



Clinical value of dual-phase F-18 sodium fluoride PET/CT for diagnosing bone metastasis in cancer patients with solitary bone lesion

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Background: The present study aimed to investigate whether dual-phase F-18 sodium-fluoride (NaF) positron emission tomography/computed tomography (PET/CT) could improve the diagnostic accuracy of detecting bone metastasis in cancer patients with a solitary bone lesion compared to conventional F-18 NaF PET/CT.

Methods: We retrospectively enrolled 113 cancer patients who underwent dual-phase F-18 NaF PET/CT for the differential diagnosis of a solitary bone lesion seen on bone scintigraphy. According to the dual-phase PET/CT protocol, an early-phase scan was acquired immediately after radiotracer injection and a conventional F-18 NaF PET/CT scan was performed. The diagnostic abilities of the visual analysis of conventional and dual-phase PET/CT scans and two quantitative parameters (lesion-to-blood pool uptake ratio on early-phase scan and lesion-to-bone uptake ratio on conventional scan) for detecting bone metastasis were compared. The final diagnosis of bone metastasis was made by histopathological confirmation or follow-up imaging studies.

Results: A metastatic bone lesion was diagnosed in 28 patients (24.8%). The sensitivity, specificity, and accuracy were 100.0%, 70.6%, and 77.9%, respectively, for visual analysis of conventional F-18 NaF PET/CT, 92.9%, 42.4%, 54.9%, respectively, for lesion-to-bone uptake ratio, 96.4%, 88.2%, and 90.3%, respectively, for visual analysis of dual-phase PET/CT, and 92.9%, 81.2%, and 83.2%, respectively, for lesion-to-blood pool uptake ratio. Visual analysis of dual-phase PET/CT was shown to have the highest area under the receiver operating characteristic curve value (0.923; 95% CI, 0.858–0.965) among all parameters.

Conclusions: Dual-phase F-18 NaF PET/CT showed a high diagnostic ability for detecting bone metastasis with improved specificity and accuracy compared to conventional F-18 NaF PET/CT in cancer patients. Dual-phase F-18 NaF PET/CT might help diagnose bone metastasis in patients with malignancies who were shown to have a solitary bone lesion on bone scintigraphy.

Keywords: Bone; diagnosis; F-18 Sodium-fluoride (NaF); metastasis; positron emission tomography (PET)

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Introduction

F-18 Sodium-fluoride (NaF) is a widely used bone-specific imaging radiotracer for positron emission tomography (PET) (1). Although F-18 NaF has a similar pharmacological behavior to that of Tc-99m labeled diphosphonate agents used for bone scintigraphy (1-4), F-18 NaF has superior pharmacokinetic characteristics for bone imaging including higher bone uptake, faster blood clearance and lower protein binding (3-6). Therefore, F-18 NaF PET was shown to have a significantly higher diagnostic accuracy for detecting bone metastasis than bone scintigraphy using Tc-99m labeled diphosphonate agents in patients with diverse malignant diseases (7-9). However, nonmetastatic bone lesions such as degenerative, traumatic, and inflammatory bone lesions can also show increased F-18 NaF uptake, which are considered false-positive findings in the detection of bone metastasis, thereby limiting its specificity (6,10). Consequently, in contrast to the sensitivity which was consistently high in previous studies, inconsistent results have been found regarding the specificity of F-18 NaF PET/CT (10-12).

A dual-phase F-18 NaF PET/CT imaging protocol was recently used to enhance the diagnostic ability in various bone and joint diseases (2,13-15). In the dual-phase PET/CT imaging protocol, early-phase PET/CT imaging is acquired within 10 minutes of F-18 NaF administration, in addition to conventional PET/CT imaging which is performed 30–45 minutes after F-18 NaF injection (2,16). An early-phase F-18 NaF PET/CT scan is known to provide the same information that can be acquired with the perfusion- and blood-pool phase images of the three-phase bone scintigraphy, showing increased radiotracer uptake in the lesion with regional hyperemia (2). Because metastatic bone lesions have high density of vasculature, metastatic bone lesions revealed increased radiotracer uptake on early-phase images of the three-phase bone scintigraphy and dual-phase F-18 NaF PET/CT in previous case reports (17-20). Considering the findings of these previous studies, F-18 NaF PET/CT with additional acquisition of early-phase images may help with the diagnosis of bone metastasis. However, in previously published literature, no studies have investigated the clinical value of dual-phase F-18 NaF

PET/CT in detecting bone metastasis.

Therefore, in the present study, we retrospectively enrolled patients with malignancies who had undergone dual-phase F-18 NaF PET/CT scan for evaluating a solitary bone lesion on bone scintigraphy and investigated whether dual-phase PET/CT could enhance the diagnostic ability to detect bone metastasis compared to conventional F-18 NaF PET/CT.

Methods

Study population

We retrospectively reviewed the electronic medical records of 148 patients with histopathologically diagnosed malignant diseases who underwent F-18 NaF PET/CT for diagnosing bone metastasis in our medical center between January 2015 and December 2018. Among these patients, a total of 113 patients (80 men and 33 women; age range of 39–84 years) were finally enrolled in the present study according to the following inclusion criteria: patients (I) who showed a solitary bone lesion suggestive of potential bone metastasis on staging Tc-99m methylene diphosphonate bone scintigraphy or a newly appeared solitary bone lesion suggestive of potential bone metastasis on surveillance bone scintigraphy without a previous history of bone metastasis, (II) who had undergone dual-phase F-18 NaF PET/CT for the differential diagnosis of the solitary bone lesion seen on bone scintigraphy, and (III) who had a histopathological confirmation of a bone lesion or had undergone follow-up imaging examinations for a clinical diagnosis of the bone lesion. We excluded the patients (I) who had a history of bone metastasis, (II) who were shown to have multifocal bone lesions suggestive of potential bone metastasis on bone scintigraphy, (III) in whom an early phase F-18 NaF PET/CT scan was not performed, (IV) in whom the final diagnosis of the bone lesion could not be determined, and (V) that had undergone any treatment for bone metastasis between their bone scintigraphy and PET/CT scan. The median interval between bone scintigraphy and F-18 NaF PET/CT was 17 days (range, 1–61 days).

This retrospective study was approved by the Institutional Review Board of our medical center (IRB

number: 2020-03-026). The study protocol was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Informed consent for dual-phase F-18 NaF PET/CT was obtained from the all patients enrolled in the present study before PET/CT scan.

Dual-phase F-18 NaF PET/CT scan

An F-18 NaF PET/CT scan was performed with a dedicated PET/CT scanner (Biograph mCT 128 scanner, Siemens Healthcare, Knoxville, TN, USA). A dual-phase F-18 NaF PET/CT scan consists of an early-phase scan and a conventional scan with both phase scans performed with static imaging as described in our previous study (2). There were no special patient preparations before PET/CT scanning. For the early-phase PET/CT scan, the anatomical parts of patients in which the solitary bone lesion were observed on bone scintigraphy were placed at the center of the field of view. Immediately after intravenous injection of 185 MBq of F-18 NaF, early-phase PET/CT images were acquired. Initially, a noncontrast-enhanced CT scan was performed at 100 mA and 120 kVp with a slice thickness of 5 mm. Subsequently, a PET scan was performed in one or two bed positions at 2 minutes for bed position using a three-dimensional acquisition mode. After the early-phase PET/CT scan, a conventional PET/CT scan was performed approximately 45 minutes after the F-18 NaF injection. The conventional PET/CT scan was performed from the vertex to the proximal femur or from the vertex to the feet according to the clinical condition of the patient using the same setting as in the early-phase scan. All PET images were reconstructed using point-spread-function modeling and time-of-flight reconstruction with attenuation correction.

F-18 NaF PET/CT image analysis

All dual-phase F-18 NaF PET/CT images were retrospectively reviewed by four nuclear medicine physicians and two quantitative parameters, the lesion-to-blood pool uptake ratio and the lesion-to-bone uptake ratio, were measured. Two nuclear medicine physicians (JWL and SJJ) visually assessed only the conventional PET/CT images and measured the lesion-to-bone uptake ratio. The other two nuclear medicine physicians (YJP and SML) visually evaluated the dual-phase PET/CT scan images and measured the lesion-to-blood pool uptake ratio. Discrepancies between

the two readers were resolved by discussion in order to reach a consensus. Only primary tumor sites and bone scintigraphy images performed before the PET/CT were provided to the nuclear medicine physicians who were blinded to any other clinical information.

On visual analysis of the conventional scan images, suspected bone lesions corresponding to solitary bone lesions on bone scintigraphy were interpreted as positive or negative for bone metastasis. Bone lesions that showed intense radiotracer uptake and were considered unrelated to benign processes were determined to be positive bone lesions. Negative bone lesions were defined as lesions in which radiotracer uptake was not intense, located around the joint area, or lesions related to benign processes, such as enthesopathies, degenerative changes, or iatrogenic lesions. For visual analysis of the dual-phase PET/CT images, conventional PET/CT images were evaluated first; for the bone lesions that were positive on conventional PET/CT images, early-phase scan images were further assessed. On early-phase scans, a positive bone lesion was defined as a bone lesion with increased radiotracer uptake similar to or greater than the uptake of the blood pool. Bone lesions that showed positive uptake on both early-phase and conventional scans images were classified as positive bone lesion on dual-phase PET/CT.

For quantitative analysis, the lesion-to-blood pool uptake ratio on early-phase images and the lesion-to-bone uptake ratio on conventional scan images were measured. The standardized uptake value (SUV) was used as a descriptive indicator for the degree of uptake by the bone lesion. On both early-phase and bone-phase PET/CT images, a spheroid-shaped volume-of-interest (VOI) was manually drawn for the suspected bone lesion, and the maximum SUV of the suspected bone lesion was calculated. For measuring reference organ uptake, the mean SUVs of the blood pool uptake on early-phase scan images and the normal bone uptake on conventional scan images were calculated. For analysis of blood pool uptake, VOIs were manually drawn over the artery, and the arterial wall containing calcified plaques was excluded from the VOIs. For normal bone uptake, three VOIs were manually drawn over the vertebral bodies of the thoracic and lumbar spines and the mean SUV of those three VOIs were calculated. Using the maximum SUV of the bone lesion and mean SUV of blood pool and normal bone, the lesion-to-blood pool uptake ratio and lesion-to-bone uptake ratio were calculated for each suspected bone lesion.

Standard of reference

All patient clinical information, including the results of physical, laboratory, imaging, and histopathological examinations, were obtained from their electronic medical records. In patients who had undergone bone biopsy, the final diagnosis was made by histopathological evaluation. In patients who had not undergone bone biopsy, an imaging-based diagnosis was made using follow-up imaging studies that were performed at least 1 year after the PET/CT scan. Patients who demonstrated signs of progression of their bone lesion, osteolytic lesions changing into osteosclerotic lesions during treatment, or an increased number of bone lesions suggestive of potential bone metastasis on follow-up imaging examinations were considered to have metastatic bone lesions. A multidisciplinary team consisting of three experienced board-certified physicians who did not participate in the PET/CT imaging analysis reviewed medical records and follow-up imaging examinations of patients, making the final clinical diagnosis of suspected bone lesions without knowing the dual-phase PET/CT results. According to the final diagnosis, all patients were categorized into two groups: patients with metastatic bone lesions and patients with nonmetastatic bone lesions.

Statistical analysis

Based on the results of the visual image analysis, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the visual analysis of conventional and dual-phase PET/CT for detecting bone metastasis were determined. The diagnostic accuracies of four parameters of PET/CT (visual analysis and lesion-to-bone uptake ratio on conventional PET/CT and visual analysis and lesion-to-blood pool uptake ratio on dual-phase PET/CT scans) were evaluated on the basis of the area under the receiver operating characteristic (ROC) curve (AUC) values. With the optimal cut-off values determined by the ROC curve analysis, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of lesion-to-blood pool uptake ratio and lesion-to-bone uptake ratio were assessed. On comparing AUC values between parameters, a Bonferroni correction was performed to adjust for multiple comparisons. Mann-Whitney test was performed to compare differences in the lesion-to-blood pool uptake ratios on early-phase scans and lesion-to-bone uptake ratios on conventional scans between metastatic bone lesions and nonmetastatic bone lesions. The Kruskal-

Wallis test with post-hoc comparisons was performed to compare the lesion-to-blood pool uptake ratio and lesion-to-bone uptake ratio according to the dual-phase PET/CT findings and CT findings. MedCalc Statistical Software (version 19.2, MedCalc Software, Ostend, Belgium) was used for all statistical tests. A P value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

The characteristics of the 113 enrolled patients are summarized in *Table 1*. The most common site of primary cancer lesions in enrolled patients was prostate (62.8%), followed by breast (20.4%). No enrolled patients had any previous history of bone metastasis or metabolic bone disease or any other recent major traumatic events. Of all patients, 38 (33.6%) had a solitary bone lesion on initial staging bone scintigraphy, and the remaining 75 (65.4%) had a newly appeared solitary bone lesion on surveillance bone scintigraphy during or after treatment. Most of the solitary bone lesions suggestive of potential bone metastasis were located in spine, pelvic bone, or sacrum.

Of the enrolled patients, metastatic bone lesions were diagnosed in 28 patients (24.8%) and the remaining 85 patients (75.2%) were diagnosed with nonmetastatic bone lesions. The most common site of bone metastasis was pelvic bone (10 patients, 35.7%), followed by spine (7 patients, 25.0%), rib (5 patients, 17.9%), sacrum (4 patients, 14.3%), femur (1 patient, 3.6%), and scapula (1 patient, 3.6%). Among the 28 patients with metastatic bone lesions, 6 patients (21.4%) were diagnosed by bone biopsy and the diagnosis of the remaining 22 patients (78.6%) was made by follow-up imaging studies. On CT images of F-18 NaF PET/CT, 16 metastatic bone lesions (57.1%) showed osteolytic features, 6 lesions (21.4%) osteosclerotic features, 3 lesions (10.7%) mixed features, and the remaining 3 lesions (10.7%) showed no abnormal findings.

Diagnostic ability of conventional PET/CT

The results of the visual analysis of F-18 NaF PET/CT images are shown in *Table 2*. On visual analysis of conventional PET/CT, all 28 metastatic bone lesions were considered to be positive bone lesions, resulting in a sensitivity of 100% (*Figure 1*). Meanwhile, there were 25

Table 1 Patient demographics (n=113)

Characteristics	Number of patients (%)
Age	67 years (39–84 years) [†]
Sex	
Men	80 (70.8)
Women	33 (29.2)
Primary tumor	
Prostate cancer	71 (62.8)
Breast cancer	23 (20.4)
Renal cell carcinoma	7 (6.2)
Urothelial carcinoma	3 (2.7)
Gastric cancer	3 (2.7)
Others [‡]	6 (5.3)
Reason for bone scintigraphy	
Initial staging	38 (33.6)
Surveillance	75 (65.4)
Anatomical sites of single bone lesion	
Spine	35 (31.0)
Pelvic bone	29 (25.7)
Sacrum	17 (15.0)
Rib	14 (12.4)
Femur	8 (7.1)
Sternum	6 (5.3)
Skull	2 (1.8)
Scapula	1 (0.9)
Clavicle	1 (0.9)

[†], expressed as median (range); [‡], Consisted of one patient with thymic cancer, one with rectal cancer, one with pancreatic cancer, one with lung cancer, one with gallbladder cancer, and one with malignant gastrointestinal stromal tumor.

false-positive bone lesions identified on visual analysis of conventional PET/CT images among the 85 nonmetastatic bone lesions. The visual analysis of conventional PET/CT showed a sensitivity of 100.0% (95% CI, 87.7–100.0%), specificity of 70.6% (95% CI, 59.7–80.0%), positive predictive value of 52.8% (95% CI, 44.6–60.9%), negative predictive value of 100.0%, (95% CI, 93.5–100.0%), and accuracy of 77.9% (Table 3). Among 28 patients with metastatic bone lesions, F-18 NaF PET/CT detected additional metastatic bone lesions in 7 patients (25.0%)

Table 2 The results of the visual analysis of dual-phase F-18 NaF bone PET/CT scan for detecting bone metastasis in 113 patients

	Final diagnosis	
	Bone metastasis	Nonmetastatic bone lesion
Conventional PET/CT		
Positive	28	25
Negative	0	60
Dual-phase PET/CT		
Positive	27	10
Negative	1	75

F-18 NaF, F-18 sodium fluoride; PET/CT, positron emission tomography/computed tomography.

which were not observed on bone scintigraphy (Figure 1).

On ROC curve analysis, the optimal cut-off value was 2.50 for the lesion-to-bone uptake ratio on the conventional scan. Using a cut-off value of 2.50, the lesion-to-bone uptake ratio on conventional scans showed a sensitivity of 92.9% (95% CI, 76.5–99.1%), specificity of 42.4% (95% CI, 31.7–53.6%), positive predictive value of 34.7% (95% CI, 30.1–59.5%), negative predictive value of 94.7% (95% CI, 82.2–98.6%), and accuracy of 54.9% (Table 3).

Diagnostic ability of dual-phase PET/CT

Of 28 metastatic bone lesions, the visual analysis of dual-phase PET/CT images detected 27 lesions, resulting in a sensitivity of 96.4% (Table 2). One patient with prostate cancer showed a false-negative finding on visual analysis of the dual-phase PET/CT images (Figure 2). Compared to the results of the visual analysis of conventional PET/CT images, the number of patients with false-positive findings was significantly reduced with the visual analysis of dual-phase PET/CT (P=0.005). The 15 lesions that were considered false-positive lesions on conventional PET/CT, but negative lesions on dual-phase PET/CT were located in the spine (5 lesions; Figure 3), rib (4 lesions), pelvic bone (2 lesions), skull (1 lesion), sternum (1 lesion), sacrum (1 lesion), and femur (1 lesion). The sites of primary cancers in those 15 lesions were the prostate (8 patients), breast (5 patients), kidney (1 patient), and thymus (1 patient). The final diagnosis of the 15 lesions were degenerative lesions (7 lesions), compression fractures or post-traumatic lesions (7 lesions), and benign bone tumor (1 lesion). Those 10

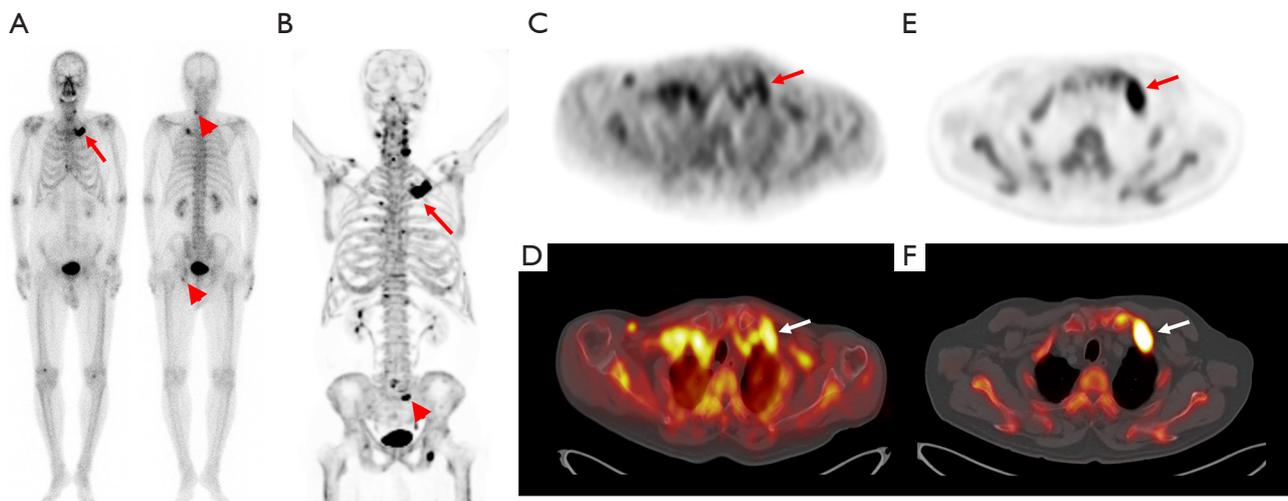


Figure 1 Bone scintigraphy (A) and transaxial PET (C) and fused PET/CT (D) from the early-phase scan and a maximum intensity projection image (B) and transaxial PET (E) fused PET/CT (F) images from the conventional scan in F-18 NaF PET/CT of a 78-year-old man with prostate cancer. During clinical follow-up after starting hormone treatment, he underwent surveillance bone scintigraphy because of his increased serum prostate-specific antigen level (24.55 ng/mL). On bone scintigraphy images (A), focally increased radiotracer uptake newly appears in his left 1st rib (arrow in A), while focally increased radiotracer uptake in the lower cervical spine and left acetabulum (arrowheads in A) is seen in a previous bone scintigraphy, and considered degenerative bone lesions. Both early-phase and conventional scan images show intensely increased radiotracer uptake at the left 1st rib (arrows in B-F) with a lesion-to-blood pool uptake ratio of 0.94, suggesting metastatic bone lesion. Furthermore, another focally increased radiotracer uptake is observed in the sacrum (arrowhead in B), suggesting another metastatic bone lesion. The left rib lesion was histopathologically confirmed to be a metastatic bone lesion from prostate cancer. PET/CT, positron emission tomography/computed tomography.

Table 3 Diagnostic accuracy of the visual analysis, lesion-to-blood pool uptake ratio on early-phase scan, and lesion-to-bone uptake ratio on convention scan

Diagnostic ability	Early-phase scan		Convention scan	
	Visual analysis	Lesion-to-blood pool uptake ratio	Visual analysis	Lesion-to-bone uptake ratio
Cut-off value	–	0.76	–	2.50
Sensitivity (%), (95% CI)	96.4 (81.7–100.0)	92.9 (76.5–99.1)	100.0 (87.7–100.0)	92.9 (76.5–99.1)
Specificity (%), (95% CI)	88.2 (79.4–94.2)	81.2 (71.2–88.8)	70.6 (59.7–80.0)	42.4 (31.7–53.6)
PPV (%), (95% CI)	73.0 (60.0–82.9)	61.9 (50.8–71.9)	52.8 (44.6–60.9)	34.7 (30.1–39.5)
NPV (%), (95% CI)	98.7 (91.6–100.0)	97.2 (90.0–99.2)	100.0 (93.5–100.0)	94.7 (82.2–98.6)
Accuracy (%)	90.3	83.2	77.9	54.9
AUC (95% CI)	0.923 (0.858–0.965)	0.917 (0.850–0.960)	0.853 (0.774–0.913)	0.756 (0.666–0.832)

PET/CT, positron emission tomography/computed tomography; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating characteristic curve.

lesions that still showed false-positive findings on dual-phase PET/CT images were clinically diagnosed with degenerative lesions, compression fractures or post-traumatic lesions on follow-up imaging studies (Figure 4).

The visual analysis of dual-phase PET/CT showed a sensitivity of 96.4% (95% CI, 81.7–100.0%), specificity of 88.2% (95% CI, 79.4–94.2%), positive predictive value of 73.0% (95% CI, 60.0–82.9%), negative predictive value

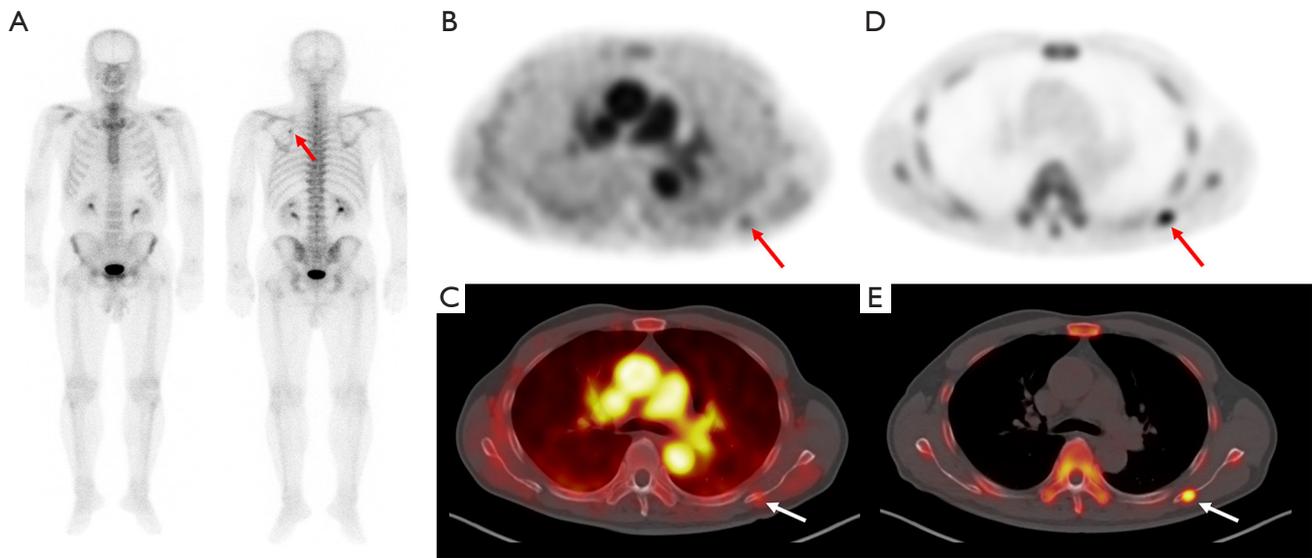


Figure 2 Bone scintigraphy (A) and transaxial PET (B) and fused PET/CT (C) from the early-phase scan and transaxial PET (D) and fused PET/CT (E) from the conventional scan in F-18 NaF PET/CT of a 72-year-old man with prostate cancer. Staging bone scintigraphy images show focally increased radiotracer uptake in the left scapula (arrow on A) with serum prostate-specific antigen level of 55.70 ng/mL. Bone-phase scan images show focal intensely increased radiotracer uptake in the left scapula (arrows on D and E); however, only mildly increased radiotracer uptake is observed on early-phase scan images (arrows on B and C) with a lesion-to-blood pool uptake ratio of 0.43. The lesion was clinically diagnosed as being a metastatic bone lesion. PET/CT, positron emission tomography/computed tomography.

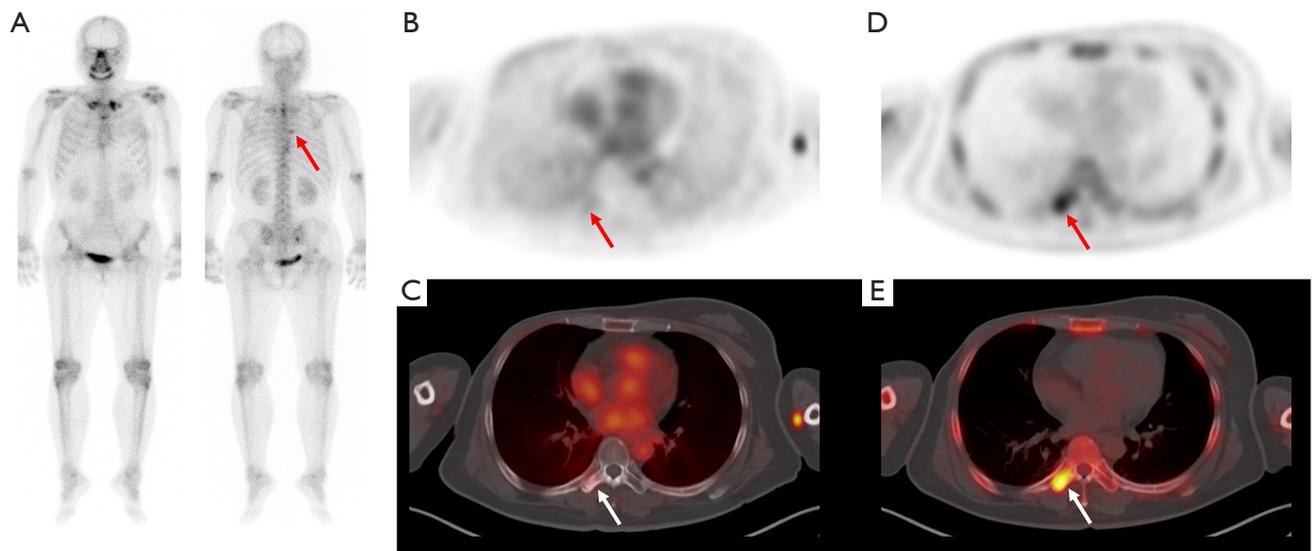


Figure 3 Bone scintigraphy (A) and transaxial PET (B) and fused PET/CT (C) from the early-phase scan and transaxial PET (D) and fused PET/CT (E) from the conventional scan in F-18 NaF PET/CT of a 47-year-old woman with breast cancer. On surveillance bone scintigraphy after right mastectomy, focally increased radiotracer uptake is newly observed in the T7 spine (arrow in A). On bone-phase scan images, focal intensely increased radiotracer uptake is shown in the right transverse process of T7 spine (arrows on D and E), but only minimal radiotracer uptake was shown on early-phase scan images (arrows on B and C) with a lesion-to-blood pool uptake ratio of 0.29. On follow-up imaging studies, the bone lesion was clinically diagnosed as nonmetastatic bone lesion. PET/CT, positron emission tomography/computed tomography.

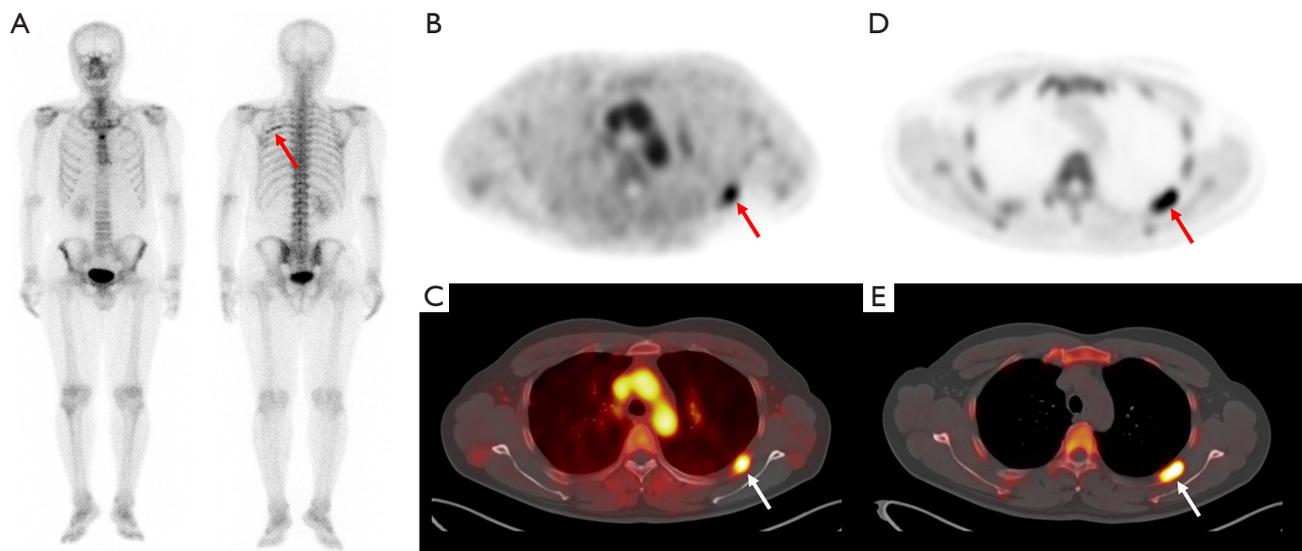


Figure 4 Bone scintigraphy (A) and transaxial (B) and fused PET/CT (C) from the early-phase scan and transaxial PET (D) and fused PET/CT (E) from the conventional scan in F-18 NaF PET/CT of a 39-year-old man with renal cell carcinoma. On surveillance bone scintigraphy performed after curative surgical resection, an elongated rib lesion is shown (arrow on A). The rib lesion shows intensely increased radiotracer uptake on early-phase scan images (arrows on B and C) with a lesion-to-blood pool uptake ratio of 1.48 as well as on bone-phase scan images (arrows on D and E). The rib lesion was clinically diagnosed as nonmetastatic post-traumatic bone lesion by follow-up imaging studies. PET/CT, positron emission tomography/computed tomography.

of 98.7% (95% CI, 91.6–100.0%), and accuracy of 90.3% (Table 3). Because the additional metastatic bone lesions detected by F-18 NaF PET/CT were not included in the scan fields of early-phase scans in all 7 patients, those lesions could not be evaluated by early-phase scan images.

On the ROC curve analysis, using an optimal cut-off value of 0.76, the lesion-to-blood pool uptake ratio on early-phase scan showed a sensitivity of 92.9% (95% CI, 76.5–99.1%), specificity of 81.2% (95% CI, 71.2–88.8%), positive predictive value of 61.9% (95% CI, 50.8–71.9%), negative predictive value of 97.2% (95% CI, 90.0–99.2%), and accuracy of 83.2% (Table 3).

Comparison of quantitative parameters

In comparisons of quantitative parameters between metastatic and nonmetastatic bone lesions, 28 patients with metastatic bone lesions showed significantly higher values of both the lesion-to-blood pool uptake ratio on early-phase scan (1.59 ± 0.89 vs. 0.60 ± 0.31) and the lesion-to-bone uptake ratio on conventional scan (6.57 ± 3.58 vs. 3.65 ± 2.57) than 85 patients with nonmetastatic bone lesions ($P < 0.001$ for all; Figure 5). Of the 28 metastatic

bone lesions, 20 lesions (71.4%) had lesion-to-blood pool uptake ratios > 1.0 . In comparison of quantitative parameters according to the findings of dual-phase PET/CT (Table 4), the Kruskal-Wallis test revealed significant differences of both quantitative parameters among the groups ($P < 0.001$ for all). On post-hoc analysis, 28 patients with metastatic bone lesions and 10 patients with false-positive lesions on dual-phase PET/CT had significantly higher values of the lesion-to-blood pool uptake ratio and lesion-to-bone uptake ratio than 15 patients with false-positive lesions only on conventional PET/CT and 60 patients with negative findings on conventional PET/CT ($P < 0.05$). In comparison of quantitative parameters of 28 metastatic bone lesions according to the CT findings, there were no significant differences of either quantitative parameters between lesions with osteosclerotic features, osteolytic features, mixed features, and no abnormal CT findings by the Kruskal-Wallis test ($P > 0.05$; Table 4).

Comparison of ROC curves

On the ROC curve analysis, the results of the visual analysis of dual-phase PET/CT images revealed the highest AUC

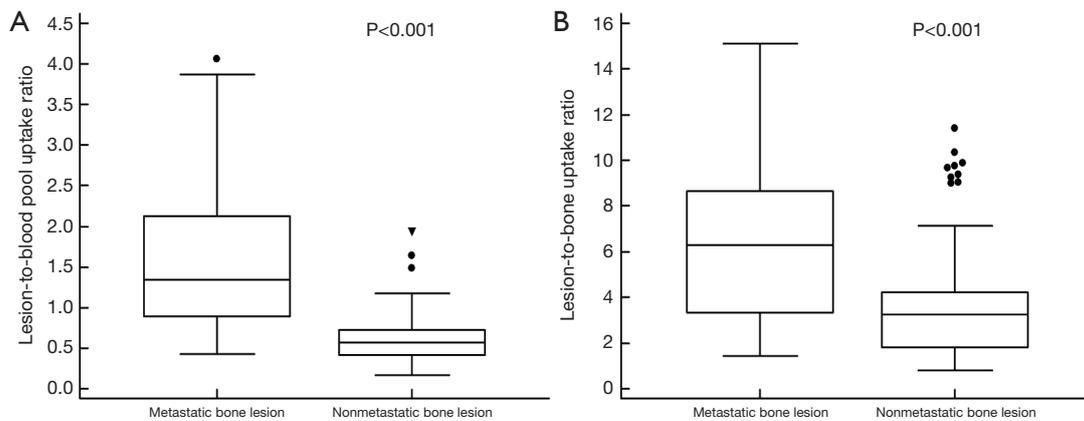


Figure 5 Distribution of the lesion-to-blood pool uptake ratio on an early-phase scan (A) and the lesion-to-bone uptake ratio on a conventional scan (B) in 28 metastatic bone lesions and 85 nonmetastatic bone lesions.

Table 4 The lesion-to-blood pool uptake ratio on early-phase scan and lesion-to-bone uptake ratio on conventional scan according to the findings of F-18 NaF PET/CT

Patient groups	CT findings	Lesion-to-blood pool uptake ratio	Lesion-to-bone uptake ratio
28 patients with metastatic bone lesions	Total	1.59±0.89	6.57±3.58
	Osteolytic (n=6)	1.65±1.34	5.66±4.11
	Osteosclerotic (n=16)	1.51±0.62	6.85±3.54
	Mixed (n=3)	1.28±0.55	6.92±5.83
	No abnormal finding (n=3)	2.18±1.46	6.55±0.46
10 patients with false-positive on dual-phase PET/CT		1.11±0.36	6.63±3.45
15 patients with false-positive only on conventional PET/CT		0.49±0.18	3.86±1.72
60 patients with true-negative on conventional PET/CT		0.53±0.26	3.28±2.28

F-18 NaF, F-18 sodium fluoride; PET/CT, positron emission tomography/computed tomography.

value (0.923; 95% CI, 0.858–0.965), followed by the lesion-to-blood pool uptake ratio in early-phase scans (AUC value, 0.917; 95% CI, 0.850–0.960), the results of the visual analysis of conventional PET/CT images (AUC value, 0.853; 95% CI, 0.774–0.913), and the lesion-to-bone uptake ratio in conventional scans (AUC value, 0.756; 95% CI, 0.666–0.832; *Table 3*; *Figure 6*). In the pairwise comparisons of AUC values between parameters of F-18 NaF PET/CT images after Bonferroni correction, the results of the visual analysis of the dual-phase PET/CT images showed significantly higher AUC values than the results of the visual analysis of conventional PET/CT images ($P=0.040$) and the lesion-to-bone uptake ratio in conventional scans ($P=0.003$). Moreover, the lesion-to-blood pool uptake ratio

in early-phase scans showed significantly higher AUC values than the lesion-to-bone uptake ratio in conventional scans ($P=0.004$). In contrast, other comparisons of AUC values failed to reveal any statistical significance ($P>0.05$).

Discussion

In this study, using a dual-phase protocol, we were able to improve the diagnostic ability of F-18 NaF PET/CT for diagnosing bone metastasis. Dual-phase F-18 NaF PET/CT was first introduced in 2014 for clinical use in patients with chronic osteomyelitis (13). Afterwards, several studies have shown the clinical value of dual-phase PET/CT imaging for evaluating surgical site infections following orthopedic

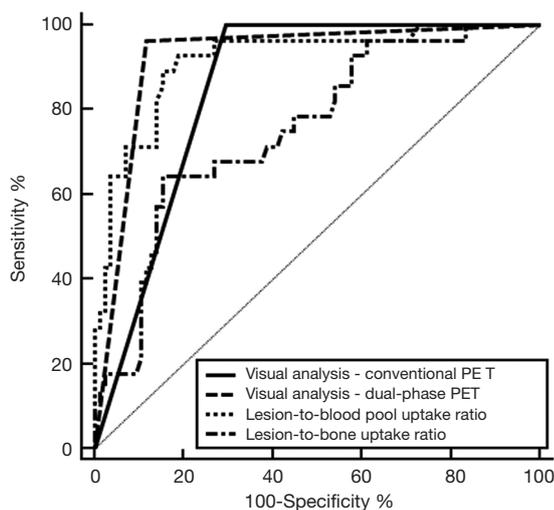


Figure 6 Comparison of receiver operating characteristic curves for the visual analysis of conventional PET/CT (conventional PET) and dual-phase PET/CT (dual-phase PET), the lesion-to-blood pool uptake ratio on the early-phase scan, and the lesion-to-bone uptake ratio on the conventional scan. PET/CT, positron emission tomography/computed tomography.

surgery, septic hip joints, and sacroiliitis (2,14,21-23). Since the degree of radiotracer uptake in early-phase scan images can reflect the regional hyperemia of a lesion, dual-phase F-18 NaF PET/CT has been shown to have a high diagnostic ability in the context of infectious inflammation and active sacroiliitis (2,14,23). In metastatic bone lesions, metastatic cancer cells stimulate angiogenesis by various tumor-derived growth factors to support the growth of the lesion, resulting in increased vascular structure densities (20,24). Our previous case report documented the case of a breast cancer patient who showed increased radiotracer uptake in early-phase F-18 NaF PET/CT images in metastatic bone lesions that was subsequently decreased after chemotherapy, suggesting that dual-phase scans might have a clinical role in diagnosing and evaluating treatment responses of bone metastasis (19). The present study assessed the clinical use of dual-phase F-18 NaF PET/CT imaging protocols for bone metastases and showed that 71.4% of metastatic bone lesions had higher radiotracer uptake than the blood pool on early-phase scan images, indicating increased perfusion and blood pool in metastatic bone lesions. With the help of early-phase scan findings, dual-phase F-18 NaF PET/CT showed high sensitivity and specificity for diagnosing bone metastasis.

Solitary bone metastasis is a very rare clinical condition,

accounting for only 2–3% of all malignant spread situations in the skeletal system (25). Although the spine and pelvic bone are the most common sites for solitary bone metastases and solitary bone metastases in the rib, skull, and extremities remain uncommon (25-29), the lesion site has no clinical value when differentiating metastatic bone lesions from benign bone lesions (30). Although planar bone scintigraphy has a high sensitivity for detecting bone metastasis with examining the whole-body skeleton, the ability of bone scintigraphy to differentiate metastatic bone lesions from benign bone lesions remains limited (31,32). Therefore, diverse imaging examinations, including single-photon emission computed tomography (SPECT)/CT, F-18 NaF PET/CT, F-18 fluorodeoxyglucose (FDG) PET/CT, and magnetic resonance imaging (MRI), have been used to improve the diagnostic accuracy for bone metastasis in patients with abnormal findings on bone scintigraphy (10,30,32-34). However, for patients who showed solitary bone lesions on bone scintigraphy, only a small number of studies have investigated the clinical value of the aforementioned imaging methods. SPECT/CT intrinsically had an inferior sensitivity and resolution than did F-18 NaF PET/CT images; however, previous studies demonstrated that SPECT/CT could improve the specificity for detecting bone metastasis and reduce the number of equivocal bone lesions (7,11,35,36). In previous studies comparing the diagnostic ability of FDG PET/CT with bone scintigraphy, most false-positive lesions on FDG PET/CT consisted of solitary bone lesions, and there was no significant difference in terms of the accuracy of diagnosis of solitary bone metastasis between them (32,37). Furthermore, another study with solitary bone lesions revealed the limited diagnostic accuracy for FDG PET/CT in differentiating metastasis among rib lesions (69.2%) (30). In terms of MRI, because only a few studies focused on the assessment of solitary bone lesion, its diagnostic ability cannot be properly estimated (34). In terms of F-18 NaF PET/CT, the present study was the first study to evaluate its diagnostic accuracy in the context of a solitary bone lesion. Similar to the results of studies in patients with multiple bone lesions (7-9), our study also revealed a high sensitivity of 100.0% for conventional PET/CT imaging in diagnosing bone metastasis in patients with solitary bone lesions. Meanwhile, a moderate specificity of 70.6% and accuracy of 77.9% were shown, which were quite a bit lower than the results of previous studies. Considering that solitary bone lesions on F-18 NaF PET/CT had often been categorized as inconclusive bone lesions in previously published studies

(6,7,9), conventional F-18 NaF PET/CT images could have a limited value in differentiating metastatic bone lesions from benign bone lesions in the context of solitary bone lesions. On the other hand, the specificity and accuracy of dual-phase F-18 NaF PET/CT increased to 88.2% and 90.3%, respectively, suggesting that F-18 NaF PET/CT with the dual-phase protocol could help with the differential diagnosis of bone metastasis. Along with other known imaging methods, dual-phase PET/CT could be considered another imaging method option for assessment of solitary bone lesions.

In contrast, the present study also revealed several limitations inherent to dual-phase F-18 NaF PET/CT. Since traumatic and inflammatory bone lesions are also accompanied by regional hyperemia, those bone lesions can still show false-positive findings on dual-phase PET/CT images (2,23,38), which limit the positive predictive value of dual-phase PET/CT. Furthermore, as shown in *Figure 4*, a metastatic bone lesion can show only mild radiotracer uptake in early-phase scan images, which would eventually lower the sensitivity of the scan compared to conventional PET/CT. Above all, dual-phase PET/CT can be performed only for a patient in whom the region of the target bone lesion can be selected, because early-phase scanning cannot cover the whole-body skeleton. Therefore, rather than being incorporated into routine clinical use, the selected use of dual-phase imaging protocol might be more beneficial in a context as shown in the present study.

Although one of the advantages of F-18 NaF PET/CT, as compared with bone scintigraphy, lies in its ability to quantitatively measure radiotracer uptake, the clinical values of the quantitative parameters of F-18 NaF PET/CT remain undefined (2,16,39). In our study, we also measured two quantitative parameters, the lesion-to-blood pool uptake ratio on early-phase scan and the lesion-to-bone uptake ratio on bone-phase scan, and compared their diagnostic ability to the results of the visual analysis. On comparing quantitative parameters, metastatic bone lesions were shown to have significant higher values of both parameters than did nonmetastatic bone lesions. However, given that the uptake levels of metastatic bone lesions overlapped with nonmetastatic bone lesions and that the location and pattern of uptake are also considered in the interpretation of F-18 NaF PET/CT images (7), the characterization of bone lesions solely based on quantitative parameters would have limited value. Accordingly, the present study showed that the quantitative parameter in each phase scan had a lower AUC value for diagnosing bone metastasis than the

results of the visual analysis. Nevertheless, considering the significant differences in the lesion-to-bone uptake ratios according to the findings of dual-phase PET/CT scan, the quantitative parameters measured on F-18 NaF PET/CT may play an auxiliary role in the characterization of bone lesions. Further studies are warranted to clarify their role.

This study has a number of unaddressed limitations. First, because a relatively small number of patients, with a broad age range, an unequal sex distribution, and selected from a single medical center, were enrolled in the study, the results need to be further validated. Moreover, due to its retrospective design, we were not able to investigate whether dual-phase PET/CT can lead to changes in treatment planning as compared to conventional PET/CT. Second, because only the patients who showed a solitary bone lesion on bone scintigraphy were enrolled in the study, the proportion of patients with metastatic bone lesions were relatively low, which might cause misunderstanding of clinical significance of dual-phase F-18 NaF PET/CT. Third, since SPECT/CT is known to have high diagnostic accuracy for detecting bone metastasis and to show similar ability to F-18 NaF PET/CT in reducing the equivocal lesions on bone scintigraphy (11,35,36), a future study that compares the diagnostic ability between SPECT/CT and dual-phase PET/CT is needed. Another limitation is that various types of cancer were included in the study, thereby leading increased clinical heterogeneity and inevitably affecting the results. Finally, histopathological confirmation, the current gold standard to prove a bone metastasis, was not performed in most metastatic bone lesions. However, performing a biopsy in every patient is impractical, and follow-up imaging studies have been commonly used as the standard of reference in other studies (40,41).

Conclusions

In the present study, conventional F-18 NaF PET/CT showed a sensitivity of 100% in the context of diagnosing bone metastasis in cancer patients with solitary bone lesions and detecting additional bone metastases in 25.0% of patients with metastatic bone lesions. However, because of the significant portion of patients with false-positive findings, conventional PET/CT was shown to have only moderate specificity and accuracy. Dual-phase F-18 NaF PET/CT showed both high sensitivity and specificity, improving the diagnostic accuracy to 90.3%, and the visual analysis of dual-phase PET/CT was shown to have the highest AUC value of 0.923 for diagnosing bone metastasis.

Dual-phase F-18 NaF PET/CT might be helpful for differentiating metastatic bone lesions in patients with malignancies who had been shown to have a solitary bone lesion on bone scintigraphy.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/qims-20-607>). The authors have no conflicts of interest to declare.

Ethical Statement: This retrospective study was approved by the Institutional Review Board of Soonchunhyang University Cheonan Hospital (IRB number: 2020-03-026), and the study protocol was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Informed consent for dual-phase F-18 NaF PET/CT was obtained from the all patients enrolled in the present study before the PET/CT scan.

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