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ORIGINAL ARTICLE

Clinical Usefulness of ^{18}F-fluoride Bone PET

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Abstract
Purpose ^{18}F-fluoride bone positron emission tomography (PET) has been reported as a useful bone imaging modality. However, no clinical bone PET study had been performed previously in Korea. The authors investigated the usefulness of ^{18}F-fluoride bone PET in Korean patients with malignant or benign bone disease.
Methods Eighteen consecutive patients (eight women, ten men; mean age, 55±12 years) who had undergone ^{18}F-fluoride bone PET for the evaluation of bone metastasis (n=13) or benign bone lesions (n=5) were included. The interpretation of bone lesions on ^{18}F-fluoride bone PET was determined by consensus of two nuclear medicine physicians, and final results were confirmed using combination of all imaging studies and/or clinical follow-up. The analysis was performed on the basis of lesion group.
Results Thirteen patients with malignant disease had 15 lesion groups, among which seven were confirmed as metastatic bone lesions and eight were confirmed as non-metastatic lesions. ^{18}F-fluoride bone PET correctly identified six of seven metastatic lesions (sensitivity, 86%), and seven of eight non-metastatic lesions (specificity, 88%). On the other hand, five patients with benign conditions had five bone lesion groups; four were confirmed as benign bone diseases and the other one was confirmed as not a bone lesion. ^{18}F-fluoride bone PET showed correct results in all the five lesion groups.
Conclusions ^{18}F-fluoride bone PET showed promising potential for bone imaging in Korean patients with malignant diseases as well as with various benign bone conditions. Therefore, further studies are required on the diagnostic performance and cost-effectiveness of ^{18}F-fluoride bone PET.

Keywords ^{18}F-fluoride · Bone · Positron emission tomography

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Introduction

^{18}F-fluoride has been a clinically useful bone imaging agent since the early 1960s; that is before positron emission tomography (PET) technology was introduced [1]. The main mechanism for bone uptake of ^{18}F-fluoride is chemisorption, which is also the mechanism for the uptake of ^{99m}Tc-labeled phosphonate compounds. With this mechanism, the OH^- ion of hydroxyapatite crystals is replaced with $^{18}F^-$. As ^{18}F-fluoride has double the bone uptake and faster blood clearance than ^{99m}Tc-labeled phosphonate compounds, it may provide better image quality than ^{99m}Tc-labeled phosphonate compounds [2]. The United States Food and Drug Administration approved clinical application of ^{18}F-fluoride in 1972 [3]. However, ^{18}F-fluoride has not been widely used in clinical practice because its high-energy photon (511 keV) is inadequate for Anger-type gamma cameras. On the other hand, ^{99m}Tc-labeled phosphonate compounds were introduced in early 1970s, and rapidly spread to be the most widely used bone

imaging agents due to the excellent availability of ^{99m}Tc and its compatibility with Anger-type gamma cameras [4]. Accordingly, clinicians have paid limited attention to ^{18}F-fluoride as a bone imaging agent.

Since the early 1990s, however, PET scanners and cyclotrons have been disseminated worldwide, provoking renewed interest in ^{18}F-fluoride bone PET, and a number of papers on ^{18}F-fluoride bone PET have been published. ^{18}F-fluoride bone PET has been shown to be useful for evaluating bone diseases, including both malignant [5–7] and benign [8–11] diseases. Moreover, the diagnostic accuracies of ^{18}F-fluoride bone PET for bone diseases have been reported to be superior to those of ^{99m}Tc-labeled phosphonate compounds [3]. However, no clinical study on ^{18}F-fluoride bone PET had been reported in Korea. In this study, we investigated the clinical usefulness of ^{18}F-fluoride bone PET in Korean patients with malignant or benign bone diseases.

Materials and Methods

Patients

Eighteen consecutive patients (eight women, ten men; mean age 55±12 years) who had undergone ^{18}F-fluoride bone PET were enrolled in this study. Underlying diseases were malignant diseases in 13 (two prostate cancers, three thyroid cancers, five breast cancers, one stomach cancer, one colon cancer, and one multiple myeloma) (Table 1) and benign conditions in five patients (one intramuscular hemangioma, one post-traumatic syndrome, one infectious spondylitis, one arthritic joint pain, one non-specific joint pain) (Table 2). The purpose of ^{18}F-fluoride bone PET in the patients with malignant disease was the differential diagnosis of bone lesions that were equivocal on other imaging studies [bone scan, ^{18}F-FDG PET, magnetic resonance imaging (MRI), or computed tomography (CT)] (n=8) or the re-evaluation of known bone metastasis (n=5). The purpose of ^{18}F-fluoride bone PET in the patients with benign condition was the evaluation of bone invasion of intramuscular hemangioma (n=1), evaluation of bone destruction by infectious spondylitis (n=1), and the identification of bone pain etiology (n=3).

Acquisition and Interpretation of ^{18}F-Fluoride Bone PET

^{18}F-fluoride bone PET images were acquired using a dedicated PET scanner (Allegro, Philips Medical Systems, USA). Food intake or parenteral infusion of sugar-containing fluids was not prohibited. ^{18}F-fluoride of 0.14 mCi/kg was administered by intravenous injection and image acquisition was started 50 min after administration. Images were acquired from the skull to the upper thigh or from the upper thigh to the feet, to include lesions of interest. Images were acquired

Table 1 Characteristics of patients with underlying malignant diseases (*M* male, *F* female, *BS* bone scan using ^{99m}Tc-HDP, *NC* no change, *TP* true positive, *TN* true negative, *FN* false negative, *FP* false positive, *meta (+)* metastasis present, *meta (–)* metastasis absent, *F/U* follow-up, *TP* true positive, *RT* radiotherapy)

No.	Age	Sex	Underling disease	Issues on bone metastasis	Bone PET finding	No. of lesion group	Final result	Accuracy of bone PET
1	61	M	Prostate cancer	Equivocal on BS	Meta (+)	1	Meta (+) on MR, start RT	TP
2	47	F	Thyroid cancer	Equivocal on BS	Meta (–)	1	Meta (–) on F/U (14 months)	TN
3	45	F	Breast cancer	Equivocal on BS	Meta (–)	1	Meta (–) on F/U (17 months) and BS NC	TN
4	63	F	Breast cancer	Equivocal on BS	Meta (–)	1	Meta (–) on F/U (17 months) and BS (–)	TN
5	63	M	Thyroid cancer	Equivocal on BS	Meta (–)	1	Meta (–) on F/U (12 months) and BS NC	TN
6	49	F	Breast cancer	Equivocal on BS, FDG-PET, and MRI	Meta (+)	1	Meta (+) on clinical context	TP
7	53	F	Breast cancer	Equivocal on CT and MRI	Meta (–)	1	Meta (+) on clinical context	FN (small lesions)
8	47	F	Breast cancer	Known bone meta, aggravation on MRI, equivocal on BS, humerus	Meta (+), meta (–) humerus	2	Meta (+) on chemo change, meta (–) humerus	TP, TN
9	57	M	Multiple myeloma	Known bone meta on MRI, shoulder and elbow pain	Meta (+), meta (–) shoulder and elbow	2	Meta (+) on FDG–PET, meta (–) shoulder, elbow on F/U (12 months)	TP, TN
10	55	M	Stomach cancer	Known bone meta on BS, intractable shoulder pain	Meta (+)	1	Meta (+) on clinical context	TP (more extensive bone meta than BS
11	62	M	Thyroid cancer	Known bone meta s/p op and RT	Meta (+)	1	Meta (–) on I-131 scan	FP (post-op change)
12	84	M	Prostate cancer	Known bone meta on BS s/p hormonal therapy	Meta (+)	1	Meta (+) on clinical context	TP
13	59	M	Colon cancer	Equivocal on CT	Meta (–)	1	Meta (–) on F/U (6 months) and FDG-PET	TN

Table 2 Characteristics of the five patients with benign conditions (*SD* syndrome)

No.	Age	Sex	Underling disease	Issues on bone lesion	Bone PET finding	No. of lesion group	Final result	Accuracy of bone PET
1	25	F	Intramuscular hemangioma	Mild uptake on BS[a]	Bone lesion (+)	1	Bone lesion (+) on X-ray	TP (more extensive bone lesion than BS)
2	50	F	Post-traumatic SD	Bone pain etiology	Bone lesion (+)	1	Bone lesion (+) on clinical context	TP
3	60	M	Infectious spondylitis	Mild uptake on BS	Bone lesion (+)	1	Bone lesion (+) on MRI and clinical context	TP (more extensive bone lesion than BS)
4	50	M	Lt. hip pain	Bone pain etiology	Bone lesion (−)	1	Bone lesion (−) on F/U (10 months)	TN
5	56	M	Low back pain	Bone pain etiology	Bone lesion (+)	1	Bone lesion (+) on treatment response	TP

over seven to nine beds, and the acquisition time per bed was 2.5 min for emission scan plus 40 s for transmission scan. Images were reconstructed using the three-dimensional row action maximum likelihood algorithm.

^{18}F-fluoride bone PET images were interpreted by consensus between two nuclear medicine physicians. Prominent ^{18}F-fluoride uptake (uptake clearly discriminated from surrounding normal bone) were considered positive bone uptake. For bone metastasis evaluation, a lesion was interpreted based on the intensity and location of uptake. ^{18}F-fluoride uptake in the definite degenerative lesions such as bony spur or known traumatic lesion was excluded from the analysis. Afterwards, interpretation was dichotomized into presence or absence of bone metastasis [metastasis (+) or (−)]. Interpretation of benign conditions was also dichotomized into presence or absence of benign bone lesions [bone lesion (+) or (−)].

Lesion Group Analysis

The diagnostic accuracy of bone PET was investigated on the basis of lesion group. This lesion group analysis is basically similar to a patient-basis analysis, but is more practical. A lesion group was defined as a group of bone lesions that could be regarded as lesions of the same characteristics. For example, if a cancer patient complained of pain in two sites, it was classified as one lesion group (Fig. 3). Similarly, multiple metastatic bone lesions detected in the staging work-up were also classified as one lesion group (Fig. 4). On the other hand, if a cancer patient with known bone metastasis presented new bone lesions (patients 8 and 9 in Table 1), the patient was considered to have two lesion groups.

Confirmation of ^{18}F-Fluoride Bone PET Findings

^{18}F-fluoride bone PET findings were considered true-positive when subsequent imaging studies demonstrated the presence of the bone lesion; and if not, bone PET findings were considered false-positive. ^{18}F-fluoride bone PET findings were considered true-negative when subsequent imaging studies and follow-up clinical studies demonstrated no evidence of a bone lesion in concordance with bone PET findings; and if not, bone PET findings were considered false-negative.

Results

Malignant Diseases

In 13 patients with malignant disease, 15 lesion groups were identified; seven were metastatic bone lesions and eight were not. The sensitivity of ^{18}F-fluoride bone PET for detecting bone metastasis was 86% (6/7), and its specificity was 88% (7/8) (Table 3). The single false-negative case (patient 7 in Table 1) was multiple spinal metastases, the sizes of which were less than 3 mm. In this case, metastasis was confirmed by subsequent CT and MRI, although tissue biopsy was not confirmed. The single false-positive case (patient 11 in Table 1) showed increased ^{18}F-fluoride uptake around the lumbar spine. In this case, operation and radiotherapy had already been performed for the previously confirmed lumbar metastasis, and the uptake was diagnosed as non-specific uptake after operation and radiotherapy.

Table 3 Diagnostic accuracy of ^{18}F-fluoride bone PET for detecting bone metastases in 13 patients with underlying malignant disease (15 lesion groups)

	Bone metastasis (+)	Bone metastasis (−)	
Bone PET (+)	6	1	7
Bone PET (−)	1	7	8
	7	8	15

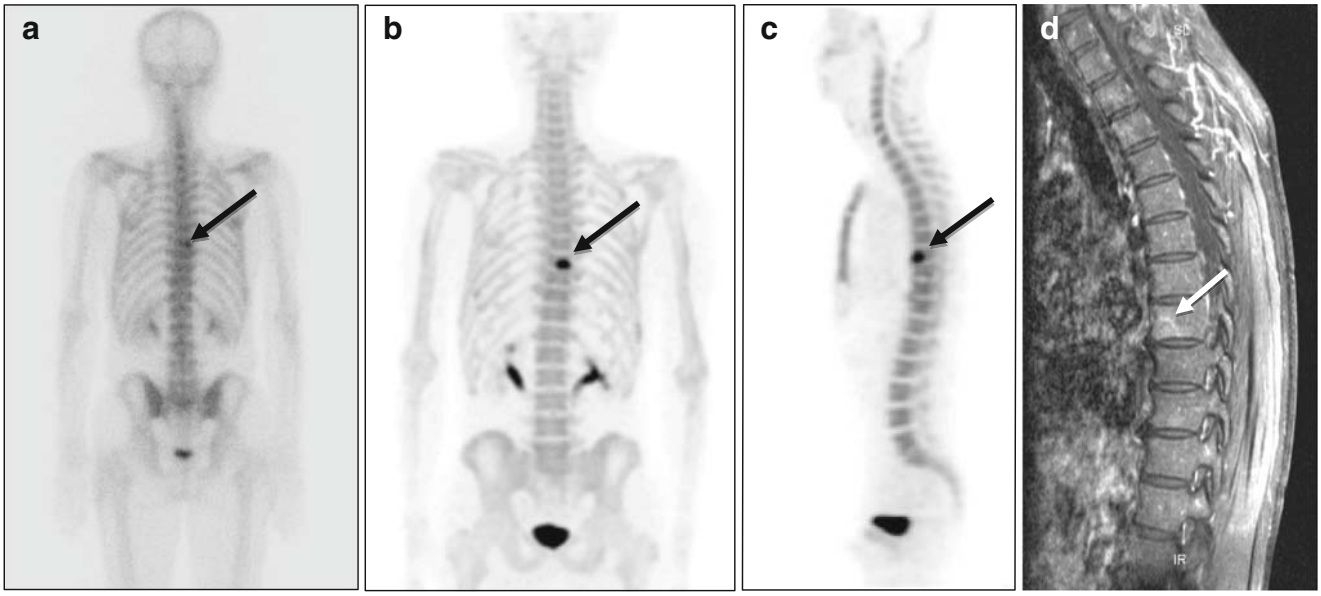

Fig. 1a–d ^{18}F-fluoride bone PET of a 61-year-old male patient with prostate cancer. **a** A lesion was suspected to have bone metastasis in the T-8 area (*black arrow*) in a ^{99m}Tc-HDP bone scan (posterior whole body image). **b** ^{18}F-fluoride bone PET readily revealed bone metastasis at the T-8 vertebral body in a maximum intensity projection (MIP) posterior view image, and **c** in a sagittal image. **d** T1-weighted gadolinium-enhanced MRI also demonstrated metastasis at the T-8 vertebral body (*white arrow*). Radiation therapy was applied to the lesion, and a follow-up bone scan revealed improvement

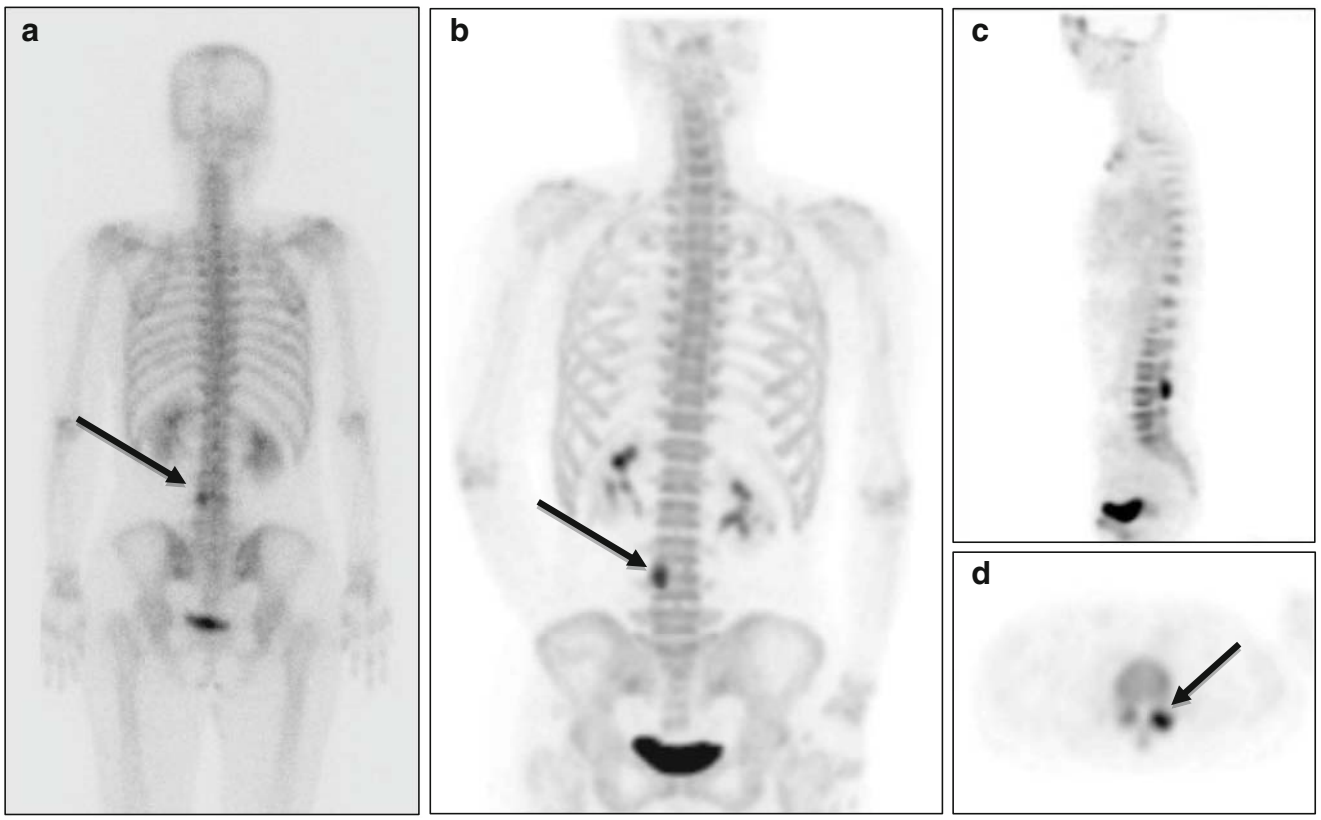

Fig. 2a–d ^{18}F-fluoride bone PET ruled out the presence of bone metastasis. **a** A 45-year-old female patient with breast cancer was suspected of having bone metastasis at L-4 (*black arrow*) in a ^{99m}Tc-HDP bone scan (posterior whole body image). **b** ^{18}F-fluoride bone PET indicated that the lesion was located at left L3-4 facet joint in a MIP posterior view image, **c** a sagittal image, and **d** a transaxial image. A follow-up bone scan conducted at 17 months after the bone PET study did not show any change in the lesion, and the patient showed no clinical evidence of bone metastasis

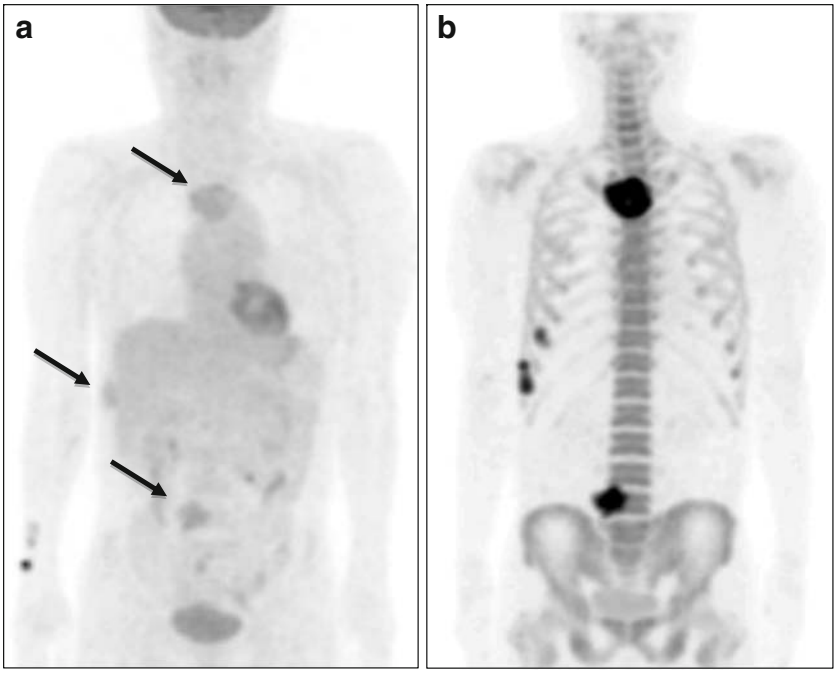

Fig. 3a, b ^{18}F-fluoride bone PET confirmed the presence and absence of bone metastasis. **a** The 57-year-old male patient with multiple myeloma had multiple hypermetabolic bone lesions (*long arrows*) by ^{18}F-FDG PET (MIP anterior view image). He complained of non-specific pain at the right shoulder and elbow joints. **b** ^{18}F-fluoride bone PET showed multiple metastatic lesions compatible with hypermetabolic lesions, but no other lesions were found. There was no evidence of bone metastasis at right shoulder or elbow joints areas at 12 months after the bone PET study

Figure 1 shows a true-positive ^{18}F-fluoride PET finding in a prostate cancer patient (patient 1 in Table 1). In this patient, an equivocal lesion on ^{99m}Tc-HDP bone scan showed definite uptake on ^{18}F-fluoride bone PET, and confirmed as metastasis. Figure 2 shows a true-negative ^{18}F-fluoride bone PET finding in a breast cancer patient (patient 3 in Table 1). In this patient, bone scan showed an equivocal bone lesion, while ^{18}F-fluoride bone PET clearly demonstrated the location of uptake as facet joint. The patient was diagnosed as facet joint arthritis.

In most cases, ^{18}F-fluoride bone PET showed metastatic bone lesions more definitely than ^{18}F-FDG PET. In a patient with multiple myeloma (patient 9 in Table 1), bone involvement of multiple myeloma was more definitely depicted on ^{18}F-fluoride bone PET than on ^{18}F-FDG PET (Fig. 3). In addition, assessment of number and extent of

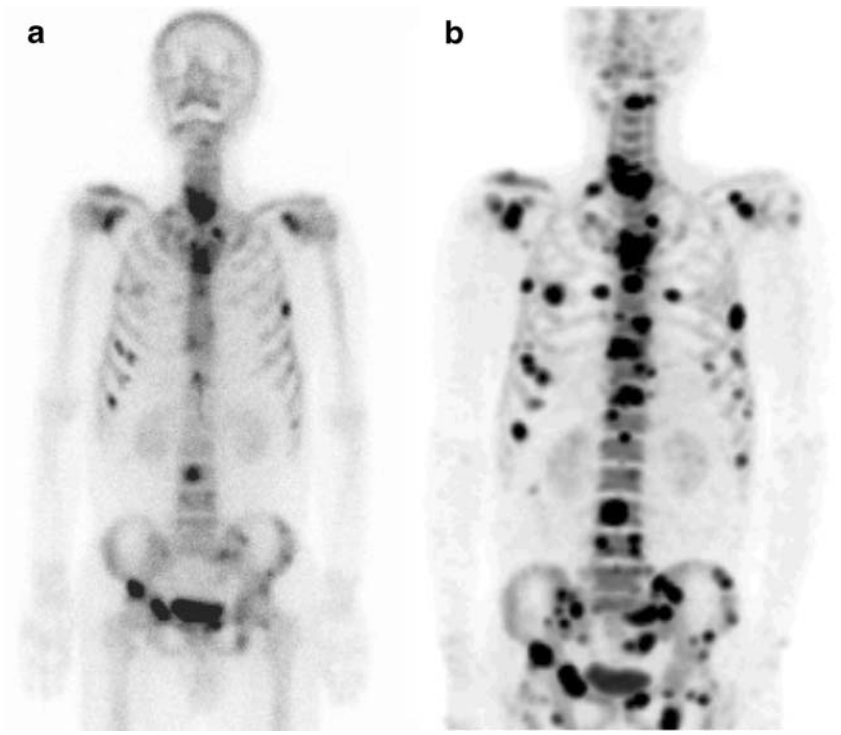

Fig. 4a, b ^{18}F-fluoride bone PET identified more metastatic lesions than ^{99m}Tc-HDP bone scan. **a** A 55-year-old male patient with stomach cancer showed multiple bone lesions suggestive of metastases in his ^{99m}Tc-HDP bone scan. **b** Subsequent ^{18}F-fluoride bone PET identified more metastatic lesions

Table 4 Diagnostic accuracy of ^{18}F-fluoride bone PET for detecting benign bone lesions in five patients without underlying malignant disease (five lesion groups)

	Bone lesion (+)	Bone lesion (−)	
Bone PET (+)	4	0	4
Bone PET (−)	0	1	1
	4	1	5

bone metastasis was more accurate with ^{18}F-fluoride bone PET than with ^{99m}Tc-HDP bone scan. In a patient with stomach cancer (patient 10 in Table 1), ^{18}F-fluoride bone PET showed much more metastatic lesions of wider extent than ^{99m}Tc-HDP bone scan (Fig. 4).

Benign Conditions

In five patients with benign conditions, five bone lesion groups were identified (Table 2). In four patients, bone lesions were correctly detected on ^{18}F-fluoride bone PET, which was confirmed by other imaging study and follow-up. In another one patient, the absence of bone lesion was also correctly determined on ^{18}F-fluoride bone PET. Therefore, all the five lesion groups were correctly diagnosed on ^{18}F-fluoride bone PET (Table 4).

The extent of a benign bone lesion was more accurately assessed on ^{18}F-fluoride bone PET than on ^{99m}Tc-HDP bone scan, as was in malignant diseases. In a patient with intramuscular hemangioma (patient 1 in Table 2), the reactive bone lesions of the right tibia and fibula attributed to intramuscular hemangioma of the right tibialis posterior muscle were more clearly delineated from surrounding normal bone on ^{18}F-fluoride bone PET than on ^{99m}Tc-HDP bone scan (Fig. 5). Also in another benign bone disease (patient 3 in Table 2), the extent of bone lesion was greater on bone PET than on bone scan.

Discussion

This is the first clinical report on ^{18}F-fluoride bone PET in Korea. In the present study, patients were divided into two groups: a malignant bone disease group (n=13) and a benign condition group (n=5). The diagnostic accuracy of ^{18}F-fluoride bone PET was excellent in both the groups. The single false-negative finding on ^{18}F-fluoride PET was attributable to its low spatial resolution because the lesions were very small, and the single false-positive finding was related to underlying bone destruction or inflammation after operation and radiotherapy. Therefore, when bone metasta-

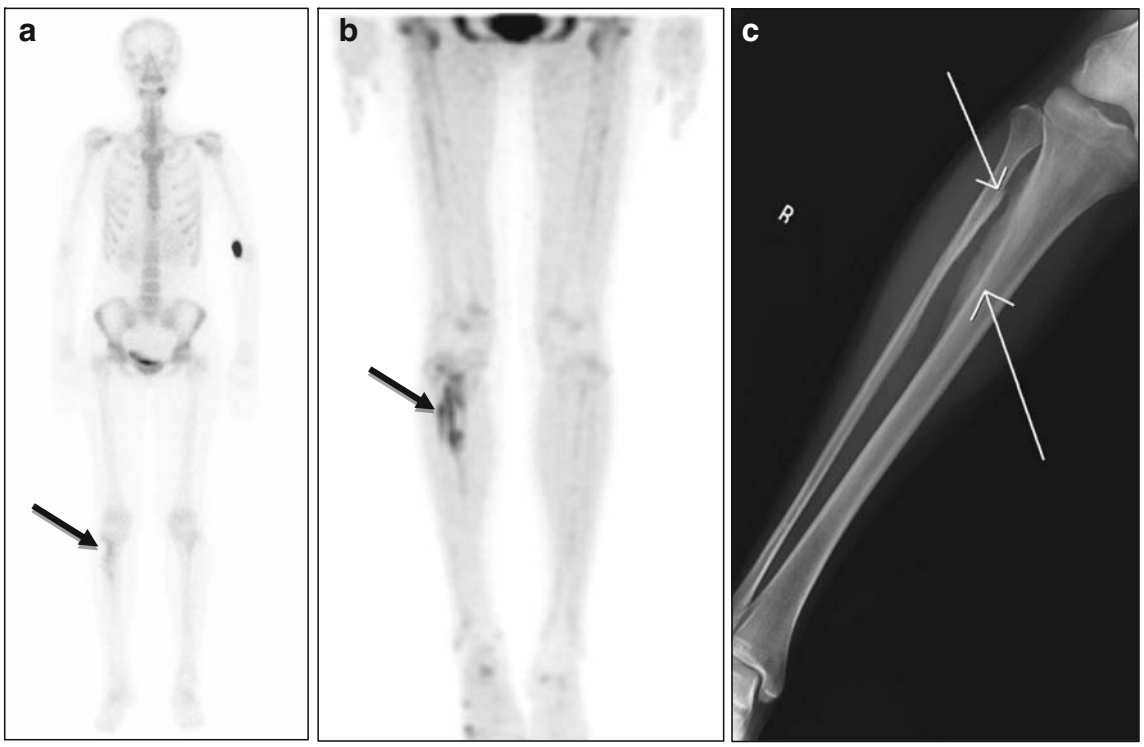

Fig. 5a–c ^{18}F-fluoride bone PET depicted more intense and more extensive reactive bone lesions than ^{99m}Tc-HDP bone scan. **a** A 25-year-old female patient with intramuscular hemangioma in the right tibialis posterior muscle was found to have reactive bone lesions in the right tibia and fibular by ^{99m}Tc-HDP bone scan (*black arrow*). **b** However, ^{18}F-fluoride bone PET demonstrated more intensive and extensive bone lesions. **c** Simple radiography visualized reactive bone lesions of the right tibia and fibular (*white arrows*)

sis was an issue in the management of malignant disease, ^{18}F-fluoride bone PET could provide the information on the presence of bone metastasis. Benign conditions were also effectively diagnosed using ^{18}F-fluoride bone PET. Of the whole 20 lesion groups evaluated in this study, 18 (90%) were correctly identified by ^{18}F-fluoride bone PET.

In malignant bone diseases, the sensitivity and the specificity were calculated as 86% and 88%, respectively. However, the specificity of ^{18}F-fluoride bone PET in this study should be interpreted with caution because uptake of ^{18}F-fluoride in degenerative lesions was excluded from the analysis. Although uptake of ^{18}F-fluoride in degenerative lesions such as bony spur or spinal endplate is a frequently observed finding and can be easily differentiated on ^{18}F-fluoride bone PET, it is usually not a concern in the evaluation of bone lesions in cancer patients. If such bone lesions had been included, the specificity of ^{18}F-fluoride bone PET would be much higher.

Patients with benign bone diseases are also good candidates for ^{18}F-fluoride bone PET. Bone turnover was successfully evaluated using dynamic ^{18}F-fluoride bone PET [10] in bone graft [8] and in gastrectomy-induced osteopenia [9]. As in malignant diseases, ^{18}F-fluoride bone PET is a promising bone imaging method in benign bone conditions. Because ^{18}F-fluoride has better chemical and physical characteristics than ^{99m}Tc-phosphonate compounds, ^{18}F-fluoride PET can provide images of higher quality and better correlation with bone metabolism. Also in this study, ^{18}F-fluoride bone PET showed good results in benign conditions, especially in the assessment of the etiology of bone pain (Table 2), like previous reports [12, 13]. In terms of radiation safety, radiation exposure in ^{18}F-fluoride PET was reported to be similar to that in bone scans using ^{99m}Tc-phosphonate compounds [3].

In this study, the analysis was performed on the basis of lesion group. Because the number of bone lesions varied so much among the patients, the diagnostic performance would have been distorted if the analysis was performed on a lesion basis. For example, some patients (patients 7 and 10 in Table 1) had multiple bone lesions, which showed results similar to false-positive or true-positive, while most patients had only one bone lesion. These extreme cases may induce distorted results if the analysis was performed on a lesion basis. On the other hand, analysis on a patient basis also has some limitations. If a cancer patient complains of new bone pain, the pain site should be assessed apart from known bone metastasis. As a result, we adopted analysis on a lesion-group basis, and 20 lesion groups of 18 patients were included in the analysis.

The small number of patients enrolled in this study is a limitation for a more reliable conclusion about the diagnostic accuracy of ^{18}F-fluoride bone PET. Another limitation of this study is that it was not a systematic comparison study between ^{18}F-fluoride bone PET and well-established imaging studies such as bone scan, CT, and MRI. Because ^{18}F-fluoride bone PET was performed at the request of clinicians, matched bone scan or MRI was not strictly acquired.

This is the first clinical study on ^{18}F-fluoride bone PET in Korea, and showed promising potential of ^{18}F-fluoride bone PET in malignant diseases and various benign conditions. Therefore, further studies are requested on the diagnostic performance of ^{18}F-fluoride bone PET in comparison with other imaging modalities, and on the cost-effectiveness of ^{18}F-fluoride bone PET.

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