Aim of the study: Bone scintigraphy (BS) and fluorine-18 deoxyglucose positron emission tomography computed tomography (^{18}F-FDG-PET/CT) are widely used for the detection of bone involvement. The optimal imaging modality for the detection of bone metastases in histological subgroups of non-small cell lung cancer (NSCLC) remains ambiguous. The aim of this study was to compare the efficacy of ^{18}F-FDG-PET/C and 99mTc-methylene diphosphonate (^{99m}Tc-MDP) BS in the detection of bone metastases of patients in NSCLC. Specifically, we compared the diagnostic accuracies of these imaging techniques evaluating bone metastasis in histological subgroups of NSCLC.

Material and methods: Fifty-three patients with advanced NSCLC, who had undergone both ^{18}F-FDG-PET/CT and BS and were eventually diagnosed as having bone metastasis, were enrolled in this retrospective study.

Results: The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ^{18}F-FDG-PET/CT and BS were 90.4%, 99.4%, 98.1%, 96.6%, 97.0% and 84.6%, 93.1%, 82.5%, 93.2, 90.8%, respectively. The κ statistics were calculated for ^{18}F-FDG-PET/CT and BS. The κ-value was 0.67 between ^{18}F-FDG-PET/CT and BS in all patients. On the other hand, the κ-value was 0.65 in adenocarcinoma, and 0.61 in squamous cell carcinoma between ^{18}F-FDG-PET/CT and BS. The κ-values suggested excellent agreement between all patients and histological subgroups of NSCLC.

Conclusions: ^{18}F-FDG-PET/CT was more favorable than BS in the screening of metastatic bone lesions, but the trend did not reach statistical significance in all patients and histological subgroups of NSCLC. Our results need to be validated in prospective and larger study clinical trials to further clarify this topic.

Key words: ^{18}F-FDG-PET/CT, ^{99m}Tc- methylene diphosphonate bone scintigraphy, bone metastases, non-small cell lung cancer.

Is there any significance of lung cancer histology to compare the diagnostic accuracies of ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP BS for the detection of bone metastases in advanced NSCLC?

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Introduction

Lung cancer is the most common among cancer-related deaths worldwide and non-small cell lung cancer (NSCLC) represents between 80% and 85% of all lung cancer cases [1]. At the time of diagnosis, two-thirds of patients with lung cancer are diagnosed with advanced disease. Bone is one of the most common metastatic sites of lung cancer patients. Bone metastases are seen in up to 30–40% of patients with advanced lung cancer. Once patients develop bone metastases, their disease is considered incurable. The median overall survival (OS) for these patients is 8–10 months [2, 3]. The consequences of bone metastasis include bone pain, life-threatening hypercalcemia, pathological fracture and spinal cord compression [4]. Diagnosis of bone metastasis plays an important role in enhancing the patient's quality of life.

Imaging methods are strong tools in evaluating bone metastasis. ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scintigraphy (BS) and fluorine-18 deoxyglucose positron emission tomography computed tomography (^{18}F-FDG-PET/CT) are widely used for the detection of bone involvement. Bone scintigraphy is still the diagnostically most precious and most cost-effective imaging modality. Bone scintigraphy is highly sensitive but usually has a low specificity [5–7]. Positron emission tomography is a marker of enhanced glucose uptake characteristic of malignant cells. ^{18}F-FDG-PET/CT has been shown to have a high sensitivity and specificity for the detection of bone metastases [8–11]. Nevertheless, its use has been limited because of the high cost and limited access.

The aim of this study was to compare the efficacy of ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP BS in the detection of bone metastases of patients with NSCLC. Specifically, we compared the diagnostic accuracies of ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP BS for the detection of bone metastases of patients in histological subgroups of advanced NSCLC.

Material and methods

Patient population

Fifty-three patients with advanced NSCLC, who had undergone both ^{18}F-FDG-PET/CT and BS for initial staging work-up, were enrolled in this

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retrospective study. The interval between ^{99m}Tc-MDP BS and ^{18}F-FDG-PET/CT scan was within 2 months (median, 1 month). Exclusion criteria were as follows: any prior therapeutic intervention; and history of any other malignancy.

FDG-PET imaging

Fluorine-18 deoxyglucose-PET was performed prior to the start of chemotherapy treatment. Whole-body FDG-PET was scanned using the same scanner, a Biograph 6 PET/CT scanner (CTI/Siemens, Knoxville, TN). After a 4-hour fast, patients were injected with 370-555 MBq ^{18}F-FDG intravenously. Then, 1 hour after the injection, CT and PET scans were performed. Blood sugar levels were required to be less than 150 mg/dl prior to FDG injection.

Bone scintigraphy

Bone scintigraphy was performed using a dual-head gamma camera (Infinia Hawkeye, GE Healthcare, Milwaukee, WI, USA) equipped with a low-energy general-purpose collimator. Bone scan images were acquired 3–4 h after the intravenous injection of 740 MBq (20 mCi) of ^{99m}Tc-MDP at a scanning speed of 15 cm/min.

Image analysis

The skeletal system was divided into eight regions (skull, vertebra, sternum and clavicles, scapula, ribs, pelvis, upper limbs, and lower limbs). The detection rates of ^{18}F-FDG-PET/CT and BS for bone metastases were calculated on a per-lesion basis. Two experienced nuclear medicine physicians and one radiologist interpreted the ^{18}F-FDG-PET/CT studies and BS. Patients were monitored for at least 6 months.

Bone involvement was confirmed using the following criteria: 1) follow-up screening to progression of bone lesions; 2) bone metastases were confirmed by simple X-ray or magnetic resonance imaging (MRI); and 3) positive initial findings on both BS and ^{18}F-FDG-PET/CT in the same bone lesion with symptoms.

They commented ^{18}F-FDG-PET/CT or BS images independently using a 3-point visual scale for bone metastases according to a 3-point categorical scale [0 = negative (normal or benign), 1 = indefinite, and 2 = positive]. When the reviewers did not agree, they interpreted the images together to reach a consensus. ^{18}F-FDG-PET/CT or BS studies with a score of 2 were read as positive, while scores of less than 2 were read as negative. Patients who demonstrated no evidence suggesting bone metastases during the follow-up period were accepted to have no bone metastases.

Statistical analysis

All of the analyses were performed using the SPSS statistical software program package (SPSS, version 11.5 for Windows). The differences of the clinical characteristics between the two groups were analyzed by chi-square test and Student's t-test. In addition, for each of the modalities, the sensitivity, specificity, positive predictive, negative predictive, and accuracy values were calculated. The detection of bone metastasis by ^{18}F-FDG-PET/CT, and BS were compared by the McNemar test. Differences were assumed to be significant when the P value was less than 0.05. To evaluate the independent contributions of ^{18}F-FDG-PET/CT and BS in predicting bone metastasis, the kappa (κ) statistic was calculated to determine the agreement between variables. The κ value was categorized as follows: poor (< 0.30), good (0.31–0.60), and excellent (0.61–1.0).

Results

Patient characteristics

The median age of patients was 56.0 years (range 28–76) with 47 (88.7%) males and 6 (11.3%) females. Adenocarcinoma was the most common histological subgroups (43.4%). In 14 NSCLC cases (26.4%), type determination could not be made. The patient baseline characteristics are listed in Table 1.

Forty-seven patients (88.7%) had metastatic NSCLC at the time of diagnosis. The bone metastasis was often detected in more than one area in 64.1% of the patients. The most common metastasis area was the vertebral bones (58.5%). The localization of bone metastasis is shown in Table 2.

PET/CT

The results of ^{18}F-FDG-PET/CT and BS on a lesion-basis analysis are shown in Table 3. ^{18}F-FDG-PET/CT detected 103

Table 1. Patient and disease characteristics

Characteristics	N (%)
Sex	
male	47 (88.7%)
female	6 (11.3%)
Age, years, median (range)	56.0 (range 28–76)
Histology	
adenocarcinoma	23 (43.4%)
squamous cell carcinoma	16 (30.2%)
unknown	14 (26.41%)

Table 2. Localization of bone metastasis

Location	N (%)
vertebra	33 (62.3%)
costa	28 (52.8%)
pelvis	24 (45.3%)
lower limbs	17 (32.1%)
upper limbs	11 (20.8%)
sternum	9 (17.0%)
scapula	8 (15.1%)
skull	8 (15.1%)

Table 3. The results of PET/CT and BS for detecting bone metastasis on a lesion-basis analysis

	Clinical and pathological findings	
	positive	negative
PET/CT		
positive	103	2
negative	11	308
Bone scintigraphy		
positive	99	18
negative	21	286

lesions and there were two false-positive bone lesions. In contrast, BS only detected 99 metastatic bone lesions and 18 false-positive lesions were found.

The ^{18}F-FDG-PET/CT had 90.4% sensitivity, 99.4% specificity, 98.1% positive predictive value, 96.6% negative predictive value, and 97.0% accuracy in all patients. For adenocarcinoma histology, the ^{18}F-FDG-PET/CT had 95.5% sensitivity, 99.3% specificity, 97.7% positive predictive value, 98.6.7% negative predictive value, and 98.4% accuracy, while this imaging method had 97.4% sensitivity, 98.9% specificity, 97.4% positive predictive value, 98.9% negative predictive value, and 98.4% accuracy in squamous cell carcinoma histology. The sensitivity, specificity, positive predictive value,

Table 4. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET/CT

	Sensitivity	Specificity	PPV	NPV	Accuracy
NSCLC (all patients)	90.4%	99.4%	98.1%	96.6%	97.0%
Adenocarcinoma	95.5%	99.3%	97.7%	98.6.7%	98.4%
Squamous cell carcinoma	97.4%	98.9%	97.4%	98.9%	98.4%

PPV – positive predictive value; NPV – negative predictive value

Table 5. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of BS

	Sensitivity	Specificity	PPV	NPV	Accuracy
NSCLC (all patients)	84.6%	93.1%	82.5%	93.2%	90.8%
Adenocarcinoma	82.2%	96.4%	88.1%	94.4%	92.9%
Squamous cell carcinoma	79.5%	92.2%	81.6%	91.2%	89.0%

PPV – positive predictive value; NPV – negative predictive value

Table 6. Agreement between PET/CT and bone scintigraphy

	κ	*p*
NSCLC (all patients)	0.67	< 0.001
Adenocarcinoma	0.65	0.001
Squamous cell carcinoma	0.61	0.01

negative predictive value, and accuracy were similar in histological subgroups of NSCLC ($p > 0.05$) (Table 4).

Bone scan

The BS sensitivity was 84.6%, specificity was 93.1%, positive predictive value was 82.5%, negative predictive value was 93.2%, and accuracy was 90.8%. For adenocarcinoma histology, the BS had 82.2% sensitivity, 96.4% specificity, 88.1% positive predictive value, 94.4% negative predictive value, and 92.9% accuracy, whereas this imaging method had 79.5% sensitivity, 92.2% specificity, 81.6% positive predictive value, 91.2% negative predictive value, and 89.0% accuracy in squamous cell carcinoma histology. The sensitivity, specificity, positive predictive value, negative predictive value, and accu-

racy were similar in histological subgroups of NSCLC ($p > 0.05$) (Table 5).

Accuracy and agreement between diagnostic modalities of bone metastasis

The McNemar comparison test showed that the specificity, positive predictive value, negative predictive value, and accuracy were similar between the two diagnostic modalities ($p = 0.27$).

The κ statistics were calculated for ^{18}F-FDG-PET/CT and BS. The κ-value was 0.67 between PET/CT and BS in all patients. On the other hand, the κ-value was 0.65 in adenocarcinoma, and 0.61 in squamous cell carcinoma between ^{18}F-FDG-PET/CT and BS. The κ-values suggested excellent agreement between the three groups (Table 6).

Discussion

Lung cancer is the most common among cancer-related deaths in both men and women worldwide [1]. Non-small cell lung cancer represents 80% to 85% of all lung cancer cases and the incidence of bone metastasis has been reported to range from 15% to 40%. Once patients develop bone metastases, the median survival time for these pa-

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tients is shorter than 1 year [2, 3]. Diagnosis of bone metastases plays an important role in enhancing the patient's quality of life [4, 12]. We performed a retrospective analysis of the diagnostic accuracies of ^{18}F-FDG-PET/CT and BS for the detection of bone metastases in advanced NSCLC. Specifically, we compared the diagnostic accuracies of these imaging techniques evaluating bone metastasis in histological subgroups.

Several studies have demonstrated the sensitivity of BS in the detection of bone metastases and it can easily evaluate the skeleton at a relatively low cost [13–17]. However, one limitation of skeletal scintigraphy is low specificity. Benign processes, such as infection, fractures, arthritis and osteomyelitis, cause increased bone turnover, result in a high false-positive rate and reduce the specificity of BS [18, 19].

^{18}F-FDG-PET/CT is a marker of enhanced glucose uptake characteristic of malignant cells. On the other hand, ^{18}F-FDG-PET/CT is suitable to use when assessing tumor viability during treatment in addition to morphologic monitoring by the CT portion. ^{18}F-FDG-PET/CT has been shown to have high sensitivity and specificity for the detection of bone metastases. Nevertheless, its use has been limited due to the high cost and limited access. ^{18}F-FDG-PET/CT has recently been reported to be valuable in assessing bone metastasis of NSCLC and has been shown to have similar sensitivity to BS [8–10]. In another study [14] it was found that ^{18}F-FDG-PET/CT and BS had similar sensitivity, but ^{18}F-FDG-PET/CT had better specificity and accuracy than BS. In a recent meta-analysis [20] it was found that the pooled sensitivity estimates for ^{18}F-FDG-PET/CT and BS were 91.9 and 91.8%, respectively. There was no significant difference between ^{18}F-FDG-PET/CT and BS ($p > 0.05$). This analysis [20] indicated that the specificity for ^{18}F-FDG-PET/CT and BS was 96.8 and 68.8%, respectively. The specificity of ^{18}F-FDG-PET/CT was significantly higher than BS ($p < 0.05$). In our study, ^{18}F-FDG-PET/CT had higher sensitivity and specificity than did BS, although it was not significant ($p = 0.27$). Our data showed that ^{18}F-FDG-PET/CT had a sensitivity of 90.4% and a specificity of 99.4%, and BS values were 84.6% and 93.1% in the diagnosis of bone metastasis in NSCLC. The specificity, positive predictive value, and accuracy of BS in the present study were higher than those of BS in previous studies because the majority of patients in our study (88.7%) had metastatic NSCLC at the time of diagnosis.

In spite of the fact that several studies were performed to compare the usefulness of ^{18}F-FDG-PET/CT and BS in detecting bone metastases in patients with NSCLC, these imaging methods were not investigated in the histological subgroups of advanced NSCLC. The McNemar comparison test in the histological subgroups of advanced NSCLC showed that the specificity, positive predictive value, negative predictive value, and accuracy were similar between the two diagnostic modalities ($p > 0.05$).

The present study has some limitations. Firstly, it is a retrospective study. Secondly, it lacks histopathological proof of lesions detected with ^{18}F-FDG-PET/CT or BS. Thirdly, there was a small number of patients. Fourth, there was no sub-analysis according to the radiologic pattern of metastases.

In conclusion, ^{18}F-FDG-PET/CT did not show statistically significantly better results than BS in this series. Our results need to be validated in prospective and larger clinical trials to further clarify this topic.

The authors declare no conflicts of interest.

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