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ORIGINAL ARTICLE

Usefulness of ^{18}F-fluoride PET/CT in Breast Cancer Patients with Osteosclerotic Bone Metastases

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Abstract
Purpose Bone metastasis is an important factor for the treatment and prognosis of breast cancer patients. Whole-body bone scintigraphy (WBBS) can evaluate skeletal metastases, and ^{18}F-FDG PET/CT seems to exhibit high specificity and accuracy in detecting bone metastases. However, there is a limitation of ^{18}F-FDG PET in assessing sclerotic bone metastases because some lesions may be undetectable. Recent studies showed that ^{18}F-fluoride PET/CT is more sensitive than WBBS in detecting bone metastases. This study aims to evaluate the usefulness of ^{18}F-fluoride PET/CT by comparing it with WBBS and ^{18}F-FDG PET/CT in breast cancer patients with osteosclerotic skeletal metastases.
Materials and Methods Nine breast cancer patients with suspected bone metastases (9 females; mean age ± SD, 55.6 ± 10.0 years) underwent ^{99m}Tc-MDP WBBS, ^{18}F-FDG PET/CT and ^{18}F-fluoride PET/CT. Lesion-based analysis of five regions of the skeletons (skull, vertebral column, thoracic cage, pelvic bones and long bones of extremities) and patient-based analysis were performed.
Results ^{18}F-fluoride PET/CT, ^{18}F-FDG PET/CT and WBBS detected 49, 20 and 25 true metastases, respectively. Sensitivity, specificity, positive predictive value and negative predictive value of ^{18}F-fluoride PET/CT were 94.2 %, 46.3 %, 57.7 % and 91.2 %, respectively. Most true metastatic lesions on ^{18}F-fluoride PET/CT had osteosclerotic change (45/49, 91.8 %), and only four lesions showed osteolytic change. Most lesions on ^{18}F-FDG PET/CT also demonstrated osteosclerotic change (17/20, 85.0 %) with three osteolytic lesions. All true metastatic lesions detected on WBBS and ^{18}F-FDG PET/CT were identified on ^{18}F-fluoride PET/CT.
Conclusion ^{18}F-fluoride PET/CT is superior to WBBS or ^{18}F-FDG PET/CT in detecting osteosclerotic metastatic lesions. ^{18}F-fluoride PET/CT might be useful in evaluating osteosclerotic metastases in breast cancer patients.

Keywords ^{18}F-fluoride · ^{18}F-NaF · PET/CT · Breast cancer · Skeletal metastases

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Introduction

Breast cancer is the most common malignant tumor in women in the Western world [1] and is associated with a high incidence of skeletal metastases. Early detection and accurate assessment of bone involvement are required because skeletal metastasis is an important factor in treatment and prognosis. Conventional nuclear imaging to assess bone involvement is done by whole-body bone scintigraphy (WBBS) with ^{99m}Tc-labeled polyphosphates [2]. WBBS using ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) and gamma cameras is highly sensitive and cost-effective, thus

having contributed to the development and clinical spread of nuclear medicine imaging studies since the 1970s [3, 4]. Furthermore, 2-deoxy-2-(^{18}F)fluoro-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has recently emerged as an important tool for detecting breast cancer and skeletal metastases by providing functional and metabolic imaging of cancer with high spatial resolution [5].

However, there have been few improvements in radiopharmaceuticals and gamma camera technology for WBBS during the past decades, and the supply of ^{99m}Tc has become unstable because of the decrease in the number of active nuclear reactors in recent years [6]. ^{18}F-FDG PET/CT is sensitive for the detection of osteolytic bone metastases, but has limitations for the evaluation of osteosclerotic bone involvement due to low or absent activity in osteosclerotic metastases [7]. Therefore, new radiopharmaceuticals or imaging techniques to remove the drawback of WBBS and ^{18}F-FDG PET/CT are highly needed.

^{18}F-fluoride was widely used for bone scintigraphy after its introduction by Blau in the early 1960s [8]. However, some technical limitations of ^{18}F-fluoride and the widespread availability of ^{99}Mo/^{99m}Tc generators encouraged the development of ^{99m}Tc-labeled polyphosphates, though the pharmacokinetic properties of ^{18}F-fluoride are superior, resulting in higher bone uptake and faster blood clearance [9]. In the past decade, however, the availability of PET/CT scanners and cyclotron facilities has increased, and clinical interest in ^{18}F-fluoride for skeletal imaging has been renewed, with studies reporting the value of ^{18}F-fluoride PET/CT as a diagnostic tool for benign and malignant bone disease. In this study, we prospectively evaluated the usefulness of ^{18}F-fluoride PET/CT in Korean breast cancer patients with osteosclerotic bone metastasis by comparing WBBS, ^{18}F-FDG PET/CT and ^{18}F-fluoride PET/CT.

Materials and Methods

Patients

We prospectively enrolled nine breast cancer patients (9 females; mean age ± SD, 55.6 ± 10.0 years) with suspected skeletal metastases on follow-up WBBS or ^{18}F-FDG PET/CT. All patients underwent WBBS, ^{18}F-FDG PET/CT and ^{18}F-fluoride PET/CT within an interval of 1 month. The clinical design of our study was approved by the Ajou University Institutional Review Board, and all patients gave informed consent to participate in the study.

All patients had clinical follow-up by blood tests and imaging studies after ^{18}F-fluoride PET/CT. The mean duration of follow-up was 14.3 ± 7.6 months (mean ± SD, range 3.4–26.5 months). They all were on antihormone therapy, and five patients received chemotherapy several months before ^{18}F-fluoride PET/CT.

^{18}F-fluoride PET/CT

No specific pretreatment such as fasting or prohibiting parenteral infusion of sugar-containing fluids was required before PET/CT scanning. First 370 MBq of ^{18}F-fluoride was administered intravenously, and patients were asked to urinate just before scanning. Image acquisition started 60 min after intravenous injection. PET/CT images were acquired using the Discovery ST scanner (GE Healthcare, Milwaukee, WI, USA). Seven to eight frames (3 min/frame) of emission PET data were acquired in a three-dimensional mode after non-contrast CT scans from the base of the skull to the upper thigh (tube rotation time of 1 s/revolution, 120 kV, 60 mA, 7.5 mm/rotation and acquisition time of 60.9 s for a scan length of 867 mm). Emission PET images were reconstructed with non-contrast CT using iterative reconstruction (ordered-subset expectation maximization with 2 iterations and 30 subsets, field of view = 600 mm, slice thickness = 3.27 mm). Attenuation-corrected PET/CT images were reviewed on the GE AW workstation (GE Healthcare).

^{18}F-FDG PET/CT

Patients were fasted and prohibited from parenteral infusion of sugar-containing fluids at least 6 h before scanning. They were also asked not to undertake strenuous exercise for 1 day before the examination. Their blood glucose was measured before intravenous administration of ^{18}F-FDG to ensure a level of < 150 mg/dl. After injection of 370 MBq ^{18}F-FDG, all patients were instructed to rest comfortably for 60 min and empty their bladder just before scanning. PET/CT images were obtained using the same scanner and the same method as for ^{18}F-fluoride PET/CT. Attenuation-corrected PET/CT images were reviewed on the GE AW workstation (GE Healthcare). Standardized uptake value (SUV) was calculated based on the injected dose and the patient's body weight.

Whole Body Bone Scintigraphy

WBBS was performed 4 h after injection of 740 MBq ^{99m}Tc-MDP. Anterior and posterior view images were acquired using a double-headed gamma camera with low-energy, high-resolution collimators (Infinia Hawkeye 4; GE Healthcare). Additional lateral or oblique view images were obtained when it was not possible to determine the exact location of increased uptake.

Image Interpretation and Analysis

Two nuclear medicine physicians interpreted WBBS, ^{18}F-fluoride PET/CT and ^{18}F-FDG PET/CT by visual analysis based on consensus. Focally increased ^{18}F-fluoride or ^{18}F-FDG uptake in bones (not in the joints or edges of vertebral

bodies) on PET/CT fused images without evidence of degenerative or traumatic changes on CT images was interpreted as a putative metastasis. Osteosclerotic and osteolytic lesions were also classified by evaluating low-dose non-enhanced CT images of PET/CT. Abnormally increased uptake of ^{99m}Tc-MDP on WBBS was categorized as a putative metastasis when it was not located around joints; involved the posterior aspect of the vertebral body and pedicle; or presented as an elongated shape in the ribs.

Lesion-based analysis was performed for all putative metastatic lesions on WBBS, ^{18}F-fluoride PET/CT and ^{18}F-FDG PET/CT. Each lesion was grouped into the five skeletal regions (skull, vertebral column, thoracic cage, pelvic bones and long bones of extremities). The ribs, manubrium, sternum, clavicle and scapula were included in thoracic cage region. For patient-based analysis, five-region analysis of the skeleton was applied to each patient.

The presence or absence of skeletal metastases in putative lesions that were shown on ^{18}F-fluoride PET/CT was determined by combining their clinical, imaging and histopathological results. Skeletal metastasis was confirmed if any of the following criteria were present: positive histopathology, other radiographic confirmation (MRI or CT) or progression of the skeletal lesion on subsequent imaging studies (^{18}F-FDG PET/CT or WBBS) in 12 months.

Results

Lesion-Based Analysis

Eighty-five putative metastatic lesions were detected on ^{18}F-fluoride PET/CT, whereas 24 and 31 lesions were found on ^{18}F-FDG PET/CT and WBBS, respectively (Table 1). No abnormal uptake was recognized in the skull region on ^{18}F-FDG PET/CT and WBBS, but ^{18}F-fluoride PET/CT showed four lesions. Also ^{18}F-fluoride PET/CT identified five lesions in the long bones of the extremities that were not detected on ^{18}F-FDG PET/CT. All putative metastatic lesions on ^{18}F-FDG PET/CT and WBBS were identified on ^{18}F-fluoride PET/CT. Of the 85 putative metastases on ^{18}F-fluoride PET/CT, 37 lesions were at the vertebral column, 24 at the pelvic bones, 15 at the thoracic cage, 5 at the long bones of the extremities and 4 at the skull.

The presence or absence of skeletal metastasis in putative lesions on ^{18}F-fluoride PET/CT was determined by histopathology, radiographic study or progression of the skeletal lesion depending on the patient's condition (Table 2). Of 52 true metastases, ^{18}F-fluoride PET/CT, ^{18}F-FDG PET/CT and WBBS detected 49, 20 and 25 lesions, respectively (Table 1). Table 3 shows the number of true-positive, false-positive, false-negative and true-negative lesions detected on ^{18}F-fluoride PET/CT in the skeletal regions. All true metastatic lesions on ^{18}F-FDG PET/CT and WBBS were identified on ^{18}F-fluoride PET/CT. Of the 49 true-positive lesions, 20 were at the vertebral column, 19 at the pelvic bones, 8 at the thoracic cage and 2 at the long bones of extremities. Sensitivity, specificity, positive predictive value and negative predictive value of ^{18}F-fluoride PET/CT were 94.2 %, 46.3 %, 57.7 % and 91.2 %, respectively.

Morphological Characteristics of Metastatic Lesions on PET/CT

Most true metastatic lesions on ^{18}F-fluoride PET/CT had osteosclerotic change (45/49, 91.8 %), and only four lesions (T3 vertebra, T10 vertebra, acetabulum and femoral head) showed osteolytic change on corresponding CT images (Table 4). Also most true lesions on ^{18}F-FDG PET/CT demonstrated osteosclerotic change (17/20, 85.0 %) with three osteolytic lesions, which were identical with lesions on ^{18}F-fluoride PET/CT except the femoral head. The same results were observed in putative metastasis on ^{18}F-fluoride PET/CT (81/85, 95 %) and ^{18}F-FDG PET/CT (21/24, 88 %).

Patient-Based Analysis

Skeletal metastases of eight patients were correctly diagnosed with ^{18}F-fluoride PET/CT (7 with metastasis, 1 without metastasis). Eight patients showed putative metastasis on ^{18}F-fluoride PET/CT, but seven patients were confirmed to have skeletal metastasis. Patient 4 had a suspicious lesion in the vertebral column on WBBS, but no focal ^{18}F-fluoride uptake was found on PET/CT. The MRI and follow-up WBBS showed no bone metastasis. Table 2 shows the number of putative metastases detected on WBBS, ^{18}F-FDG PET/CT and ^{18}F-fluoride PET/CT, and the number of true metastases for each patient. The extent of bone metastasis was correctly estimated in three patients (patient 1, 3 and 4) and overestimated in the other six patients on ^{18}F-fluoride PET/CT. Five patients (patient 3, 5, 6, 8 and 9) were underestimated on WBBS and ^{18}F-FDG PET/CT.

Discussion

WBBS showed planar images, whereas PET/CT enabled evaluation of the region of radiopharmaceutical uptake by high spatial resolution. Moreover, tumor or functional imaging can be obtained by using suitable radiopharmaceuticals in PET/CT. The development of imaging technology and radiopharmaceuticals is currently in progress [9].

The mechanism of ^{18}F-fluoride bone uptake is known as chemical adsorption, similar to ^{99m}Tc-MDP used for WBBS, but the pharmacokinetic properties of ^{18}F-fluoride

Table 1 Number of putative and true metastases detected on WBBS, ^{18}F-FDG PET/CT and ^{18}F-fluoride PET/CT in skeletal regions

Regions	Bone scintigraphy		^{18}F-FDG PET/CT		^{18}F-fluoride PET/CT	
	Putative	True	Putative	True	Putative	True
Skull	0	0	0	0	4	0
Vertebral column	18	12	12	9	37	20
Thoracic cage	3	3	4	3	15	8
Pelvic bones	9	9	8	8	24	19
Long bones of extremities	1	1	0	0	5	2
Total	31	25	24	20	85	49

are superior to those of ^{99m}Tc-MDP. The half-life of ^{18}F-fluoride is 110 min, which is shorter than that of ^{99m}Tc-MDP (approximately 6 h). The bone uptake amount of ^{18}F-fluoride is about 50 % of the injected dose, similar to that of ^{99m}Tc-MDP. ^{18}F-fluoride is rapidly excreted through the kidneys because plasma protein binding of ^{18}F-fluoride is negligibly small under normal physiological conditions [10]. Therefore, the waiting time from injection of radiotracer to acquisition of images is less than 1 h in ^{18}F-fluoride PET/CT, but 3–4 h in ^{99m}Tc-MDP WBBS [11].

^{18}F-fluoride PET and ^{99m}Tc-MDP WBBS are known to have no significant differences in radiation exposure. According to the reports of the 1999 and the 1987 International Commission on Radiologic Protection (ICRP), the effective dose after WBBS with injection of 518 MBq ^{99m}Tc-MDP was 3.0 mSv, and after PET scan with injection of 148 MBq ^{18}F-fluoride was 4.0 mSv in a 70 kg adult [12, 13]. In the case of ^{18}F-fluoride PET/CT, the additional effective dose by CT scan should be considered. Though low-dose CT is applied, radiation less than 5 mSv is generated by CT scanning equipment. Therefore, radiation exposure of ^{18}F-fluoride PET/CT might be two or three times that of ^{99m}Tc-MDP WBBS [14].

In the past decade, the clinical applications of ^{18}F-fluoride PET and PET/CT have been reported frequently. Several studies have demonstrated the utility of ^{18}F-fluoride PET/CT in detecting primary bone tumors and skeletal metastasis of several primary malignancies. Other reports claimed that ^{18}F-fluoride PET/CT can be used for the evaluation of benign disease such as unexplained bone pain, child abuse, osteomyelitis, trauma, degenerative arthritis, avascular bone necrosis, metabolic bone diseases and Paget's disease. They also showed that ^{18}F-fluoride PET/CT can predict bone viability after trauma or reconstructive surgery and complications after joint replacement operation [15]. Recently, the usefulness of ^{18}F-fluoride PET in malignant and benign bone disease in South Korea was reported, and the sensitivity and specificity for skeletal metastases in this study were 86 % and 88 %, respectively [16].

The initial studies to compare the diagnostic performance of ^{99m}Tc-MDP WBBS and ^{18}F-fluoride PET in the assessment of bone metastases have reported higher sensitivity,

Table 2 Interval from the first bone metastasis to ^{18}F-fluoride PET/CT, follow-up periods, confirmative diagnostic studies for true metastasis and number of putative metastases detected on each study and true metastases for each patient

Patient	Sex	Age	Interval (months)	Follow-up (months)	Confirmation of true metastasis	Number of lesions			
						WBBS	FDG	Fluoride	True metastasis
1	F	49	5.8	3.6	Biopsy	1	1	1	1
2	F	62	13.3	3.4	MRI, FDG	0	1	4	0
3	F	44	3.9	13.0	CT, WBBS, FDG	1	1	2	2
4	F	50	0.47	18.4	MRI, WBBS, FDG	1	0	0	0
5	F	74	6.7	19.6	WBBS, FDG	16	13	45	22
6	F	53	1.47	18.6	WBBS, FDG	2	2	12	11
7	F	63	11.5	26.5	WBBS, FDG	2	1	5	1
8	F	50	8.6	11.0	WBBS, FDG	3	2	6	5
9	F	55	4.0	14.5	WBBS, FDG	5	3	10	7

Interval, interval from first bone metastasis to ^{18}F-fluoride PET/CT; WBBS, whole body bone scintigraphy; FDG, ^{18}F-FDG PET/CT; Fluoride, ^{18}F-fluoride PET/CT

Table 3 Number of true-positive, false-positive, false-negative and true-negative lesions detected on ^{18}F-fluoride PET/CT in skeletal regions

Region	True positive	False positive	False negative	True negative
Skull	0	4	0	3
Vertebral column	20	17	2	19
Thoracic cage	8	7	1	6
Pelvic bones	19	5	0	1
Long bones of the extremities	2	3	0	2
Total	49	36	3	31

specificity and accuracy of ^{18}F-fluoride [17–19]. According to a recent study, ^{18}F-fluoride PET/CT is more specific than ^{18}F-fluoride PET for evaluating skeletal metastases. Specificity of ^{18}F-fluoride PET and ^{18}F-fluoride PET/CT were 62 % and 100 %, respectively [20]. In the present study, ^{18}F-fluoride PET/CT found twice the number of putative metastases than ^{99m}Tc-MDP WBBS (Table 1). This result was in accord with a recent study, which showed that ^{18}F-fluoride PET/CT has higher sensitivity (81 %) than WBBS (43 %) for assessing bone involvement in breast cancers [21].

In the present study, ^{18}F-fluoride PET/CT detected the largest number of putative metastatic lesions in the vertebral column (37 lesions), followed by the pelvic bones (24), thoracic cage (15), long bones of the extremities (5) and skull (4). ^{99m}Tc-MDP WBBS and ^{18}F-FDG PET/CT showed the same order of skeletal regions. Also, this result was the same as that of previous reports evaluating skeletal metastases in breast cancer [22].

On the contrary to our definition of putative metastasis on ^{18}F-fluoride PET/CT, we indicated the benign lesion as focally increased ^{18}F-fluoride uptake in joints, edges of vertebral bodies or bony lesions with evidence of degenerative or traumatic changes on corresponding CT images. All patients showed benign lesions except patient 1. Particularly, patient 4 had no putative metastatic lesions but four benign ones according to ^{18}F-fluoride uptake in the vertebral column, thoracic cage and long bones of the extremities; these were confirmed to have no metastases by MRI and follow-up WBBS. Three benign lesions of patient 6 (thoracic cage) and 8 (vertebral column) were demonstrated to have true metastases with follow-up ^{18}F-FDG PET/CT.

Table 3 shows the number of true-positive, false-positive, false-negative and true-negative lesions detected on ^{18}F-fluoride PET/CT in skeletal regions. Of the 49 true-positive lesions, 20 lesions were at the vertebral column, 19 at the pelvic bones, 8 at the thoracic cage, 2 at the long bones of the extremities and 0 at the skull. There was a similar number of true-positive and false-positive lesions in skeletal regions of the vertebral column and thoracic cage, but about four times more true-positive lesions in the pelvic bones region. We could assume that ^{18}F-fluoride PET/CT may be helpful to determine skeletal metastasis in pelvic bones that is ambiguous on WBBS or ^{18}F-FDG PET/CT. Sensitivity, specificity, positive predictive value and negative predictive value of ^{18}F-fluoride PET/CT were 94.2 %, 46.3 %, 57.7 % and 91.2 %, respectively.

In the present study, the true metastasis was confirmed by histopathological or other radiographic examinations (MRI or CT). If the histopathological or other radiographic study was unavailable, the lesion was regarded as true metastasis when it showed progression with imaging follow-up (^{18}F-FDG PET/CT or WBBS) in 12 months. In fact, many putative metastatic lesions were determined by follow-up ^{18}F-FDG PET/CT performed 3–6 months later, not by histopathological confirmation or other radiographic studies (Table 2). Therefore, 36 false-positive lesions on ^{18}F-fluoride PET/CT might include healed metastases on follow-up ^{18}F-FDG PET/CT or WBBS. In addition, ^{18}F-FDG PET/CT has limitations in detecting osteosclerotic metastases. We

Table 4 Number of osteosclerotic and osteolytic metastatic lesions detected on ^{18}F-FDG PET/CT and ^{18}F-fluoride PET/CT in skeletal regions

Region	^{18}F-FDG PET/CT				^{18}F-fluoride PET/CT			
	Osteosclerotic		Osteolytic		Osteosclerotic		Osteolytic	
	Putative	True	Putative	True	Putative	True	Putative	True
Skull	0	0	0	0	4	0	0	0
Vertebral column	10	7	2	2	35	18	2	2
Thoracic cage	4	3	0	0	15	8	0	0
Pelvic bones	7	7	1	1	23	18	1	1
Long bones of extremities	0	0	0	0	4	1	1	1
Total	21	17	3	3	81	45	4	4

presumed that many false-positive lesions were healing and osteosclerotic metastases, and this is the reason for the lower specificity of the present study than in other related studies. If we had enrolled pre-treated patients or performed more histopathological or other radiographic studies, the specificity might have been higher. A recent study that used full diagnostic CT or MRI as a gold standard reported that the specificity of ^{18}F-fluoride PET/CT was 68.3 % for breast cancer patients on antihormone therapy [21].

^{18}F-FDG PET/CT has high sensitivity in the detection of osteolytic bone metastases, but has limitations in the evaluation of osteosclerotic bone involvement due to low or absent activity in osteosclerotic metastases [7]. However, ^{18}F-fluoride PET/CT is highly sensitive in detecting both osteosclerotic and osteolytic metastatic lesions [23, 24]. Withofs et al. reported the sensitivity of ^{18}F-fluoride PET/CT for detecting osteolytic and osteosclerotic lesions as 58.3 % and 90.9 %, respectively [21]. Many osteosclerotic lesions of true metastasis with increased ^{18}F-fluoride uptake showed no ^{18}F-FDG uptake (Fig. 1), so the counted number of osteosclerotic lesions on ^{18}F-fluoride PET/CT was about three times that seen on ^{18}F-FDG PET/CT (Table 4). Moreover, one more osteolytic lesion without ^{18}F-FDG uptake was found on ^{18}F-fluoride PET/CT (Fig. 2, Table 4).

Metastatic bone lesions were of three types clinically: osteolytic, osteosclerotic and mixed type [25]. But purely osteosclerotic metastatic lesions were infrequently detected on CT images of PET/CT in the present study, so metastatic lesions showing any sclerotic change were classified as 'osteosclerotic,' and lesions with no osteosclerotic change were classified as 'osteolytic.' In other words, mixed metastatic lesions were included in the osteosclerotic metastatic lesions in the present study. If all osteosclerotic lesions that appeared on ^{18}F-FDG PET/CT were supposed to be mixed lesions, the ratio of 'pure osteosclerotic' to mixed lesions on ^{18}F-fluoride PET/CT might be 3:1.

It has been reported that the majority of patients with breast cancer have predominantly osteolytic lesions, whereas approximately 15 % to 20 % of them have osteosclerotic lesions [26]. However, the present study showed that most true metastatic lesions on ^{18}F-fluoride PET/CT (45/49, 91.8 %) and ^{18}F-FDG PET/CT (17/20, 85.0 %) were osteosclerotic (Table 4). We assumed that the cause of this difference was the treatment with antihormone therapy or chemotherapy. According to the report by Yong Du et al., the majority of the osteolytic lesions became ^{18}F-FDG negative and gradually became osteosclerotic on CT after treatment, and sequential ^{18}F-FDG PET/CT studies revealed a gradual osteosclerotic process after effective treatment. This process seemed to be independent of the type of anticancer therapy [26]. All patients in the present study were diagnosed with skeletal metastases and continued to have treatment several months prior to ^{18}F-fluoride PET/CT (Table 2). The treatment might influence the osteoclastic/osteoblastic process in metastatic lesions. This report by Yong Du et al. also accounts for the lower estimation of metastatic lesions by ^{18}F-FDG PET/CT than WBBS. Osteolytic metastatic lesions might be reduced by treatment and became ^{18}F-FDG negative. But increased osteosclerotic lesions might be detected by WBBS (Fig. 3). Sensitivity and specificity of ^{18}F-FDG PET/CT were 38.5 % and 42.9 % and of WBBS were 48.1 % and 62.5 %, respectively, in the present study. We presumed that many true metastatic lesions were healing or were osteosclerotic metastases, and therefore ^{18}F-FDG

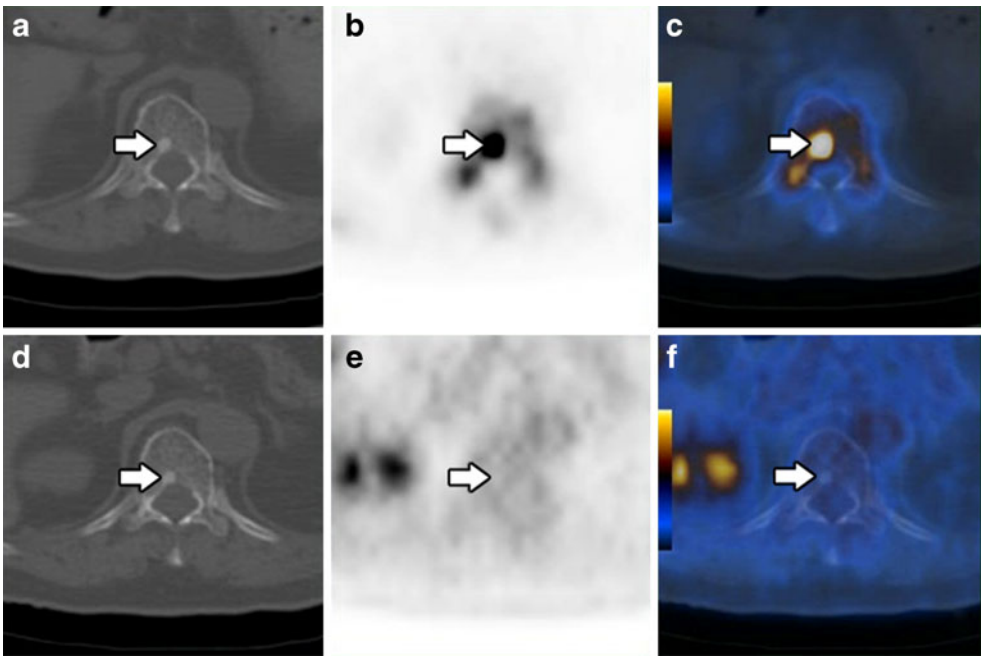

Fig. 1 Osteosclerotic metastatic lesion in the thoracic vertebra (*arrow*). ^{18}F-fluoride PET/CT shows focally increased uptake (transaxial view; **a** CT; **b** PET; **c** fused PET/CT image). But ^{18}F-FDG PET/CT does not show increased uptake (transaxial view; **d** CT; **e** PET; **f** fused PET/CT image)

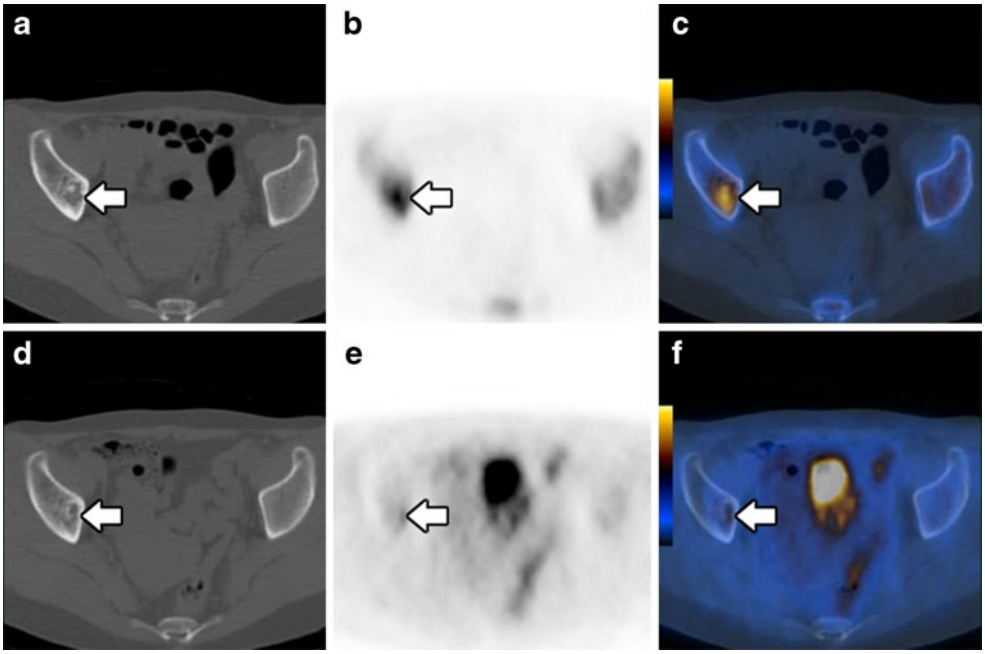

Fig. 2 Osteolytic metastatic lesion in pelvic bone (arrow). Focally increased uptake was demonstrated on ^{18}F-fluoride PET/CT (transaxial view; **a** CT; **b** PET; **c** fused PET/CT image), but not on ^{18}F-FDG PET/CT (transaxial view; **d** CT; **e** PET; **f** fused PET/CT image)

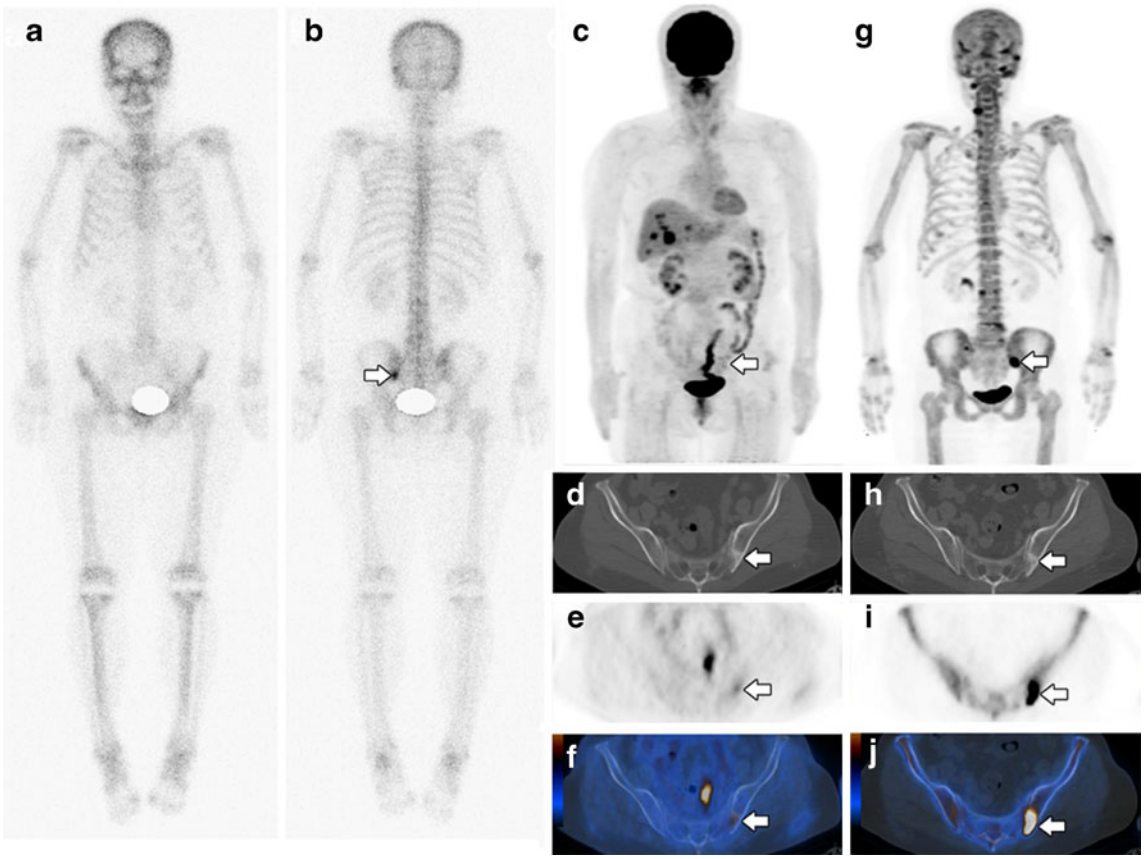

Fig. 3 Comparison of the features of WBBS, ^{18}F-FDG PET/CT and ^{18}F-fluoride PET/CT in patient 7. She was diagnosed with bone metastasis 11.5 months before ^{18}F-fluoride PET/CT and treated with chemotherapy for several weeks until ^{18}F-fluoride PET/CT. WBBS (**a** anterior; **b** posterior) shows focally increased uptake in the left lower sacroiliac joint (*arrow*). But mild increased FDG uptake was seen in the left iliac bone (*arrow*) on ^{18}F-FDG PET/CT [**c** maximum intensity projection (MIP) anterior view; **d**–**f** transaxial view CT, PET, fused]. ^{18}F-fluoride PET/CT (**g** MIP anterior view; **h**–**j** transaxial view CT, PET, fused) shows intense focal uptake in the left iliac bone (*arrow*). The lesion was confirmed to have metastasis by follow-up ^{18}F-FDG PET/CT

PET/CT showed low sensitivity and specificity. The sensitivity and specificity of WBBS was in accord with a recent study for breast cancer patients on antihormone therapy (sensitivity 43.0 %, specificity 70.7 %) [21].

One patient with many putative metastatic lesions on ^{18}F-fluoride PET/CT showed only a few lesions on ^{18}F-FDG PET/CT and ^{99m}Tc-MDP WBBS. She underwent ^{18}F-FDG PET/CT 3 months later for follow-up, and many areas of ^{18}F-FDG uptake were found at the same locations of ^{18}F-fluoride PET/CT. This indicates that ^{18}F-fluoride PET/CT could help in the early detection of skeletal metastases. Of course, it was just one case and therefore has no statistical significance, but we tentatively suggest the possible utility of ^{18}F-fluoride PET/CT as a routine follow-up modality for the early detection of bone metastases in breast cancer.

The present study had limitations. First, the study enrolled only nine patients, and a larger patient cohort is required for the findings to have reliable statistical significance. The second limitation resulted from the method used to determine morphological changes of metastatic lesions. A previous report showed that morphological changes of skeletal metastatic lesions at low-dose CT components of PET/CT were observed in just half [27]. Our result may have a bias because only low-dose CT images of PET/CT were used to determine morphological characteristics in the present study. Lastly, choosing patients under anticancer therapy who were not not pre-treated and the few histopathological confirmations led to lower specificity than in other related studies.

Conclusion

^{18}F-fluoride PET/CT is superior to ^{99m}Tc-MDP WBBS or ^{18}F-FDG PET/CT in detecting skeletal metastases, particularly osteosclerotic lesions in breast cancer patients. ^{18}F-fluoride PET/CT appears to have a role in the detection of bone metastases with high sensitivity and negative predictive value, which results in an effective treatment and good prognosis.

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