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Comparison of ^{18}FDG-PET with ^{99m}Tc-HMDP scintigraphy for the detection of bone metastases in patients with breast cancer

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Objective: Bone is one of the most common sites of metastasis in breast cancer patients. Although bone scintigraphy is widely used to detect metastatic breast cancer, the usefulness of ^{18}FDG-PET for detecting bone metastasis has not been clearly evaluated. The purpose of this study was to compare the diagnostic accuracy of ^{18}FDG-PET with bone scintigraphy in detecting bone metastasis in breast cancer patients. ***Methods:*** Forty-four women aged 35 to 81 years (mean, 56 years) with breast cancer were examined in this study. Both ^{18}FDG-PET and bone scintigraphy were performed for each patient with 0–69 day intervals (mean, 11.5 days). The results of each image interpretation were compared retrospectively. Whole-body bones were classified into 9 anatomical regions. Metastases were confirmed at 45/187 regions in 14 patients by bone biopsy or clinical follow-up including other imaging techniques for a period of at least 6 months afterwards. ***Results:*** On a region basis, the sensitivity, specificity, and accuracy of ^{18}FDG-PET were 84%, 99% and 95%, respectively. Although these results were comparable to those of bone scintigraphy, the combination of ^{18}FDG-PET and bone scintigraphy improved the sensitivity (98%) and accuracy (97%) of detection. False negative lesions of bone scintigraphy were mostly bone marrow metastases and those of ^{18}FDG-PET were mostly osteoblastic metastases. ^{18}FDG-PET was superior to bone scintigraphy in the detection of osteolytic lesions (92% vs. 73%), but inferior in the detection of osteoblastic lesions (74% vs. 95%). ***Conclusions:*** This study shows that ^{18}FDG-PET tends to be superior to bone scintigraphy in the detection of osteolytic lesions, but inferior in the detection of osteoblastic lesions. ^{18}FDG-PET should play a complementary role in detecting bone metastasis with bone scintigraphy.

Key words: ^{18}FDG-PET, bone scintigraphy, bone metastasis, breast cancer

INTRODUCTION

BREAST CANCER is the most common malignant tumor found in women in Western countries. In Japan, the incidence of breast cancer has been increasing, and it has been the leading cancer site in women since 1995.[1] Bone is one of the most common sites of metastasis in breast cancer patients. Complications such as pathologic fractures, nerve root compression, and myelosuppression greatly impact the patients' quality of life. Detection of metastatic bone lesions is important not only for predicting patients' prognosis, but also for determining the proper therapeutic protocol.

For the detection and evaluation of bone metastasis, ^{99m}Tc labeled phosphate compound bone scintigraphy has been widely accepted because of its high sensitivity and easy evaluation of the whole skeletal system. Although the advantage of bone scintigraphy in bone metastasis has been well documented,[2] benign processes, including degenerative and inflammatory bone disease, can confuse the diagnosis. A recent study demonstrated that whole-body spin-echo magnetic resonance imaging (MRI) was superior to bone scintigraphy for the detection of bone metastasis.[3] However, this technique is not yet

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clinically applicable.

Positron emission tomography (PET) using 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}FDG-PET) is known to be a powerful tool for the detection of metastatic or recurrent lesions in various malignant tumors.[4–8] Several studies have demonstrated that ^{18}FDG-PET is also useful for the detection of bone metastasis.[9–11] Because of higher spatial resolution and because this technique uses a different mechanism to detect metastatic lesions, ^{18}FDG-PET may be able to replace conventional bone scintigraphy in the evaluation of bone metastasis. However, its usefulness in the detection of bone metastasis is still controversial. Sherve et al. reported that ^{18}FDG-PET is less sensitive than bone scintigraphy in the identification of osseous metastases in the analysis of prostate cancer patients.[12] Hoegerle et al. indicated the difficulty of ^{18}FDG-PET for the anatomic localization of cancer lesions.[13]

In this study, we examined retrospectively how well ^{18}FDG-PET could detect bone metastasis in breast cancer patients compared with ^{99m}Tc-hydroxymethylene diphosphonate (HMDP) bone scintigraphy. We further analyzed the two detection methods by focusing on the character of metastatic bone lesions, such as osteolytic and osteoblastic.

MATERIALS AND METHODS

Patients

Forty-four women with breast cancer were examined in this study. The patients' age ranged from 35 to 81 (mean, 56 ± 12) years. The clinical stages based on the TNM status of the patients were as follows: stage I, 16: stage IIA, 12: stage IIB, 2: stage IIIA, 3: stage IV, 4: unknown, 7. Both ^{18}FDG-PET and ^{99m}Tc-HMDP bone scintigraphy were performed for each patient with a 0–69 (mean, 11.5 ± 16.7) day intervals. None of these patients had received radiotherapy at the site of bone lesions or aggressive chemotherapy other than hormone manipulation therapy before the examinations. The final diagnoses of bone metastases were confirmed by biopsy and follow-up studies using other imaging techniques, including computed tomography (CT), MRI, and plain film radiography. All patients underwent follow-up exams for at least 6 months after the ^{18}FDG-PET and bone scintigraphy had been performed.

This study was approved by the Committee for the Clinical Application of Cyclotron-Produced Radionuclides at Kyushu University Hospital.

^{18}FDG-PET

The ^{18}FDG-PET studies were performed with an ECAT EXACT HR^{+} (SIEMENS, Knoxville, TN, USA). Intrinsic resolution was 4.6 mm full-width at half-maximum at the center. The data acquisition was initiated 60 min after the intravenous administration of 101.0–434.4 (mean, 219.2 ± 55.5) MBq ^{18}FDG. Emission scans were obtained in a 3-dimensional (3D) mode from head to thigh with 9 bed positions. The acquisition time was 2 min for each bed position. Transmission scans were obtained in a 2-dimensional (2D) mode using a ^{68}Ga/^{68}Ge rod source after the emission scan. The acquisition time was 2 min for each bed position. Attenuation-corrected images were reconstructed with an ordered-subset expectation maximization (OSEM) algorithm (2 iterations with 16 ordered subsets) using the segmented attenuation correction method. All patients fasted for at least 4 hrs before the examination, and their blood glucose level was 86.5–134.5 (mean, 104.0 ± 9.9) mg/dl.

Table 1 Detection of bone metastasis with ^{99m}Tc-HMDP bone scintigraphy and ^{18}FDG-PET on a patient basis

	^{99m}Tc-HMDP	^{18}FDG-PET	^{99m}Tc-HMDP + ^{18}FDG-PET
Sensitivity	78.6% (11/14)	100% (14/14)	100% (14/14)
Specificity	100% (30/30)	96.7% (29/30)	96.7% (29/30)
Accuracy	93.2% (41/44)	97.7% (43/44)	97.7% (43/44)

( ): Number of patients

Table 2 Detection of bone metastasis with ^{99m}Tc-HMDP bone scintigraphy and ^{18}FDG-PET on a region basis

	^{99m}Tc-HMDP	^{18}FDG-PET	^{99m}Tc-HMDP + ^{18}FDG-PET
Sensitivity	80.0% (36/45)	84.4% (38/45)	97.7% (44/45)*
Specificity	98.6% (140/142)	98.6% (140/142)	97.2% (138/142)
Accuracy	94.1% (176/187)	95.2% (178/187)	97.3% (182/187)**

( ): Number of regions

* significant difference compared with both ^{99m}Tc-HMDP ($p < 0.02$) and ^{18}FDG-PET ($p < 0.05$)

** significant difference compared with both ^{99m}Tc-HMDP ($p < 0.01$) and ^{18}FDG-PET ($p < 0.02$)

Table 3 Detection of bone metastasis with ^{99m}Tc-HMDP bone scintigraphy and ^{18}FDG-PET concerning metastatic sites

region	sensitivity (%)	
	^{99m}Tc-HMDP	^{18}FDG-PET
skull	100 (3/3)	66.7 (2/3)
C-spine	60.0 (3/5)	60.0 (3/5)
T-spine	75.0 (6/8)	87.5 (7/8)
L-spine	71.4 (5/7)	85.7 (6/7)
ribs	83.3 (5/6)	100 (6/6)
sternum	100 (5/5)	80.0 (4/5)
pelvic bones	80.0 (4/5)	80.0 (4/5)
upper limbs	100 (2/2)	100 (2/2)
lower limbs	75.0 (3/4)	100 (4/4)
total	80.0 (36/45)	84.4 (38/45)

( ): Number of regions with positive bone metastases

^{99m}Tc-HMDP bone scintigraphy

^{99m}Tc-HMDP bone scintigraphy was performed 4 hrs after the intravenous injection of 740 MBq ^{99m}Tc-HMDP. Both anterior and posterior whole body planar images were simultaneously obtained with a dual-headed gamma camera (GCA-901A/WB, TOSHIBA, Tokyo, Japan; E.CAM, SIEMENS, Hoffman Estates, IL, USA). No single photon emission computed tomography (SPECT) studies were performed.

Data analysis

The ^{18}FDG-PET and ^{99m}Tc-HMDP bone scintigraphy findings were retrospectively evaluated by three nuclear medicine physicians. The evaluation was conducted visually and without any clinical information. Whole-body bones were classified into the following 9 anatomical regions: skull, C-spine, T-spine, L-spine, ribs, sternum, pelvic bones, upper limbs, including scapulas and clavicles, and lower limbs. When metastasis was found in at least one part of a region, the region was interpreted as positive. When metastasis was positive on either ^{99m}Tc-HMDP or ^{18}FDG-PET, it was also counted as positive for bone metastasis on combined ^{99m}Tc-HMDP and ^{18}FDG-PET (^{99m}Tc-HMDP + ^{18}FDG-PET). Furthermore, the positive region was categorized into either osteoblastic or osteolytic metastasis depending on the dominant change found within the region. Two diagnostic radiologists visually evaluated the character of the metastatic lesions by reading the CT scans or plain film radiographs.

Statistical analysis was performed using McNemar's test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Bone metastasis was ultimately found in 14 patients (31.8%). Bone metastases were confirmed by biopsy (2

Table 4 False positive and negative lesions in ^{99m}Tc-HMDP bone scintigraphy and ^{18}FDG-PET

	^{99m}Tc-HMDP	^{18}FDG-PET
False positive	· degenerative change (1) · suture (1)	· inflammation (2)
False negative	· diffuse bone marrow metastasis (6) · osteolytic metastasis (2) · regarded as degenerative change (1)	· osteoblastic metastasis (5) · adjacent to brain (1) · unknown (1)

( ): Number of regions

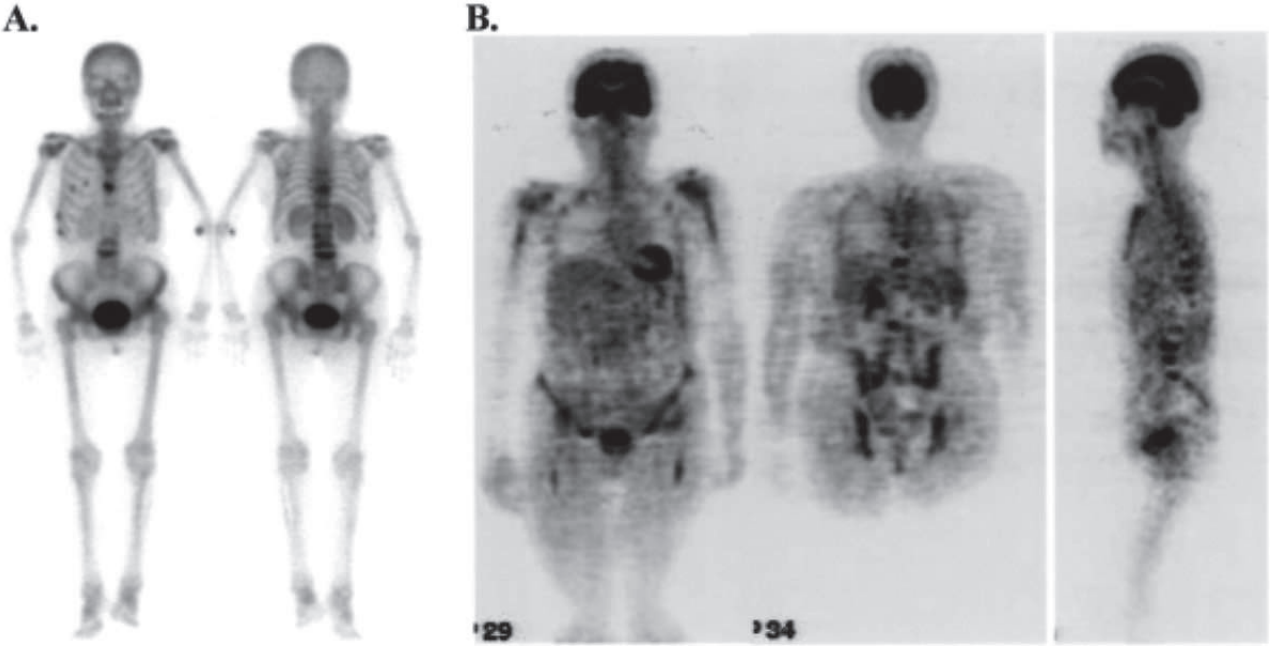

Fig. 1 A 63-year-old woman (stage IV). (A) ^{99m}Tc-HMDP bone scintigraphy showed increased accumulations in the sternum, bil. ribs, T- and L-spines, and lt. hip joint. Metastasis was suspected only at the sternum. The other accumulations were considered to be fractures, degenerative changes, and arthritis. (B) ^{18}FDG-PET demonstrated diffuse high uptakes in the whole skeletal system, suggesting diffuse bone marrow metastasis. The diagnosis was confirmed by bone marrow biopsy.

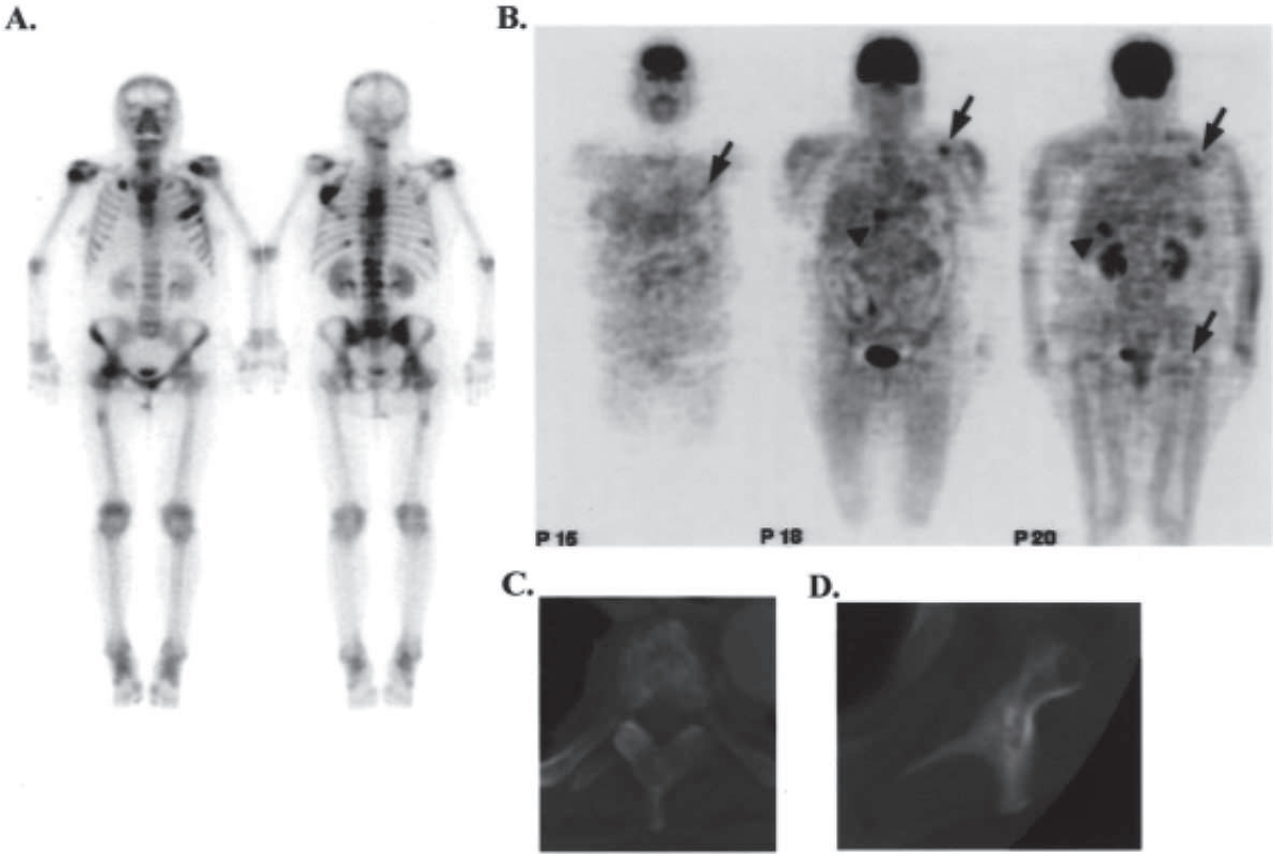

Fig. 2 A 49-year-old woman (stage IV). (A) Multiple abnormal accumulations of ^{99m}Tc-HMDP were observed, suggesting multiple bone metastases. (B) However, ^{18}FDG-PET demonstrated high uptakes only at the lt. rib, lt. scapula, and lt. femur (*arrows*). ^{18}FDG accumulations of liver metastases were also observed (*arrowheads*). CT scans demonstrated osteoblastic metastases in the T-spine (C), lt. scapula (D), and multiple other sites.

patients), CT (5 patients), and MRI (7 patients). The sensitivity, specificity, and accuracy of ^{99m}Tc-HMDP and ^{18}FDG-PET on a patient basis are shown in Table 1. Although the sensitivity of ^{18}FDG-PET was superior to that of ^{99m}Tc-HMDP bone scintigraphy (100% vs. 78.6%), no statistically significant difference was found between these two techniques. The sensitivity, specificity, and accuracy of the combined ^{99m}Tc-HMDP + ^{18}FDG-PET were 100%, 96.7%, and 97.7%, respectively. Again, there was no significant difference between ^{99m}Tc-HMDP + ^{18}FDG-PET and ^{99m}Tc-HMDP or ^{18}FDG-PET on a patient basis.

Follow-up examinations including CT, MRI, and plain film radiography were performed, and 187 regions were finally able to be identified as either positive or negative for bone metastasis. On a region basis, 45 of 187 regions (24.1%) were positive for bone metastasis in 14 patients. Table 2 shows the sensitivity, specificity, and accuracy of ^{99m}Tc-HMDP, ^{18}FDG-PET, and combined ^{99m}Tc-HMDP + ^{18}FDG-PET on a region basis. No significant difference was found between ^{99m}Tc-HMDP and ^{18}FDG-PET. However, the sensitivity and accuracy of ^{99m}Tc-HMDP + ^{18}FDG-PET were significantly higher than those of ^{99m}Tc-HMDP or ^{18}FDG-PET alone on McNemar's test.

Metastatic lesions were classified in terms of their localization, as summarized in Table 3. The sensitivities of ^{99m}Tc-HMDP and ^{18}FDG-PET were compared for each region, but no significant difference was found between the techniques.

Two false positive (2 patients) and nine false negative lesions (2 patients) were found in ^{99m}Tc-HMDP bone scintigraphy. ^{99m}Tc-HMDP bone scintigraphy tended to miss diffuse bone marrow metastasis and osteolytic metastatic lesions (Table 4). Figure 1 shows one of the patients who had diffuse bone marrow metastasis. ^{99m}Tc-HMDP bone scintigraphy showed increased accumulations in the sternum, bilateral ribs, T- and L-spines and lt. hip joint. Metastasis was suspected only at the sternum, and the other accumulations were considered to be benign fractures, degenerative changes, and arthritis (Fig. 1A). ^{18}FDG-PET demonstrated diffuse high uptakes in the whole skeletal system, suggesting diffuse bone marrow metastasis (Fig. 1B). The diagnosis was confirmed by bone marrow biopsy.

Table 5 Detection of osteoblastic and osteolytic bone metastasis with ^{99m}Tc-HMDP bone scintigraphy and ^{18}FDG-PET

	sensitivity (%)		
	^{99m}Tc-HMDP	^{18}FDG-PET	^{99m}Tc-HMDP + ^{18}FDG-PET
osteoblastic	94.7% (17/19)	73.7% (14/19)	94.7% (17/19)
osteolytic	73.1% (19/26)	92.3% (24/26)	100% (26/26)*

( ): Number of regions

* significant difference compared with ^{99m}Tc-HMDP ($p < 0.05$)

^{18}FDG-PET had two false positive (2 patients) and seven false negative lesions (2 patients). The osteoblastic lesions tended to be hard to detect by ^{18}FDG-PET. Figure 2 shows one of the cases that had osteoblastic metastases. ^{18}FDG-PET demonstrated high uptakes only at the left rib, part of the left scapula, and left femur (Fig. 2B). However, ^{99m}Tc-HMDP bone scintigraphy showed abnormal uptakes in multiple regions, most of which were not detected by ^{18}FDG-PET (Fig. 2A). CT scans demonstrated osteoblastic metastases in the T-spine (Fig. 2C), lt. scapula (Fig. 2D), and other sites.

In all 45 regions that were diagnosed as positive for bone metastasis, 19 regions contained osteoblastic and 26 regions contained osteolytic bone metastases. The sensitivities of the ^{99m}Tc-HMDP, ^{18}FDG-PET, and ^{99m}Tc-HMDP + ^{18}FDG-PET are shown in Table 5. Although a statistically significant difference was found only between ^{99m}Tc-HMDP and ^{99m}Tc-HMDP + ^{18}FDG-PET in detecting osteolytic metastases, ^{18}FDG-PET tended to be superior to ^{99m}Tc-HMDP bone scintigraphy in detecting osteolytic lesions, but inferior in detecting osteoblastic lesions. The combined ^{99m}Tc-HMDP + ^{18}FDG-PET markedly improved the sensitivities.

DISCUSSION

In the present study, we compared the diagnostic accuracy of ^{18}FDG-PET with that of ^{99m}Tc-HMDP bone scintigraphy in detecting bone metastasis in breast cancer patients. On a patient basis, the sensitivity, specificity, and accuracy of ^{18}FDG-PET in the detection of bone metastasis were similar to those of ^{99m}Tc-HMDP bone scintigraphy, with no significant difference between them (Table 1). Ohta et al. demonstrated that ^{18}FDG-PET was superior to bone scintigraphy in the detection of bone metastasis because of its higher specificity and accuracy.[10] They speculated that ^{18}FDG-PET could detect even early-stage bone metastasis. However, Dose et al. and Kao et al. reported that ^{18}FDG-PET showed either the same or lower sensitivity or specificity in comparison with bone scintigraphy.[14,15] Kao et al. indicated the possibility that some metastatic lesions were not glycolytically active.[15] Although controversy still exists, our data indicate that ^{18}FDG-PET has the same magnitude of sensitivity, specificity, and accuracy for the detection of bone metastasis when compared with bone scintigraphy on a patient basis.

Several papers have focused on the location of bone metastasis in analyzing the ability of ^{18}FDG-PET to detect it. Ohta et al. reported that false negative findings on ^{18}FDG-PET were found mainly in the lumbar spine, scapula, and sacrum. However, no analysis on the relationship between metastatic sites and false negative findings on ^{18}FDG-PET was conducted in that study.[10] Minn et al. commented that abnormal ^{18}FDG uptake was well visualized in the hips, pubic bone, and sacroiliac joints, and less clearly in the vertebral region.[16] In our study, ^{18}FDG accumulation in the skull bone metastasis was less visualized than it was with ^{99m}Tc-HMDP bone scintigraphy, probably due to the high uptake of ^{18}FDG in the adjacent brain tissue. For other regions, we found no significant difference in detectability between ^{18}FDG-PET and ^{99m}Tc-HMDP bone scintigraphy (Table 3). However, further accumulation of data is needed.

On a region basis, the sensitivity, specificity, and accuracy of ^{18}FDG-PET for the detection of bone metastasis were comparable to those of ^{99m}Tc-HMDP bone scintigraphy. However, the combination of ^{18}FDG-PET + ^{99m}Tc-HMDP improved the sensitivity and accuracy (Table 2). False negative lesions found by ^{18}FDG-PET were mostly osteoblastic metastases, while those found by ^{99m}Tc-HMDP bone scintigraphy were mostly bone marrow metastases and osteolytic lesions (Table 4). Cook et al. analyzed 16 breast cancer patients and compared ^{18}FDG-PET with bone scintigraphy in the detection of bone metastasis.[17] They demonstrated that ^{18}FDG-PET detected fewer lesions than bone scans in a subgroup with osteoblastic metastasis when compared to a subgroup with osteolytic metastasis. They also pointed out that the survival rate of the patients with osteolytic disease was lower as compared to those with osteoblastic metastases, suggesting that osteolytic metastases had a higher metabolic activity than osteoblastic lesions. Minn et al. reported that 8 of 9 patients showed increased uptake of both ^{18}FDG and ^{99m}Tc-DPD in the metastatic sites, and all of the ^{18}FDG positive bone metastases were radiographically osteolytic or mixed types.[16] Some lesions remained ^{18}FDG negative. They concluded that ^{99m}Tc-DPD was

superior in detecting bone metastasis.

Table 5 shows that ^{18}FDG-PET was superior to ^{99m}Tc-HMDP bone scintigraphy in the detection of osteolytic lesions (92% vs. 73%), but inferior in the detection of osteoblastic lesions (74% vs. 95%). It is well known that more than a few bone metastases from breast cancer form osteoblastic lesions. Hortobagyi et al. reported that more than half of bone metastases from breast cancer show osteoblastic and mixed changes.[18] This may explain why the detectability of bone metastasis using ^{18}FDG-PET was almost the same as that of ^{99m}Tc-HMDP bone scintigraphy as a whole in this study.

The reason why ^{18}FDG accumulated in osteolytic lesions more easily than in osteoblastic lesions has not been clarified. It may be explainable by the higher density of viable cells or the greater blood supply in osteolytic lesions than in osteoblastic ones.[19] Cook et al. suggested that transforming growth factor-β (TGF-β), which stimulates osteoblasts to form new bone, has an inhibitory effect on tumor growth, resulting in a low uptake of ^{18}FDG.[17] Various other factors, including parathyroid hormone-related protein (PTHrP), interleukin-1 (IL-1), IL-6, IL-8, IL-11, tumor necrosis factor (TNF)-α, insulin-like growth factors (IGF)-1, and endothelin-1 (ET-1), have been proposed as critical in the formation of osteolytic and/or osteoblastic metastatic lesions.[20–22] There are also complex interactions among tumor cells, osteoclasts, osteoblasts, and stromal cells within the bone microenvironment; further investigation into these interactions is needed.

One limitation of this study was that the ^{99m}Tc-HMDP bone scintigraphy involved simple planar images without SPECT. We could conduct SPECT only for some patients in ordinary clinical examinations because of its time-consuming property. Several papers reported that additional SPECT images increased the ability of bone scintigraphy to detect bone metastases, especially in vertebral lesions.[23,24] On the other hand, ^{18}FDG-PET is a primary tomographic method using the most advanced reconstruction algorithms of OSEM. These two methods may not be essentially comparable. Further investigations might be required. The other limitation was that there was no definite standard of reference in ^{18}FDG-PET and ^{99m}Tc-HMDP bone scintigraphy negative patients in this study. Although follow-up studies including CT and MRI were performed for the patients who were clinically suspected of bone metastases, occult bone metastases could have gone unnoticed. As a result, the false negative rate may be underestimated in this study.

^{18}FDG-PET is indeed a useful method not only for detecting primary lesions, but also for detecting bone metastasis in breast cancer patients. Our results indicate that, while ^{18}FDG-PET is inferior to ^{99m}Tc-HMDP bone scintigraphy in the detection of osteoblastic metastases, ^{18}FDG-PET is superior to ^{99m}Tc-HMDP bone scintigraphy in the detection of osteolytic lesions. The combination of ^{18}FDG-PET + ^{99m}Tc-HMDP improved diagnostic accuracy. We conclude that ^{18}FDG-PET has a complementary role to play with ^{99m}Tc-HMDP bone scintigraphy in the detection of bone metastasis.

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