Bone Metastases Detection by 18F-FDG PET/CT Versus 99mTc Bone Scintigraphy (Planar and SPECT) in Patients with Lung Cancer

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ABSTRACT

Detection of bone metastases in patients with lung cancer has important clinical significance and therapeutic implications, since it causes relevant changes in the patients' treatment. This study compared the efficacies of 18F-fludeoxyglucose positron emission tomography (18F-FDG PET)/CT, and 99mTc bone scintigraphy (planar and single photon emission CT (SPECT)) for detection of bone metastases in patients with lung cancer. 165 patients with confirmed diagnosis of lung cancer (108 men and 57 women; with a mean age of 58.36 ± 9.14 year) participated in this retrospective study, 153 patients had nonsmall cell lung cancer (NSCLC), and 12 patients had extensive stage small cell lung cancer (SCLC). All the patients underwent a BS and FDG PET/CT scintigraphy with a mean interval between both examinations of 10.23 ± 4.12 days (maximum 45 days). The sensitivity of 99mTc bone scintigraphy (SPECT) was significantly higher than those of 18F-FDG PET/CT and 99mTc bone scintigraphy (planar) (p< 0.05). There were no significant differences among the specificities of these three modalities. The accuracy of 99mTc bone scintigraphy (SPECT) was significantly higher than that of 99mTc bone scintigraphy (planar). In addition, bone metastases were confirmed in 350 metastatic bone lesions, 170 (48.57%) were classified as osteolytic and 140 (40%) as osteoblastic lesions on the basis of the CT images, but 40 (11.43%) could not be classified because of their unclear CT images. The sensitivities of 18F-FDG PET/CT and 99mTc bone scintigraphy (planar) for the osteoblastic lesions were lower than those of 99mTc bone scintigraphy (SPECT). Within the limit of this study single photon emission CT (SPECT) is superior to planar bone scintigraphy and 18F-FDG PET/CT in detecting bone metastasis among patients with lung cancer.

Key words: 18F-FDG, PET/CT, bone scintigraphy, bone metastasis, lung cancer

The sensitivities of 18F-FDG PET/CT and 99mTc bone scintigraphy (planar) for the osteoblastic lesions were lower than those of 99mTc bone scintigraphy (SPECT). Within the limit of this study single photon emission CT (SPECT) is superior to planar bone scintigraphy and 18F-FDG PET/CT in detecting bone metastasis among patients with lung cancer.

Akciğer Kanserli Hastalarda Kemik Metastazi Saptanmasında 99 mTc Kemik Sintigrafisinin 18F-FDG PET/BT ile Karşılaştırılması

ÖZET

Akciğer kanserli hastalarda kemik metastazlarının tespit edilmesi hastanın tedavisinde önemli değişikliklere neden olacağından tıropatik ve klinik önem ve sahiptir. Bu çalışmada akciğer kanserli hastalarda kemik metastazı tespitinde 18F-fludeoxyglucose pozitron emisyon tomografi (18F-FDG PET)/CT, ve 99mTc kemik sintigrafisinin (planar ve single photon emisyon CT (SPECT)) etkinliği karşılaştırılmıştır. Akciğer kanseri tanıtılan 165 hasta (108 erkek ve 57 kadın, ortalamada yaş 58.36 ± 9.14 yıl) retrospektif çalışmayı dahil edildi. 153 hastanın küçük hücreli dışı akciğer kanseri (KHDAK), ve 12 hastanın yaygın evre küçük hücreli akciğer kanseri (KHAK) mevcuttu. Tüm hastalara tetkikler arasında ortalama 10.23 ± 4.12 gün (maksimum 45 gün) olmak üzere kemik sintigrafisi ve FDG PET/CT sintigrafisi yapıldı. 99mTc kemik sintigrafisinin (SPECT) sensitivitesi 18F-FDG PET/CT ve 99mTc kemik sintigrafisininkinden (planar) belirgin olarak daha yüksekti (p< 0.05). Bu 3 yöntemin spesifitesi arasında belirgin farklılıklar yoktu. 99mTc kemik sintigrafisinin doğruluğunu (SPECT 99mTc kemik sintigrafisininkinden (planar) daha yüksekti. Ek olarak kemik metastazı 350 metastatik kemik lezyonunda tespit edildi, BT görüntüllerine göre 170'i (48.57%) osteolitik ve 140'i (40%) osteoblastik olarak sınıflandı, ancak 40'ı (11.43%) net olmayan BT görüntüleri nedeniyle sınıflandıramadı. 18F-FDG PET/CT ve 99mTc kemik sintigrafisinin (planar) osteoblastik lezyonlar için duyarlılığı 99mTc kemik sintigrafisininden (SPECT) daha düşüktü. Bu çalışmanın sınırları içinde akciğer kanserli hastalarda kemik metastazı tespitinde single foton emisyon CT (SPECT) planar kemik sintigrafisi ve 18F-FDG PET/CTinden üstün görünmektedir.

Anahtar kelimeler: 18F-FDG, PET/CT, kemik sintigrafisi, kemik metastazi, akciğer kanseri

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Introduction

Lung cancers are one of the most common causes of mortality related to cancer (about 18%) (1) and responsible for 25% of mortality related to all female cancers in 2011 (2). Currently, women have an increased risk for lung cancer, although males have higher incidence of lung cancer than females (3) annually, about 1.3 million new subject develop lung cancer all over the world (4,5). Smoking is the main risk factor for lung cancer as smokers have 20 to 30 fold higher risk of lung cancer than non-smokers and cigarette smoking is responsible for 90% of lung cancer (6). However, the second cause of lung cancer is Radon (7) and passive smoking is the third most common cause of lung cancer (8).

Bone metastasis is common among patients with lung cancer (9) as about 30% to 40% of patients with lung cancer develop bone metastasis (10). Pain, spinal cord compression, pathological fracture and hypercalcaemia are the most common complications induced by bone metastasis among patients with lung cancer (11). Magnetic resonance imaging (MRI), fluorine-18 deoxyglucose (18FDG) positron emission tomography (PET) and bone scintigraphy are the most common imaging modalities for bone metastases detection (12).

99m technetium-methylene diphosphonate (99mTc-MDP) bone scintigraphy (BS) is the commonly used imaging procedure that provides low cost whole-body radiological assessment for bone metastases (13,14). However, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT provide radiological assessment for both distant and local bone metastasis with high specificity and sensitivity (15,16). 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has a different diagnostic value than 99mTc-MDP BS with respect to malignant bone metastases. There is currently no consensus on the strengths and weaknesses of the two methods in bone metastases detection (17-20).

Table 1. Characteristics and histological type of the study participants

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>108/57</td>
<td>65.4/34.5</td>
</tr>
<tr>
<td>NSCLC</td>
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<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
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<td>41.21</td>
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<td>Squamous cell carcinoma</td>
<td>54</td>
<td>32.73</td>
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<tr>
<td>Large cell carcinoma</td>
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<td>1.82</td>
</tr>
<tr>
<td>NSCLC, undetermined</td>
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<td>13.94</td>
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<td>Miscellaneous</td>
<td>5</td>
<td>3.03</td>
</tr>
<tr>
<td>SCLC</td>
<td>12</td>
<td>7.27</td>
</tr>
</tbody>
</table>

Material and Methods

Subjects

165 patients (108 men & 57 women; their mean age was 58.36±9.14 year) with confirmed diagnosis of lung cancer participated in this retrospective study. 153 patients had nonsmall cell lung cancer (NSCLC) in addition to 12 patients with small cell lung cancer (SCLC). Bone metastasis detection with BS and FDG PET/CT scintigraphy was done for all participants with a mean interval between both examinations of 10.23±4.12 days (maximum 45 days). No patient received oncological treatment (chemotherapy or radiotherapy) between both scintigraphic studies. This study was approved by the Scientific Research Ethical Committee, Faculty of Applied Sciences, King Abdulaziz University. The scintigraphic examinations were performed after obtaining the corresponding signed informed consent from the patient.

Measurements

A. Fluorine-18-fluoro-deoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) measurements: All participants were 4-6 hours fasting before they underwent 18F-FDG PET/CT examination on a 64-slice hybrid PET/CT scanner (Biograph, TruePoint64, Siemens Medical Solutions, Inc. USA). The serum blood glucose level was <7 mmol/l in all cases prior to the intravenous injection of 5.5MBq/kg of 18F-FDG. Blood glucose level over 11mmol/L was considered as exclusion

Table 2. Sensitivity, specificity and accuracy of 18F-FDG PET/CT, 99mTc planner bone scintigraphy and single photon emission CT (SPECT) in bone metastases detection among patients with lung cancer.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18F-FDG PET/CT</td>
<td>73.21%*</td>
<td>100.0%</td>
<td>86.93%</td>
</tr>
<tr>
<td>99mTc bone scintigraphy (planar)</td>
<td>65.41%</td>
<td>97.56%</td>
<td>97.92%**</td>
</tr>
<tr>
<td>Scintigraphy (SPECT)</td>
<td>88.12%*</td>
<td>96.64%</td>
<td>98.13%**</td>
</tr>
</tbody>
</table>
criteria on PET/CT examination. Following injection of 18F-FDG, patients rested in a quiet and darkened room for 60min, after which images of PET/CT were obtained. Low-dose non-enhanced CT scans (120kV with automatic, real-time dose-modulation amperage, slice thickness of 5mm, pitch of 1,5 and a rotation time of 0.5s) and 3-dimensional PET scans (6-7 fields of view, 3min/field) were acquired from the base of the skull to the mid-thigh. The images were reconstructed using an iterative algorithm OSEM (2 iterations and 8 sub-sets), CT transmission attenuation correction and a 5 mm Gaussian filter.

B. Planar and single photon emission CT bone scintographies: Bone scintigraphy with 99mTc-DPDFor the acquisition of the images, a Siemens E.CAM gamma camera having two detectors, equipped with low-energy high-resolution collimators was used. A whole body bone scan was performed in anterior and posterior projections at 3 hours of the intravenous injection of 740 MBq of 99mTc-DPD. The table scan speed of the patient was established at 12 cm/min and a matrix of 256 × 1.024 pixels was used. Based on the criterion of the nuclear medicine physician responsible for the examination and after evaluating the clinical and radiological clinical data of each patient, a SPECT was performed after the planar study, acquiring 128 projections of 20 s. each in a non-circular orbit of 360° (180° for each detector).

Interpretation of the images: The BS and FDG PET/CT scintigraphy images were evaluated visually by two experienced physicians in nuclear medicine who were aware of all patient’s malignancy history but were blinded to the clinical findings, histopathological diagnosis, and other imaging data for each patient. Interpretation of the BS images was based on the usual criteria applied in our clinical practice. These are related with intensity, morphology, localization, number of lesions detected and information available from other structural techniques. Positive for metastasis is considered to exist with focal increase of the radiotracer uptake that was superior to uptake in normal bone or the detection of bone uptake defects (lytic bone lesions). Those BSs that did not show abnormal uptake of the radiotracer were considered to be negative. In the interpretation of the FDG PET/CT scintigraphy, images were used with and without attenuation correction as well as fused PET/CT images. As in the BS, the diagnostic criteria of systematic use in the clinical practice were also applied. In this examination, focal bone uptakes demonstrating greater metabolic activity than the normal bone were interpreted as metastasis. The CT scan images were used for localization and anatomic correlation of the lesions observed in the PET images. In this sense, detection of the metabolic activity in the joints (arthritis), in periprosthetic regions, in fractures and when located adjacent to the intervertebral disc in the border of the vertebral bodies (osteoarthroses) was not considered as metastasis.

The results obtained with BS and the FDG PET/CT scintigraphy were compared with the histological data of the lesions, when available, with structural techniques (X-rays, CT scan, magnetic resonance) and with the clinical follow-up of the patients.

**Results**

This study included 165 patients with lung cancer (108 males and 57 females), the mean age was 58.36±9.14 year, 153 patients had nonsmall cell lung cancer (NSCLC) & 12 patients with small cell lung cancer (SCLC) enrolled in this study (Table 1). The sensitivity of 99mTc bone scintigraphy (SPECT) was significantly more than those of 99mTc bone scintigraphy (planar) and 18F-FDG PET/CT (p< 0.05). However, the differences in the specificities of these three modalities were not significant. The accuracy of 99mTc bone scintigraphy (SPECT) was significantly more than that of 99mTc bone scintigraphy (planar) and 18F-FDG PET/CT (p< 0.05) (Table 2). Among 350 metastatic bone lesions, 169 (48.28%) were classified as osteolytic and 138 (39.43%) as osteoblastic lesions according to CT images, but 43 (12.29%) Not classified because of their unclear CT images. The sensitivities of 18F-FDG PET/CT and 99mTc bone scintigraphy (planar) for the osteoblastic lesions were compared with the histological data of the lesions, when available, with structural techniques (X-rays, CT scan, magnetic resonance) and with the clinical follow-up of the patients.

**Table 3. Sensitivity of 18F-FDG PET/CT, 99mTc planner bone scintigraphy and single photon emission CT (SPECT) for osteoblastic and osteolytic metastases in patients with lung cancer**

<table>
<thead>
<tr>
<th></th>
<th>Osteoblastic</th>
<th>Osteolytic</th>
<th>Unclear</th>
</tr>
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<tbody>
<tr>
<td>18F-FDG PET/CT</td>
<td>59/138 (42.75%)</td>
<td>169/169 (100%)</td>
<td>11/43 (25.58%)</td>
</tr>
<tr>
<td>99mTc bone scintigraphy (planar)</td>
<td>78/138 (56.52%)</td>
<td>150/169 (88.76%)</td>
<td>0/43 (0%)</td>
</tr>
<tr>
<td>99mTc bone scintigraphy (SPECT)</td>
<td>138/138 (100%)</td>
<td>169/169 (100%)</td>
<td>0/43 (0%)</td>
</tr>
</tbody>
</table>
sions were lower than those of 99mTc bone scintigraphy (SPECT). The sensitivities of all the three modalities for the osteolytic lesions were high (table 3).

Tartışma

Patients with bone metastases of lung cancer exhibit peripheral lower overall survival measured in months (21). Even though bone metastases are not necessarily a life-threatening component of cancer, their complications highly compromise the patients' quality of life (22). A number of different modalities have proven valuable for bone metastases detection; however, all noninvasive techniques currently in use have certain weaknesses (23). In this study, the sensitivity of 99mTc bone scintigraphy (SPECT) was significantly more than that of 99mTc bone scintigraphy (planar) and 18F-FDG PET/CT. However, the differences in the specificities of these three modalities were not significant. The accuracy of 99mTc bone scintigraphy (SPECT) was significantly more than that of 99mTc bone scintigraphy (planar); these results agreed with those of the earlier studies on 18F-fluoride PET or PET/CT with bone metastases of lung (24), breast (25), hepatocellular (26), prostate (27,28), colon and bladder (29) cancers. In the present study, the specificities of both 18F-FDG PET/CT and 99mTc bone scintigraphy (SPECT) in detecting bone metastases of DTC were similarly high and did not differ significantly from one another. Moreover, the sensitivity of 99mTc bone scintigraphy (planar) was improved when SPECT was added to a planar scan. This finding is consistent with those of the earlier studies with bone metastases of various cancers (30). Also, Shie et al. performed a meta-analysis comparing the diagnostic accuracy of 18F-FDG-PET and BS in breast cancer bone metastasis and reported that the overall PET sensitivity was 81%, specificity was 93% and the overall sensitivity of BS was 78%, the specificity was 79% regarding the diagnosis of breast cancer bone metastases (31). Al-Sugair and Coleman obtained greater sensitivity for the BS (84%) than for the scintigraphy with FDG (67%) in the diagnosis of lung cancer bone metastases. In this same paper, the scintigraphy with FDG was better than the BS in specificity: 98% versus 84%, respectively (32).

In general, Bone metastases are characterized by being osteolytic, osteoblastic or having a mixed pattern based on the CT images. Lytic bone metastases are the most common type of metastases among patients with lung cancer. In the present study, among 350 metastatic bone lesions, 169 (48.28%) were classified as osteolytic and 138 (39.43%) as osteoblastic lesions on the basis of the CT images, but 43 (12.29%) Not classified because of their unclear CT images. Our results agreed with many previous studies stated that F 18 FDG-PET/CT was superior to BS in detecting lung cancer osteolytic bone metastasis (33-35). A study into bone metastases from breast cancer showed that 18F-FDG PET had limitations in detecting osteoblastic metastatic type (36). Another study into bone metastases from breast cancer showed that 18F-FDG PET was inferior to 99mTc bone scintigraphy in osteoblastic lesions detection (74% vs 95%) but was superior in the detection of osteolytic lesions (92% vs 73%) (37). Also, Liu et al. confirmed that 18F-FDG PET/CT is superior to planar bone scintigraphy in detecting bone metastasis. The sensitivity, specificity and accuracy of bone scintigraphy and 18F-FDG PET/CT were 89.5%, 91.8%, 90.3%, 90.9%, 98.0% and 97.8%, respectively. In lytic or mixed lesions, the sensitivity of 18F-FDG PET/CT was better than bone scintigraphy, while in osteoblastic lesions bone scintigraphy was better than 18F-FDG PET/CT (38). Zhang et al. in their study on 34 patients with suspected malignant osteolytic bone metastases reported that the sensitivity, specificity, and accuracy of 18F-FDG PET/CT were 94.3%, 83.3% and 94.2% respectively, where (99m)Tc-MDP whole-body BS were 50.2%, 50.0% and 50.2% respectively. So, that 18F-FDG PET/CT achieved higher sensitivity, specificity, and accuracy in detecting osteolytic bone metastases than 99mTc-MDP whole-body BS (39). In a study conducted by Song et al., it was seen that bone metastases that were not detected with the FDG PET/CT scintigraphy were predominantly osteoblastic (66.7%), while those that were not detected with the BS were osteolytic type (78.3%) (35). Cook et al. found that scintigraphy with FDG could be less sensitive in the detection of osteoblastic type metastasis but more sensitive in the detection of lytic metastases (40).

The discrepancies between BS and the FDG PET/CT scintigraphy for the detection of lung cancer bone metastases would be related with the different uptake mechanisms of the radiotracers used in both techniques (41). In the BS, the mechanism of phosphonate incorporation depends on the blood flow and osteoblastic activity. In other words, the BS studies the osteoblastic reaction of the bone destruction produced by the invasion of tumor cells, being especially sensitive in the detection of osteoblastic lesions (42). However, the scintigraphy with FDG reflects the metabolic activity of the tumor cells (43). Among the causes that explain the FDG avidness for lytic metastases are its greater glycolytic index and the decreased blood supply, a fact that entails anaerobic metabolism given the tumor hypoxia (44).
In conclusion, within the limit of this study single photon emission CT (SPECT) is superior to planar bone scintigraphy and 18F-FDG PET/CT in detecting bone metastasis among patients with lung cancer.

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Bone metastases detection by PET/CT and bone scintigraphy in lung cancer


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