Aim of the study: Bone scintigraphy (BS) and fluorine-18 deoxyglucose positron emission tomography computed tomography (18F-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 18F-FDG-PET/CT and 99mTc-methylene diphosphonate (99mTc-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 18F-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 18F-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 18F-FDG-PET/CT and BS. The κ-value was 0.67 between 18F-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 18F-FDG-PET/CT and BS. The κ-values suggested excellent agreement between all patients and histological subgroups of NSCLC.

Conclusions: 18F-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: 18F-FDG-PET/CT, 99mTc-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 18F-FDG-PET/CT and 99mTc-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. 99mTc-methylene diphosphonate (99mTc-MDP) bone scintigraphy (BS) and fluorine-18 deoxyglucose positron emission tomography computed tomography (18F-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. 18F-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 18F-FDG-PET/CT and 99mTc-MDP BS in the detection of bone metastases of patients with NSCLC. Specifically, we compared the diagnostic accuracies of 18F-FDG-PET/CT and 99mTc-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 18F-FDG-PET/CT and BS for initial staging work-up, were enrolled in this
Is there any significance of lung cancer histology to compare the diagnostic accuracies of 18F-FDG-PET/CT and 99m Tc-MDP BS for the detection of bone metastases in advanced NSCLC?

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 18F-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 99mTc-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 18F-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 18F-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 18F-FDG-PET/CT in the same bone lesion with symptoms.

They commented 18F-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. 18F-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 18F-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 18F-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 18F-FDG-PET/CT and BS on a lesion-basis analysis are shown in Table 3. 18F-FDG-PET/CT detected 103
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 18F-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 18F-FDG-PET/CT had 95.5% sensitivity, 99.3% specificity, 97.7% positive predictive value, 98.6% 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, negative predictive value, and accuracy 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 18F-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 18F-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-

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

| Clinical and pathological findings | PET/CT |  |
|-----------------------------------|-------|---|
|                                   | positive | negative |
| PET/CT positive                   | 103    | 2   |
| PET/CT negative                   | 11     | 308 |

| Bone scintigraphy                 | positive | negative |
|-----------------------------------|----------|----------|
| positive                          | 99       | 18       |
| negative                          | 21       | 286      |

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

| NSCLC (all patients)              | Sensitivity | Specificity | PPV   | NPV   | Accuracy |
|-----------------------------------|-------------|-------------|-------|-------|----------|
| Adenocarcinoma                    | 95.5%       | 99.3%       | 97.7% | 98.6% | 98.4%    |
| Squamous cell carcinoma           | 97.4%       | 98.9%       | 97.4% | 98.9% | 98.4%    |

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

| NSCLC (all patients)              | Sensitivity | Specificity | PPV   | NPV   | Accuracy |
|-----------------------------------|-------------|-------------|-------|-------|----------|
| Adenocarcinoma                    | 82.2%       | 96.4%       | 88.1% | 94.4% | 92.9%    |
| Squamous cell carcinoma           | 79.5%       | 92.2%       | 81.6% | 91.2% | 89.0%    |

**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 |
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?

Patients 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 metastases 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 88.8%, 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.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
2. Tsuya A, Kurata T, Tamura K, Fukuo K. Skeletal metastasis in nonsmall cell lung cancer: a retrospective study. Lung Cancer 2007; 57: 229-32.
3. Roodman GD. Mechanisms of bone metastasis. N Engl J Med 2004; 350: 1655-64.
4. Kosteva J, Langer C. The changing landscape of the medical management of skeletal metastases in nonsmall cell lung cancer. Curr Opin Oncol 2008: 20; 155-61.
5. Song JW, Oh YM, Shim TS, Kim WS, Ryu JS, Choi CM. Efficacy comparison between $(18)$F-FDG PET/CT and bone scintigraphy in detecting bony metastases of non-small-cell lung cancer. Lung Cancer 2009; 65: 333-8.
6. Tyliczek EW, Gottschalk A, Ludema K. Oncologic imaging: interactions of nuclear medicine with CT and MRI using the bone scan as a model. Semin Nucl Med 1997; 27: 142-51.
7. Fischer BM, Mortensen I, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. Ann Oncol 2007; 18: 338-45.
8. Kut V, Spies W, Spies S, Gooding W, Argiris A. Staging and monitoring of small cell lung cancer using $^{18}$F fluoro-2-deoxy-d-glucose-positron emission tomography (FDG-PET). Am J Clin Oncol 2007; 30: 45-50.
9. Cheran SK, Herndon JE 2nd, Patz EF Jr. Comparison of whole-body $^{18}$F-FDG PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer. Lung Cancer 2004; 44: 317-25.
10. Alfalo-Hazan V, Gutman F, Raileanu F, Pétiaux J, Kerrou K, Grahek D, Montravers F, Talbot JN. F-18 FDG PET and bone scintigraphy to search for bone metastasis of lung cancer. Rev Pneumol Clin 2006; 62: 164-9.
11. de Arcocha M, Portilla-Quattrociocchi H, Medina-Quiroz P, Carri JM. Current status of the use of 18F-sodium fluoride in bone disease. Rev Esp Med Nucl Imagen Mol 2012; 31: 51-7.
12. Skóra T, Kowalska T, Zawila K. Effectiveness of radioisotope therapy in bone metastases, based on personal experience. Wspolczesn Onkol 2012; 16: 201-5.
13. Min JW, Um SW, Yim JJ, Yoo CG, Han SK, Shim YS, Kim YW. The role of whole-body $^{18}$F-FDG PET/CT, $^{99m}$Tc MDP bone scintigraphy, and serum alkaline phosphatase in detecting bone metastasis in patients with newly diagnosed lung cancer. J Korean Med Sci 2009; 24: 275-80.
14. Huetzel M, Hetzel J, Arslanidemir C, Nüssle K, Schirmmeister H. Reliability of symptoms to determine use of bone scans to identify bone metastases in lung cancer: prospective study. BMJ 2004; 328: 1051-2.
15. Crippa F, Seregini E, Agresti R, Bombardieri E, Buraggi GL. Bone scintigraphy in breast cancer: a ten years follow up study. J Nucl Biol Med 1993; 37: 57-61.
16. Quinn DL, Ostrow LB, Porter DK, Shelton DK Jr, Jackson DE Jr. Staging of non-small cell bronchogenic carcinoma: relationship of the clinical evaluation to organ scans. Chest 1986; 89: 270-5.
17. Algra PR, Bloem IL, Tissing H, Falke TH, Arndt JW, Verboom LJ. Detection of vertebral metastases: comparison between MRI and bone scintigraphy. Radiographics 1991; 11: 219-32.
18. Cook GJ, Fogelman I. The role of positron emission tomography in the management of bone metastases. Cancer 2000; 88: 2927-33.
19. Loeffler RK, DiSimone RN, Howland WJ. Limitations of bone scanning in clinical oncology. JAMA 1975; 234: 1228-32.
20. Liu T, Xu JY, Xu W, Bai YR, Yan WL, Yang HL. Fluorine-18 deoxyglucose positron emission tomography, magnetic resonance imaging and bone scintigraphy for the diagnosis of bone metastases in patients with lung cancer: which one is the best? – a meta-analysis. Clin Oncol (R Coll Radiol) 2011; 23: 350-8.

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