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ORIGINAL ARTICLE

Is ^{99m}Tc-MDP whole body bone scintigraphy adjuvant to ^{18}F-FDG-PET for the detection of skeletal metastases?

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Summary

Purpose: *Due to the fact that fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) and technetium-99m-methylenediphosphonate (^{99m}Tc-MDP) whole body scans identify bone metastases by different mechanisms, i.e. by using glucose metabolism and osteoblastic response in the bone, respectively, it can be expected that there may be some differences between these two methods in the number of lesions identified. The aim of this study was to compare the sensitivity,specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) in detecting bone metastases between ^{18}F-FDG-PET/CT and conventional ^{99m}Tc-MDP whole body scans.*

Methods: *Between 2006-2009, 121 patients with malignancies (62 male and 59 female, mean age 59.3±10.8 years, range 37-84) were examined with ^{18}F-FDG-PET/CT and conventional ^{99}Tc-MDP whole-body scans for detection of bone metastases.*

Results: *For ^{18}F-FDG-PET/CT and for ^{99m}TC-MDP, sensitivity, specificity, accuracy, PPV and NPV for detecting all studied bone metastases were 88.3, 83.6, 86.7, 91.7, 77.8% and 91.7, 71.0, 84.9, 86.6, 80.8%, respectively. For bone metastases of breast and lung cancers, the specificity and accuracy of PET/CT was higher than that of bone scintigraphy. On the other hand, the sensitivity of bone scintigraphy was higher than PET/CT in breast and lung cancers groups and all patients. In the detection of osteolytic and osteosclerotic metastases no difference was found between the two methods, while for osteolytic lesions the mean standardized uptake value (SUV) max was higher than for osteosclerotic lesions.*

Conclusion: *For the detection of bone metastases the spesificity and accuracy of ^{18}F-FDG-PET/CT were higher compared to bone scintigraphy, while the sensivity was lower. It is the opinion of the authors that both studies are complementary to final diagnosis.*

Key words: *bone metastases, bone scintigraphy, FDG-PET, ^{99m}Tc-MDP*

Introduction

Early diagnosis of skeletal metastases is important for treatment, monitoring and prognosis of cancer [1-9].Due to the fact that ^{18}F-FDG-PET/CT and ^{99m}Tc-MDP whole body scans identify bone metastases by different mechanisms, i.e. by using glucose metabolism and osteoblastic response in the bone, respectively, it can be expected that there may be some differences in the number of lesions identified by these two methods.

In this article we studied the sensitivity, specificity, PPV, NPV and accuracy of these two methods in the detection of bone metastases.

Methods

For this retrospective study, permission from Gaziantep University Medical Faculty Ethics Committee, number: 809, 13.11.2006 was granted. Between 2006-2009, we studied 121 patients (62 male and 59 female, age range 37-84, mean age 59.3±10.8 years) by ^{99m}Tc-MDP whole-body scintigraphy and ^{18}F-FDG-PET/CT scan performed for the diagnosis of metastases. Sixty-five of these patients had lung cancer, 41 breast cancer, 4 prostate cancer, 3 unknown primary tumor, 3 esophageal cancer, 2 laryngeal cancer, 2 renal cell carcinoma, and 1 multiple myeloma. Patients were studied when first diagnosed, before receiving anticancer treatment.

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All patients were examined by the whole body ^{18}F-FDG-PET/CT scanner (Siemens Biograph 2 dual slice PET/CT). The whole body bone scan for 107 patients was performed in our department using Philips Forte Dual Head Gamma Camera© and low energy-high resolution collimators, while 14 patients were examined in another hospital (11 patients by Siemens E-cam Dual Head Gamma Camera© and 3 patients by MIE Diacam Gamma Camera© Siemens USA).

Bone scans and ^{18}F-FDG-PET/CT images were evaluated by 3 nuclear medicine specialists and by radiologists at different times and without being aware of each others' findings. For both imaging modalities a 4-point scoring system was used for the evaluation of bone metastases as follows: a) absolutely no pathological involvement; b) suspected pathological involvement with slightly increased radiopharmaceutical uptake; c) quite pathological involvement with moderately increased radiopharmaceutical uptake; and d) definitely pathological involvement with intense increase of radiopharmaceutical uptake.

Bone metastases of CT images were classified in 4 categories as follows: a) lytic, b) sclerotic, c) of mixed character and d) benign, like degenerative, traumatic, arthritic changes, etc.

While giving the final decision on whether the bone lesions were metastatic, lesion appearance and distribution in the PET/CT and/or bone scintigraphy, and if any, CT and/or MR images and biopsy results were taken into account. For subjects who had no biopsy, thus creating doubt, decision was taken considering the other laboratory examinations, foresight of the clinician who was following the subject or the clinical course of the subjects.

Statistics

For bone scintigraphy and ^{18}F-FDG-PET/CT the number of bone lesions, sensitivity, specificity, accuracy, PPD and NPD were calculated for the entire study group and also separately for patients with lung and breast cancer who represented the majority of our study group. Differences between the percentages of the two studies were evaluated by McNemar's test. A p-value < 0.05 was considered as statistically significant. All statistical analyses were performed using SPSS version 9.

Results

Distribution of the metastatic bone lesions

In total, 653 bone lesions were detected in 121 patients included in this study by examining their PET/CT and bone scintigraphy images. Four hundred and thirty nine (67.2%) of these lesions were interpreted as skeletal metastases and 214 (32.8%) of them were evaluated as bone lesions with benign character. While 66% of the skeletal metastatic lesions were detected in axial and 34%

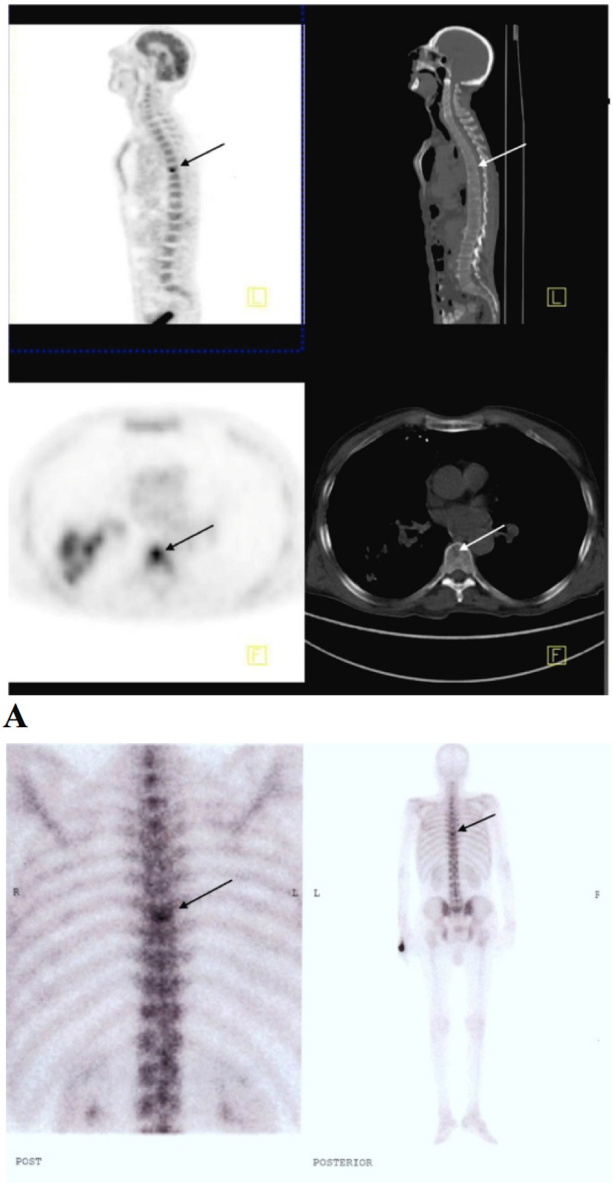

Figure 1. A solitary bone lesion in the thoracic spine in a patient with lung cancer ; ^{18}F-FDG-PET/CT **(A)** and ^{99m}Tc-MDP bone scan **(B)** images. Metastasis is shown with arrows.

of them were detected in appendicular skeleton, 43% of them were seen in the vertebral column. In the cranial bones, 11 metastatic lesions were detected in 2 patients with breast cancer, 1 patient with lung cancer and 1 patient with multiple myeloma. While the metastatic bone lesions were in multiple sites in 120 (99.1%) patients, they were solitary in the thoracic spine in 1 patient with lung cancer (Figure 1a,b). The metastatic nature of this lesion was clarified with biopsy. While 436 of the 439 (99.3%) lesions were interpreted as skeletal metastases with imaging methods or on clinical grounds, 3 lesions were diagnosed as metastatic following biopsy.

PET/CT findings

Accuracy, sensitivity, specificity, PPD and NPD values which were obtained both in general and whether they were detected in lung and breast cancer patients in accordance with the metastatic bone lesions in PET/CT imaging are shown in Table 1.

While 230 (52.4%) of the 439 metastatic bone lesions detected by PET/CT in all patients were mixed, 117 (26.7%) of them were lytic and 62 (14.1%) sclerotic. Thirty lesions (6.8%) could not be detected in CT images; 21 of these 30 lesions which could not be detected in CT were in the ribs and 9 in the humerus medulla (Figure 2a,b).

On the other hand, 21 (78%) of the 27 metastatic bone lesions detected in 4 patients with prostate cancer were sclerotic and 6 (22%) had mixed character. While 9 (82%) of the 11 metastatic bone lesions detected in 1 patient with multiple myeloma were lytic, 2 (18%) of them had mixed character.

In addition, mean SUVmax values of the metastatic bone lesions were determined to show a statistically significant difference in the lytic and sclerotic lesions; mean SUVmax values were 8.3±2.8 (2.2-19.7) in lytic lesions and 3.1±1.7 (1.9-8.1) in sclerotic lesions ($p<0.001$). On the other hand, mean SUVmax values of the mixed lesions were similar with the lytic lesions as 9.2±3.7 (2.7-17.6).

Bone scintigraphy findings

While 403 (91.7%) of the 439 bone lesions seen in all of the patients were detected with whole-body bone scintigraphy, 36 (8.3%) of them could not be detected. Sixty-two (28.9%) of the 214 bone lesions which were characterized as benign were evaluated as bone metastases in the whole-body bone scintigraphy. As expected, the sensitivity of bone scintigraphy was high for the detection of bone lesions.

Accuracy, sensitivity, specificity, PPD and NPD values which were obtained both in general and according to the lung and breast cancers and based on the results of whole-body bone scintigraphy are displayed in Table 2.

Comparison of PET with bone scintigraphy

While accuracy, specificity and PPV of the FDG-PET were found higher compared to bone scintigraphy in the whole group and the lung and breast cancer groups, bone scintigraphy showed higher sensitivity. On the other hand, while bone scintigraphy was superior in the entire group and in patients with lung cancer, FDG-PET was superior in patients with breast cancer. When we looked at the lesion character which was determined according to CT, no statistically significant difference was observed between FDG-PET and bone scintigraphy in the detection of the lesions (Figure 3a,b).

Discussion

Similarly to our study, other authors [10] found solitary bone metastases in the thoracic vertebrae (Figure 1). PET scan was performed from the cranial vertex to the proximal femur. As reported by others [11],

Table 1. Evaluation of ^{18}F-FDG-PET/CT imaging results

	Sensitivity	*Specificity*	*Accuracy*	*PPV*	*NPV*	*TP*	*TN*	*FP*	*FN*
All patients	*388/439 88.3%*	*179/214 83.6%*	*567/653 86.7%*	*388/423 91.7%*	*179/230 77.8%*	*388*	*179*	*35*	*51*
Lung cancer	165/185 89.1%	71/86 82.5%	236/271 87.0%	165/180 91.6%	71/91 78.0%	165	71	15	20
Breast cancer	133/150 88.6%	58/71 81.6%	191/221 86.4%	133/146 91.0%	58/75 77.3%	133	58	13	17

PPV: positive predictive value, NPV: negative predictive value, TP: true positive, TN: true negative, FP: false positive, FN: false negative

Table 2. Evaluation of ^{99m}Tc-MDP bone scintigraphy results

	Sensitivity	*Specificity*	*Accuracy*	*PPV*	*NPV*	*TP*	*TN*	*FP*	*FN*
All patients	*403/439 91.7%*	*152/214 71.0%*	*555/653 84.9%*	*403/465 86.6%*	*152/188 80.8%*	*403*	*152*	*62*	*36*
Lung cancer	174/185 94.0%	61/86 70.9%	235/271 86.7%	174/199 87.4%	61/72 84.7%	174	61	25	11
Breast cancer	139/150 92.6%	48/71 67.6%	187/221 84.6%	139/162 85.8%	48/59 81.3%	139	48	23	11

For abbreviations see footnote of Table 1

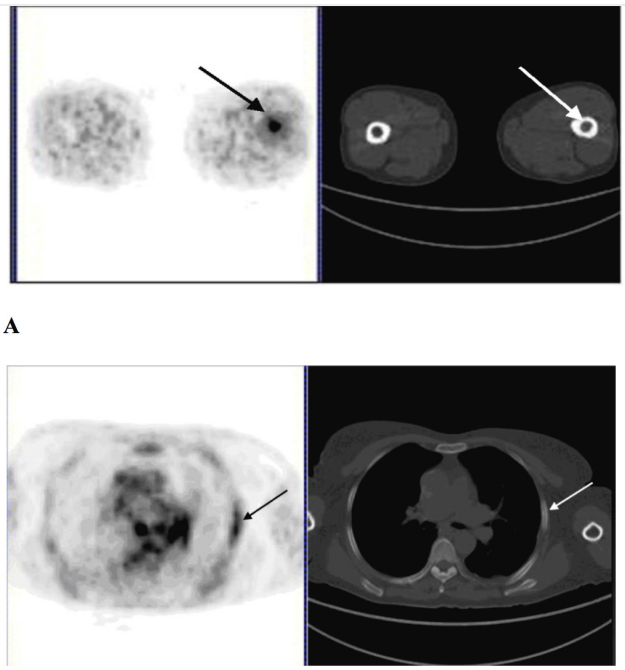

Figure 2. ^{18}F-FDG-PET images (left) and CT images (right). While CT is normal, FDG uptake is abnormal due to early bone marrow metastasis of the proximal femoral region **(A)** and a rib on left hemithorax **(B)** in PET images. Metastases are marked with arrows.

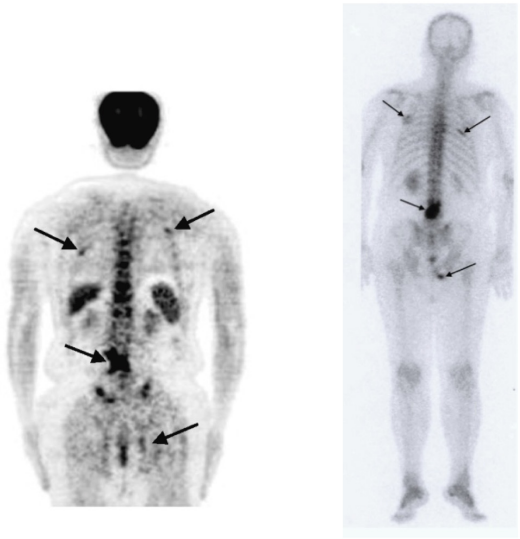

Figure 3. ^{18}F-FDG-PET **(A)** and ^{99m}Tc-MDP bone scan **(B)** images in a patient with prostate cancer. Rib, spine and pelvic metastastic bone lesions were equally detected by both imaging methods. Metastases are marked with arrows.

43% of the metastatic lesions in the present study were detected in the vertebral column. Despite the fact that other authors [9,10] have reported that PET/CT is superior to bone scintigraphy in showing metastatic lesions in the vertebrae, we found no stastistically significant difference between these two modalities.

Bone scintigraphy is not specific due to the fact that pathologic activity is found in every case of increased activity, like in the osteoblastic cases, while its sensitivity in pure lytic lesions is very low [12]. With PET/CT imaging the majority of the body can be scanned at once and bone marrow metastases which have not yet caused destruction in the cortical bone structures and metastases in other organs can be better detected.

It is known that the sensitivity of PET/CT in pure osteoblastic lesions, like in prostate cancer, is rather low and it is considered that ^{18}F-FDG-PET is generally superior in the detection of osteolytic lesions [13,14]. Likewise, mean SUVmax values were 8.3 in lytic metastases, 9.2 in mixed lesions and 3.1 in pure sclerotic metastases in our study. While ^{18}F-FDG performance - being low in the osteoblastic lesions - it seems to be related to the acellular nature, lower volume and the slow growing osteoblasts. It is considered that an hypoxic environment is formed due to the excess of osteoclastic activity in osteolytic metastases and ^{18}F-FDG involvement is increased with faster glycolysis and thus osteoclasts show higher metabolic activity [14,15]. All of the metastatic lesions detected with bone scintigraphy of 4 patients with prostate cancer in our study were also detected with PET scan. While 9/11 metastatic bone lesions in the patient with multiple myeloma were considered osteolytic, 21/27 metastatic bone lesions in the 4 patients with prostate cancer were osteosclerotic. These results are similar to other studies [16,17].

In our study, the sensitivity, specificity and accuracy of ^{18}F-FDG-PET/CT were higher compared to bone scintigraphy and these findings are similar to the studies reported by other authors [18,19]. The reason behind the fact that we found the sensitivity of ^{18}F-FDG-PET/CT higher compared to other studies [20,21] in breast cancer patients could be attributed to the character of the lesions (lytic, sclerotic, mixed), or the histopathological type of the tumor.

Similarly to the studies made by others in patients with lung cancer, we found the specificity and accuracy of ^{18}F-FDG-PET/CT higher compared to bone scintigraphy [22,23].

While the specificity, accuracy and PPV of ^{18}F-FDG-PET/CT were higher compared to bone scintigraphy, its sensitivity and NPV were lower. This may have originated from several reasons, such as higher resolution of the integrated PET/CT system compared to the space resolution of gamma camera, the existence of tomographic scanning, the detection of glucose usage by tumor cells in the ^{18}F-FDG-PET scanning, while the osteoblastic response was evaluated by bone scintig-

raphy, hence its inability to visualize the lesions in the bone marrow which have not yet caused destruction, the fact that most of the metastatic bone lesions in our study were mixed or osteolytic and the activity in lesions other than metastases with benign character in bone scintigraphy.

As it was the case in many existing studies over this topic [13-25], the most important difficulty we had was the fact that, due to the impossibility to make biopsy in each bone lesion which we have detected in both examinations, the final diagnosis of the entire lesions could not be verified with biopsy. Another limitation of our study was its retrospective nature and that some of the bone scintigraphy imaging was done in other centres, making it impossible to perform additional planar or SPECT imaging from each questionable region.

Conclusion

According to our study, while the specificity and accuracy of the FDG-PET/CT was found higher compared to bone scintigraphy in the whole group and the lung and breast cancer groups, bone scintigraphy was found higher in sensitivity. The majority of bone metastases in the present study were mixed and osteolytic according to the CT images, and no statistically significant difference was found between FDG-PET/CT and the bone scintigraphy in their detection. However, mean SUVmax values of the lesions with mixed and osteolytic character were statistically higher compared to the lesions with osteosclerotic character.

In the light of these results, bone metastases may be detected with FDG-PET/CT imaging without need for performing Tc99m-MDP whole-body bone scintigraphy. However, due to the cost and availability of PET/CT and the common view that the osteosclerotic metastases can be detected with bone scintigraphy in a better way, it is concluded that - instead of using these two methods as alternatives - it would be better to see them as complementary methods. It is the opinion of the authors that both methods are complementary in clarifying the final diagnosis.

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