

Discordant findings in patients with non-small-cell lung cancer: absolutely normal bone scans versus disseminated bone metastases on positron-emission tomography/computed tomography

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Abstract

Objective: At present, metastatic bone involvement is usually assessed using bone scintigraphy, which has a high sensitivity but a poor specificity. The objective of our study was to compare the sensibility of the 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography/computed tomography (F-18 FDG PET/CT) for the detection of bone metastasis in patients with non-small-cell lung cancer (NSCLC) whose technetium 99m methylenediphosphonate (Tc-99m MDP) bone scans were absolutely normal. **Material and methods:** This study based on the retrospective analysis of 95 consecutive patients with histologically proven NSCLC who underwent F-18 FDG PET/CT and Tc-99m MDP bone scan at the Eskişehir Osmangazi University School of Medicine, Department of Nuclear Medicine between November 2006 and October 2008. Nineteen patients (19 of 95, 20%) with absolutely normal Tc-99m bone scan versus multiple high-grade F-18 FDG avid bony metastases on F-18 FDG PET/CT were selected for the review. Their ages ranged from 46 to 73 years (15 males and four females; mean: 57.2 years). **Results:** Nine patients had squamous cell carcinoma, six had adenocarcinoma, three had large cell carcinoma and one had adenosquamous cell carcinoma. Tc-99m MDP bone scan that did not reveal bony abnormalities or radiotracer uptake was characteristic of benign disease (defined as absolutely normal) in these patients. Whereas, F-18 FDG PET/CT not only showed extremely disseminated heterogeneous nest-like high-grade FDG avid metastatic foci within the marrow cavity of the upper and lower thoracic spine, lumbar spine, pelvis, rib cages and bilateral proximal long bones, but also showed disseminated osteolytic bony metastases in these areas. **Conclusion:** Discordant findings of skeletal metastasis between Tc-99m MDP bone scans and F-18 FDG PET/CT imaging may be seen in 20% of the patients with NSCLC. F-18 FDG PET/CT could detect metastatic bone involvement more accurately than bone scintigraphy. Bone scans are insensitive to early bone marrow neoplastic infiltration. Assessment of glucose metabolism with FDG PET/CT can represent a more powerful tool to detect early bone metastases in lung cancer than with traditional bone scans.

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Keywords: Tc-99m MDP bone scans; F-18 FDG PET/CT; Non-small cell-lung cancer

1. Introduction

Lung cancer remains the leading cause of cancer-related deaths around the world. Accurate staging, which is based on tumour size, regional nodal involvement and the presence of metastasis is crucial for both the treatment and the prognosis of patients with non-small-cell lung cancer (NSCLC) [1]. Staging is based on primary tumour characteristics such as size and location using a series of targeted diagnostic imaging studies including computed tomography (CT) of the thorax through the liver and adrenal glands, CT and/or magnetic resonance (MR) imaging of the brain and radionuclide bone scintigraphy. Conventional imaging limited to the thorax and

upper abdomen is unable to detect more regional nodal involvement and the presence of metastasis that is clinically unsuspected, which can occur in 9–11% of all patients with NSCLC [2,3]. Whole-body 2-deoxy-2-[18F] fluoro-D-glucose (FDG) with positron emission tomography (PET) has been suggested as an alternative study, which could provide a more accurate and efficient diagnostic approach than the combination of conventional imaging studies [4]. When used alone, the majority of the staging methods are not sufficiently accurate. The ability to supplement conventional anatomic imaging, such as CT, with metabolic and functional imaging of FDG PET has resulted in exciting new methods (PET/CT) for evaluating patients with lung cancer.

The most common sites of metastatic spread in lung cancer include the adrenal glands, brain, bones and liver [5]. Bone metastases are found at initial presentation in 3.4–60% of patients with NSCLC [6]; however, up to 40% of patients

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with proven bone metastases are asymptomatic [7]. For this reason, assessing the bone metastases in patient without bone pain at initial staging is very important. Bone metastases are clinically significant because of associated symptoms, potential complications, such as pathological fracture, and their profound implications for staging, treatment and prognosis. Currently, the most commonly used tracer for imaging the skeleton in conventional nuclear medicine is Technetium-99m labelled methylenediphosphonate (Tc-99m MDP) bone scintigraphy, which is a cost-effective and useful tool in widespread disease, and has variable diagnostic sensitivity with comparatively low specificity [8].

The objective of our study was to compare the sensibility of the F-18 FDG PET/CT for the detection of bone metastasis in patients with NSCLC whose Tc-99m MDP bone scan were absolutely normal.

2. Material and methods

2.1. Patient population

This study based on the retrospective analysis of 95 consecutive patients with proven NSCLC who underwent F-18 PET/CT and Tc-99m MDP bone scan at the Eskişehir Osmangazi University School of Medicine, Department of Nuclear Medicine, between November 2006 and October 2008. Forty-six patients had squamous cell carcinoma, 33 had adenocarcinoma, nine had large cell carcinoma and seven had adenosquamous cell carcinoma. Most patients were referred for primary tumour staging ($n = 57$) before surgery, neo-adjuvant radiochemotherapy or palliative chemotherapy. Thirty-eight patients were referred for restaging during follow-up owing to suspected local recurrence and/or distant metastases. All patients gave their informed consent about the PET/CT examination in detail. The interval between F-18 FDG PET/CT and Tc-99m MDP bone scintigraphy was, at most, 2 weeks.

2.2. Inclusion criteria

Nineteen patients with absolutely normal Tc-99m bone scan versus multiple high-grade F-18 FDG avid bony metastases on F-18 FDG PET/CT were selected for this review.

2.3. F-18 FDG PET/CT scans

2.3.1. Patient preparation

Patients fasted overnight (for at least 4 h) prior to the intravenous administration of F-18 FDG. The injected dose of F-18 FDG (Monrol, Kocaeli, Turkey) varied between 350 and 450 MBq, depending on the patient's weight. The blood glucose was measured before injection of the tracer to ensure blood glucose levels <140 mg dl⁻¹. During the uptake phase of 60 min, the patients were instructed to rest comfortably. To prevent radioactivity stasis in the urinary bladder, all patients were given diuretics (furosemide, 20 mg i.v.) and water (500–1000 ml orally) immediately following the FDG injection.

2.4. PET/CT imaging protocol

In all patients, PET/CT was performed using the Hi-Rez Biograph 6 (Siemens Medical Solutions, Biograph 6, Chicago, IL, USA), consisting of a high-resolution 3D LSO PET scanner and a state-of-the-art 6-row multi-slice CT. Emission data were acquired for six to eight bed positions, typically from the base of the skull to the upper thigh. The PET acquisition time was usually 3 min per FOV, though patients with a body mass index (BMI) >25 were examined for 4 min per FOV. CT was operated with a peak voltage of 120 kV and a tube current of 50 mAs. Patients were positioned on the scanning table with their arms raised to reduce beam-hardening artefacts.

PET images were reconstructed by using an iterative algorithm (ordered-subset expectation maximisation: two iterations, eight subsets). The reconstructed PET, CT and fused images were displayed by commercially available software (e-soft/VSIM, Siemens Medical Solutions) in axial, coronal and sagittal planes. Maximum intensity projection (MIP) PET images and integrated and co-registered PET/CT images were visually evaluated by two experienced nuclear medicine physicians (6 years of experience in PET). Any focal tracer uptake exceeding normal regional tracer accumulation at qualitative analysis and a maximum standardised uptake value (SUV_{max}) of more than 2.5 were assessed as a malignant lesion.

2.5. Bone scintigraphy

Whole-body images were obtained for time (12 cm min⁻¹) in the anterior and posterior projections 2–3 h following the intravenous injection of 740–925 MBq Tc-99m MDP using a double-head gamma camera equipped with a high-resolution parallel-hole collimator (PRISM 2000; Philips Medical Systems, Eindhoven, The Netherlands). When necessary, additional spot images were acquired. Bone scans were interpreted according to standard clinical practice, using intensity, configuration, location and number of foci of increased tracer activity. Two experienced nuclear medicine physicians (with 11 and 13 years experience) interpreted the bone scintigraphy study as positive for bone metastasis if the radiotracer activity in the lesion was greater than in the case of normal bone. Studies were considered negative if there was no significant radiotracer uptake in the bones or radiotracer uptake was characteristic of benign disease.

3. Results

Ninety-five consecutive patients with proven NSCLC who underwent F-18 PET/CT and Tc-99m MDP bone scan were analysed retrospectively. Nineteen patients with absolutely normal Tc-99m bone scan versus multiple high-grade F-18 FDG avid bony metastases on F-18 FDG PET/CT were selected for this review. Their ages ranged from 46 years to 73 years (15 males and four females; mean: 57.21 years).

Nine patients had squamous cell carcinoma, six had adenocarcinoma, three had large cell carcinoma and one had adenosquamous cell carcinoma. Tc-99m MDP bone scan that



Fig. 1. Example of a whole-body Tc-99m MDP bone scan shows normal tracer distribution in all bones. There is no focus related metastatic involvement.



Fig. 2. F-18 FDG PET/CT of the patient whose Tc-99m MDP bone scan is presented in Fig. 1. Maximum intensity projection (MIP) PET and fusion PET/CT images show extremely disseminated heterogeneous nest-like high-grade FDG avid metastatic foci within the marrow cavity of the upper and lower thoracic spine, lumbar spine, pelvis, rib cages and bilateral proximal long bones, and disseminated osteolytic bony metastases in these areas.

did not reveal bony abnormalities or radiotracer uptake was characteristic of benign disease (defined as absolutely normal) in 19 of 95 (20%) patients with NSCLC (Fig. 1). Whereas F-18 FDG PET/CT not only showed extremely disseminated heterogeneous nest-like high-grade FDG-avid metastatic foci within the marrow cavity of the upper and lower thoracic spine, lumbar spine, pelvis, rib cages and bilateral proximal long bones, but also showed disseminated osteolytic bony metastases in these areas (Fig. 2).

4. Discussion

We found that F-18 FDG PET/CT have demonstrated a disseminated bone/bone marrow metastases. Tc-99m bone scans have been absolutely normal in 20% (19 of 95) patients with NSCLC. This relative high incidence of discordant finding of skeletal metastasis between Tc-99m MDP bone scans and F-18 FDG PET/CT imaging for NSCLC is quite impressive.

Bone metastases are clinically significant because of associated symptoms, potential complications such as pathological fracture and their profound implications for staging, surgical and/or medical treatment and prognosis. Bone metastases have been characterised as osteolytic, osteoblastic or mixed lesions containing both elements [8]. Tc-99m MDP bone scintigraphy is a cost-effective and useful tool, and the most commonly used means of detecting bone metastasis and has variable diagnostic sensitivity with comparatively low specificity for easy evaluation of the entire skeleton. The exact mechanism of uptake of this tracer is not understood fully, but it is believed that this compound is chemisorbed onto bone surfaces, and its uptake depends on both local blood flow and osteoblastic activity. Because nearly all metastases are accompanied by an osteoblastic reaction at a microscopic level, there is usually focal accumulation of the tracer. Predominantly lytic lesions with no reactive osteoblastic reaction (e.g., myeloma), accordingly, may demonstrate little or no uptake [8].

F-18 FDG PET imaging is a non-invasive technique, which depends mainly on the metabolic characteristics of a tissue for the diagnosis of disease. F-18 FDG uptake in cancer tissue is well documented in the literature and is based upon the increased glycolysis that is associated with malignancy as compared with most normal tissues [9].

Although several case reports have been published [10–12], to the best of our knowledge, this is the first report which consists of series of 19 patients to show the discrepancy between the Tc-99m MDP bone scan and F-18 FDG PET/CT imaging in patients with NSCLC. The discrepancy between the Tc-99m MDP bone scan and F-18 FDG PET/CT imaging can be explained as a difference in the uptake mechanisms used to detect metastases. Tc-99m MDP bone scans depend on an osteoblastic bone reaction to malignant cells, whereas F-18 FDG PET visualises glucose metabolism in cancer cells.

Many comparative studies showed different results with regard to the sensitivity and specificity of F-18 FDG PET and conventional Tc-99m MDP bone scintigraphy for the detection of bone metastases of various kinds of carcinoma. In several studies, F-18 FDG PET and Tc-99m MDP bone scintigraphy had a similar sensitivity for the detection of bone metastases but F-18 FDG PET was more specific than Tc-99m MDP; bone scintigraphy were also obtained in patients with lung carcinoma [13–15]. Early FDG PET studies have been published showing that the technique has excellent accuracy [16–19]. However, in these studies, there were no data comparing the sensitivity and specificity of PET and of the reference imaging modality for the detection of metastasis site by site. At the same time, there were conflicting reports, which showed that F-18 FDG PET was less sensitive than conventional Tc-99m bone scintigraphy [20,21]. This might be for a variety of reasons including the relatively acellular

nature of sclerotic lesions (therefore, lower volumes of viable tumour tissue), as well as differences in blood supply and tumour hypoxia, which further increase FDG uptake. Bury et al. [14] reported that in a group of 110 patients with NSCLC, the sensitivity for detecting skeletal metastases was similar for FDG PET and Tc-99m MDP (90%), but that FDG-PETFDG PET yielded higher specificity (98% compared with 61%). The reason for greater avidity for F-18 FDG in lytic metastases is unknown but may reflect a higher glycolytic rate in this type of metastasis. Sclerotic metastases are relatively acellular [22], however, and, as such, lower volumes of viable tumour tissue within individual lesions may influence the degree of uptake of F-18 FDG. In addition, more aggressive lytic disease may be expected to outstrip its blood supply, rendering the tumour relatively hypoxic compared with sclerotic disease. Hypoxia increases F-18 FDG uptake in some cell lines and this may be an additional factor in osseous metastasis accumulation. It is interesting to note that Shreve et al. [23] found a lower sensitivity for the detection of skeletal metastases with F-18 FDG-PET compared with Tc-99m MDP scintigraphy in patients with prostate carcinoma, a tumour that results in skeletal metastases that are predominantly sclerotic. In patients who are known to have these predominantly sclerotic metastases, therefore, it may be necessary to perform both F-18 FDG-PET and a bone scan to evaluate fully the distribution of skeletal and soft tissue metastases.

Unlike other tracers, F-18 FDG is not a tracer specific to the skeleton. Assessment of glucose metabolism, apart from measurement of mineral bone turnover as seen on conventional bone scan, might represent a more powerful tool to detect bone metastases. Increased glycolysis is one of the most distinctive biochemical features of malignant cells, resulting from increased expression of the glucose transporter protein as well as increased activity of hexokinase [24]. Because F-18 FDG accumulates in viable, metabolically active tumour cells rather than reactive bone, detection of a skeletal metastasis confined to the marrow cavity may occur at an earlier stage when only the bone marrow is involved and before bone remodelling in surrounding bone can be detected on Tc-99m MDP bone scans. This common site for cancer metastasis is especially relevant in the evaluation of vertebral and long bones metastases. In addition, the limited anatomical resolution of PET can be overcome by the co-registration of functional PET images with morphological CT data with an integrated PET/CT system. Integrated PET/CT systems are especially useful for evaluating the bone marrow cavity.

5. Conclusion

Discordant findings of skeletal metastasis between Tc-99m MDP bone scans and F-18 FDG-PET/CT imaging may be seen in 20% of the patients with NSCLC. F-18 FDG-PET/CT could detect metastatic bone involvement more accurately than bone scintigraphy. Bone scans are insensitive to early bone-marrow neoplastic infiltration. Assessment of glucose metabolism with FDG PET/CT can represent a more powerful tool to detect early bone metastases in lung cancer compared with traditional bone scans.

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