the primary-known group, the most frequent primary cancer was breast cancer, followed by lung, liver and thyroid cancer. Our findings suggest the significance of the follow-up of cancer patients with bone metastasis. In the primary-unknown group, the most frequent primary cancer was lung cancer, followed by myeloma, kidney and prostate cancer. Consistent with our results, Iizuka *et al* (4) reported that myeloma was the most common primary malignancy in cases with spinal metastasis of unknown origin, followed by lung and prostate cancer. Destombe *et al* (3) reported that the most frequent primary cancer was lung, followed by breast cancer. These findings suggest that, when evaluating bone metastatic patients with unknown primary tumors, clinical examinations should be performed taking into consideration the possibility of diagnosing these primary cancers. During the follow-up period, the primary lesion was not identified in 5 cases. It was reported that lung and pancreatic cancer were the most frequent primary lesions in autopsy studies (13,14). Our findings demonstrated that pancreatic cancer was diagnosed as the primary lesion in only 2 cases (3%) in the primary-unknown group. These findings suggest that more detailed examinations, including magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography, may be required for bone metastatic patients in whom the primary lesion was not identified.

Although biopsy of the most accessible osseous lesion was routine during the examination, the proportion of an accurate final diagnosis in solid and hematopoietic tumors was low (4,5,15). In addition, biopsy requires invasive procedures. ^{18}F-FDG PET-CT whole-body imaging is non-invasive and highly sensitive. It has been reported that ^{18}F-FDG PET-CT should be used as a first-line imaging examination for patients with a primary carcinoma of unknown origin, rather than after other diagnostic procedures have failed to identify the primary lesion (16). Although ^{18}F-FDG PET-CT is useful in helping physicians locate the primary lesion, patients were required to wait an average of 7.2 days for an ^{18}F-FDG PET-CT examination, due to the long waiting list. We demonstrated that CT scans helped identify 32 of the 55 (58%) primary lesions within 3.6 days from the time of the patient's first visit. Therefore, a CT scan is a rapid examination, valuable for the identification of the primary lesion of a bone metastasis. In addition, we did not observe a statistically significant difference in utility between CT and ^{18}F-FDG PET-CT in establishing the origin of a bone metastasis. Our findings suggest that a CT scan should be performed prior to an ^{18}F-FDG PET-CT scan, particularly if the latter requires a waiting period of several days.

To improve the prognosis of patients with metastatic bone tumors, a team approach is required, comprising an orthopaedic surgeon along with a specialist to manage

treatment of the primary tumor, a radiologist, rehabilitation staff and a palliative care team (17). Collaboration is essential to developing a treatment strategy that may be tailored to the individual patient (18). In this regard, our department has established a bone metastasis registration system that encompasses all specialties in our hospital and is accessible to each specialty.

In conclusion, our findings demonstrated that several factors may be related to patient prognosis and the effectiveness of CT; these factors may prove useful in determining the origin of the primary lesion. Further examination of prognostic factors and advancements in diagnostic imaging may improve the treatment of patients with bone metastasis.

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