RESEARCH ARTICLE

Significance of Hormone Receptor Status in Comparison of 18F -FDG-PET/CT and 99mTc-MDP Bone Scintigraphy for Evaluating Bone Metastases in Patients with Breast Cancer: Single Center Experience

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Abstract

Background: Fluorine-18 deoxyglucose positron emission tomography computed tomography (18F-FDG-PET/CT) and bone scintigraphy (BS) are widely used for the detection of bone involvement. The optimal imaging modality for the detection of bone metastases in hormone receptor positive (+) and negative (-) groups of breast cancer remains ambiguous. Materials and Methods: Sixty-two patients with breast cancer, who had undergone both 18F-FDG-PET/CT and BS, being eventually diagnosed as having bone metastases, were enrolled in this study. Results: 18F-FDG-PET/CT had higher sensitivity and specificity than BS. Our data showed that 18F-FDG-PET/CT had a sensitivity of 93.4% and a specificity of 99.4%, whiel for BS they were 84.5%, and 89.6% in the diagnosis of bone metastases. κ statistics were calculated for 18F-FDGPET/CT and BS. The κ-value was 0.65 between 18F-FDG-PET/CT and BS in all patients. On the other hand, the κ-values were 0.70 in the hormone receptor (+) group, and 0.51 in hormone receptor (-) group. The κ-values suggested excellent agreement between all patient and hormone receptor (+) groups, while the κ-values suggested good agreement in the hormone receptor (-) group. Conclusions: The sensitivity and specificity for 18F-FDG-PET/CT were higher than BS in the screening of metastatic bone lesions in all patients. Similarly 18F-FDG-PET/CT had higher sensitivity and specificity in hormone receptor (+) and (-) groups.

Keywords: Breast neoplasms - radionuclide imaging - positron-emission tomography and computed tomography

Asian Pac J Cancer Prev, **16 (1)**, 387-391

Introduction

Breast cancer is the second leading cause of cancer-related deaths in women (American Cancer Society, 2006). Bone is one of the most common metastatic sites in breast cancer patients. Bone metastases are seen in up to 70% of patients with advanced breast cancer. Once patients develop bone metastases, their disease is considered incurable. Breast cancer bone metastasis causing severe morbidity is commonly encountered in daily clinical practice (Erdogan and Cicin, 2014). The median overall survival is 19-25 months (Sherry et al., 1986; Singletary et al., 2003; Roodman, 2004; Tsuya et al., 2007). The consequences of bone metastases include bone pain, life-threatening hypercalcemia, pathological fractures and spinal cord compression (Hamaoka et al., 2004). Early diagnosis of bone metastases may prevent these complications and play an important role in enhancing the patient's quality of life.

Imaging is a good method to evaluate bone metastases in breast cancer. 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. BS can easily evaluate the skeleton at a relatively low cost. BS is highly sensitive but benign processes such as infection, fractures, arthritis and osteomyelitis can create false positives (Cook and Fogelman, 1999; Deeks, 2001; Hamaoka et al., 2004). 18F-FDG-PET/CT is known to be superior to BS because it can detect lytic bone metastases with a high sensitivity (Ohta et al., 2001; SN Yang, 2002; Nakai et al., 2005; Shie et al., 2008; Liu et al., 2011). The use of 18F-FDG-PET/CT is limited because it is costly and is not widely available.

The biology of breast cancer bone metastases is poorly understood. Previous clinical trials have demonstrated that bone relapse was significantly higher in ER-positive

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tumors (Coleman and Rubens, 1987; Koenders et al., 1991). No studies have compared 18F-FDG-PET/CT and BS for the detection of bone metastases in patients with hormone receptor positive and negative breast cancer.

The aim of this study was to compare the efficacy of 18F-FDG-PET/CT and 99mTc-methylene diphosphonate (99mTc-MDP) BS for the detection of bone metastases in patients with breast cancer. Specifically, we compared the diagnostic accuracies of these imaging techniques in the evaluation of bone metastases in hormone receptor positive and negative breast cancer.

Materials and Methods

Patient Population

Sixty-two patients with breast cancer, who had undergone both 18F-FDG-PET/CT and BS during the initial staging work-up, were enrolled in this study. The interval between the BS and 18F-FDG-PET/CT scans was within 2 months (median, 1 month). The exclusion criteria were as follows: any prior therapeutic intervention or history of any other malignancy.

The ER and progesterone receptor (PR) expression of the tumors were examined via immunohistochemistry (IHC) staining of the primary tumors. The tumor was considered ER positive if >1% of the tumor cells had nuclear staining for ER. The tumor was considered PR positive if >10% of the tumor cells had nuclear staining for PR. The hormone receptor positive group consisted of patients with ER-positive and/or PR-positive tumors, whereas patients who were ER- and PR-negative were placed in the hormone receptor negative group.

FDG-PET imaging

FDG-PET was performed prior to the start of chemotherapy treatment. Whole-body FDG-PET was performed on the same scanner in all patients, a Biograph 6 PET/CT scanner (CTI/Siemens, Knoxville, USA). After a 4-hour fast, patients were injected with 370-555 MBq 18F-FDG intravenously. One hour after the injection, CT and PET scans were performed. The blood sugar levels had to be less than 150 mg/dl prior to 18F-FDG injection.

Bone scintigraphy

BS was performed using dual-head gamma cameras (Infinia Hawkeye, GE Healthcare, Milwaukee, USA) equipped with a low-energy general-purpose collimator. Bone scan images were acquired 3-4 h after the intravenous injection of 740MBq (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, 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. One radiologist and one nuclear medicine physician reviewed the 18FFDG-PET/CT studies and BS images. The patients were monitored for at least 6 months. Bone involvement was confirmed using the following methods: patients received follow-up in order to detect progression of bone lesions; bone metastases were confirmed via plain X-ray or magnetic resonance imaging (MRI); finally, positive initial findings in symptomatic patients were confirmed with both BS and 18F-FDG-PET/CT on the same bone lesion. The 18F-FDG-PET/CT and BS images were examined independently using a three-point visual scale for bone metastases and graded using 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 until a consensus was reached. 18F-FDG-PET/CT or BS studies with a score of 2 were read as positive, whereas scores less than 2 were read as negative. Patients who demonstrated no evidence of bone metastases during the follow-up period were considered bone metastases-free.

Statistical analysis

All of the analyses were performed using the SPSS statistical software program package (version 11.5, Chicago, Il, USA). Differences in the clinical characteristics of the two groups were analyzed via the chi-square test and Student's t-test. For each of the imaging modalities, the sensitivity, specificity, positive predictive, negative predictive, and accuracy values were calculated. The detection of bone metastases by 18F-FDG-PET/CT, and BS were compared using 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 metastases, the kappa (κ) value was calculated. The κ value was categorized as follows: poor (<0.30), good (0.31-0.60), and excellent (0.61-1.0).

Table 1. Patient and Disease Characteristics

Characteristics	N	%
Sex		
Male	1	1.6
Female	61	98.4
Age, years, median (range)	44.5 (range 28-81)	
Hormone receptor		
ER (+)	33	53.2
PR (+)	23	37.1
CerbB2 (+)	31	54.4
Triple-negative	9	14.5
Hormone receptor (+) (ER and PR+)	37	59.7
Hormone receptor (-) (ER and PR-)	21	33.9
Unknown	6	9.7
Histology		
Ductal	54	88.5
Lobular	2	3.3
Mucinous	1	1.6
Mixt	4	6.6
Unknown	1	1.6
Localization of bone metastasis		
Vertebra	30	48.4
Costa	24	38.7
Pelvis	28	45.2
Lower limbs	20	32.3
Upper limbs	10	16.1
Sternum	19	30.6
Scapula	12	19.4
Skull	2	3.2

Results

Patient characteristics

The median age of the patients was 44.5 years (range, 28–81). The most common type of breast cancer was pure ductal carcinomas (88.5%). The tumors were frequently estrogen receptor-positive (53.2%). Thirty-seven patients (59.7%) were hormone receptor positive (estrogen receptor-positive and progesterone receptor-positive). The baseline patient characteristics are listed in Table 1.

Thirty-five patients (56.5%) had metastatic breast cancer at the time of diagnosis. Bone metastases were detected in more than one area in 59.6% of the patients. The most common area for bone metastases were the vertebral bones (48.4%). The distribution of the locations of bone metastases is shown in Table 1.

PET/CT

The results of the 18F-FDG-PET/CT and BS imaging are shown in Table 2. The 18F-FDGPET/CT imaging detected 141 true-positive lesions and there were two false-positive bone lesions. In contrast, BS only detected 127 true-positive bone lesions and 36 false-positive lesions were found. PET/CT identified true-positive findings in 141 lesions, whereas BS detected true-positive finding in 127 lesions. Figure 1 shows that 18F-FDG-PET/CT imaging identified bone metastases more significantly than BS in woman with hormone receptor positive breast cancer.

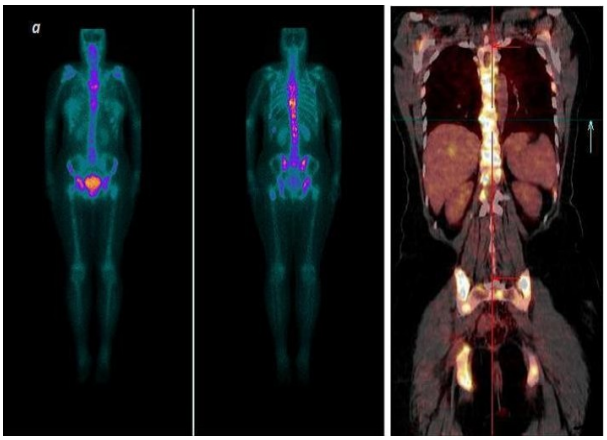

Figure 1. Examples of Varying Patterns of Bone Metastases Detected Using18F-FDG-PET/CT(a) and BS(b) in a 47-year Female Patient

Table 2. 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	141	2
	Negative	10	343
BS	Positive	127	36
	Negative	23	310

18F-FDG-PET/CT imaging had 93.4% sensitivity, 99.4% specificity, 98.6% positive predictive value, 97.1% negative predictive value and 97.6% accuracy rate in all patients. For the hormone receptor (+) group, 18F-FDG-PET/CT imaging had 95.7% sensitivity, 99.3% specificity, 99.1% positive predictive value, 97.3% negative predictive value and 98.0% accuracy. In the hormone receptor (-) group, this imaging method had 83.3% sensitivity, 99.2% specificity, 96.8% positive predictive value, 95.6% negative predictive value, and 95.8% accuracy. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were similar in the subtypes of breast cancer (statistically not significant) (Table 3).

Bone scan

The BS had a sensitivity of 84.5%, specificity of 89.6%, positive predictive value of 77.9%, negative predictive value of 93.1%, and accuracy of 88.1%. For the hormone receptor (+) group, the BS had a sensitivity of 87.8%, specificity of 89.4%, positive predictive value of 84.2%, negative predictive value of 91.2%, and accuracy of 88.8%. For the hormone receptor (-) group, this imaging method had 82.6% sensitivity, 90.2% specificity, 76.0% positive predictive value, 93.2% negative predictive value, and 88.1% accuracy. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were similar between the subtypes of breast cancer (Table 3).

Accuracy and agreement between diagnostic modalities of bone metastases

The McNemar comparison test showed that the sensitivity and specificity of 18F-FDG-PET/CT imaging were significantly higher than the BS imaging (p=0.008). The κ-value was calculated for 18F-FDG-PET/CT and BS. The κ-value was 0.65 for the 18FFDG- PET/CT and BS groups. In subgroup analysis of the 18F-FDG-PET/CT and BS groups, the κ-value was 0.70 for the hormone receptor (+) group, and 0.51 for the hormone receptor (-) group. The κ-values suggested that there is excellent concordance between all patients and hormone receptor

Table 4. Agreement between PET/CT and BS

	κ	p
Breast cancer (all patients)	0.65	<0.001
hormone receptor (+)	0.70	<0.001
hormone receptor (-)	0.51	<0.001

Table 3. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy of PET/CT and BS

	Sensitivity		Specificity		PPV		NPV		Accuracy	
	PET/CT	BS	PET/CT	BS	PET/CT	BS	PET/CT	BS	PET/CT	BS
Breast cancer (all patients)	93.4%	84.5%	99.4%	89.6%	98.6%	77.9%	97.1%	93.1%	97.6%	88.1%
hormone receptor (+)	95.7%	87.8%	99.3%	89.4%	99.1%	84.2%	97.3%	91.2%	98.0%	88.8%
hormone receptor (-)	83.3%	82.6%	99.2%	90.2%	96.8%	76.0%	95.6%	93.2%	95.8%	88.1%

*PPV, positive predictive value; NPV, negative predictive value; BS, bone scintigraphy

(+) groups. However, the κ- values suggested that the concordance was less strong between all patients and the hormone receptor (-) group (Table 4).

Discussion

Breast cancer is a serious health concern and one of the leading causes of death for women worldwide(American Cancer Society, 2006). Bone is one of the most common sites of distant metastases from breast cancer and the incidence of bone metastases has been reported to range from 65% to 75% in advanced stage disease. The median OS(Overall survival) for patients with bone metastases is 19- 25 months (Sherry et al., 1986; Singletary et al., 2003; Roodman, 2004; Tsuya et al., 2007). The consequences of bone metastases include bone pain, life-threatening hypercalcemia, pathological fractures and spinal cord compression (Hamaoka et al., 2004). The diagnosis of bone metastases has significant prognostic and therapeutic implications. We performed a retrospective analysis of the diagnostic accuracies of 18F-FDG-PET/CT and BS for the detection of bone metastases in breast cancer.

Specifically, we compared the diagnostic accuracies of these imaging techniques for the evaluation of bone metastases in hormone receptor positive and negative breast cancer. Despite the fact that several studies have compared the usefulness of different imaging methods for the detection of bone metastases in patients with suspected metastatic breast cancer, the optimal strategy for detecting bone metastases is still unknown. The National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines do not recommend specific imaging methods to evaluate patients with suspected metastatic breast cancer. Several clinical studies determined the sensitivity of BS for the detection of bone metastases. The BS technique can easily evaluate the skeleton at a relatively low cost. However, one limitation of BS is that it has low specificity. Benign processes, such as infection, fractures, arthritis and osteomyelitis cause increased bone turnover, and lead to a high false-positive rate and reduce the specificity of BS (Cook and Fogelman, 1999; Deeks, 2001; Hamaoka et al., 2004). 18F-FDG-PET/CT identifies areas of enhanced glucose uptake, which is characteristic of malignant cells. 18F-FDG-PET/CT is useful when assessing tumor viability during treatment in addition to monitoring morphological changes.

The specificity of 18F-FDG-PET/CT and BS were found to be similar in four clinical studies (Dose et al., 2002; Abe et al., 2005; Nakai et al., 2005; Mahner et al., 2008), whereas other studies showed that 18F-FDG-PET/CT had a higher specificity or sensitivity (Ohta et al., 2001; SN Yang, 2002; Gallowitsch et al., 2003; Liu NB et al., 2013). In these clinical studies, the median specificity was 82.4% (9.1%-99.0%) for BS and 92% (88.2%-99.0%) for 18F-FDG-PET/CT. There are a limited number of studies comparing integrated 18F-FDG-PET/CT with BS in patients with breast cancerm (Fuster et al., 2008; Morris et al., 2010). Fuster et al. (2008) compared 18F-FDG-PET/CT and BS and found that the sensitivity and specificity of 18F-FDG-PET/CT were higher than BS. Morris et al. (2010) compared the diagnostic performance of 18F-FDG-PET/CT and BS in women with suspected metastatic breast cancer. In their study (Morris et al., 2010), 18F-FDG-PET/CT and BS were highly concordant for the identification of bone metastases (81%). There was an 18% difference in these imaging methods. In our study, 18F-FDG-PET/CT had a higher sensitivity and specificity than BS. Our data showed that 18F-FDGPET/CT had a sensitivity of 93.4% and a specificity of 99.4%, and the sensitivity and specificity of BS were 84.5% and 89.6%, respectively, for the diagnosis of bone metastases.

The biology of breast cancer bone metastases is poorly understood. Previous clinical trials have demonstrated that the rate of bone relapse is significantly higher in ER-positive cases (Coleman and Rubens, 1987; Koenders et al., 1991). Additionally, the rate of bone metastases were significantly higher in ER-positive tumors than in ER-negative tumors (Basu et al., 2008; Wei et al., 2011). Despite the fact that past studies have compared the usefulness of 18F-FDG-PET/CT and BS in detecting bone metastases in patients with breast cancer, no studies have compared the utility of these imaging methods in hormone receptor positive and negative groups of breast cancer. The McNemar comparison test showed that the sensitivity and specificity of 18F-FDG-PET/CT were significantly higher than BS (p=0.008). The κ statistic was calculated for 18F-FDG-PET/CT and BS. The κ-value was 0.65 when comparing 18F-FDG-PET/CT and BS in all patients. The κ-value was 0.70 for the hormone receptor (+) group and 0.51 in the hormone receptor (-) group when comparing 18F-FDG-PET/CT and BS. The κ-values suggested excellent agreement between all patients and hormone receptor (+) groups, while the κ-values suggested good agreement in hormone receptor (-) group.

The present study has some limitations. Firstly, it is a retrospective study. Secondly, bone lesions detected by 18F-FDG-PET/CT or BS were not histopathologically confirmed. Thirdly, this was a small study. Lastly, there was no subgroup analysis based on the radiologic pattern of metastases.

In conclusion, the sensitivity and specificity for 18F-FDG-PET/CT were higher than BS when screening for metastatic bone lesions. Similarly, 18F-FDG-PET/CT had a higher sensitivity and specificity in hormone receptor (+) and (-) groups. These results need to be validated in large, prospective clinical trials to further clarify this topic.

Acknowledgements

We are grateful to Dicle University DUBAP for their sponsorship about English editing of this manuscript.

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