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Bone metastasis in patients with non-small cell lung cancer: The diagnostic role of F-18 FDG PET/CT

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ABSTRACT

Purpose: To evaluate the performance of F-18 FDG PET/CT in the detection of bone metastasis in non-small cell lung cancer (NSCLC) patients.
Materials and methods: Three hundred and sixty-two consecutive NSCLC patients who underwent F-18 FDG PET/CT scanning were retrospectively analyzed. Each image of PET/CT, combined CT, and PET was performed at 10 separate areas and interpreted blindly and separately. The sensitivity, specificity and accuracy of F-18 FDG PET/CT, combined CT and F-18 FDG PET were calculated and the results were statistically analyzed.
Results: Bone metastasis was confirmed in 82 patients with 331 positive segments based on the image findings and clinical follow-up. On patient-based analysis, the sensitivity of F-18 FDG PET/CT (93.9%) was significantly higher than those of combined CT (74.4%) and F-18 FDG PET (84.1%), respectively ($p < 0.05$). The overall specificity and accuracy of combined CT, F-18 FDG PET, and F-18 FDG PET/CT were 90.7%, 93.2%, 98.9% and 87.0%, 91.2%, and 97.8%, respectively (compared with PET/CT, $p < 0.05$). On segment-based analysis, the sensitivity of the three modalities were 79.5%, 94.3%, and 98.8%, respectively (compared with PET/CT, $p < 0.05$). The overall specificity and accuracy of the three modalities were 87.9%, 89.2%, 98.6% and 84.5%, 91.2%, 98.7%, respectively (compared with PET/CT, $p < 0.05$).
Conclusion: F-18 FDG PET/CT is superior to F-18 FDG PET or combined CT in detecting bone metastasis of NSCLC patients because of the complementation of CT and PET. It is worth noting that the added value of F-18 FDG PET/CT may beneficially impact the clinical management of NSCLC.

1. Introduction

Non-small cell lung cancer (NSCLC) is a significant health issue. Many advanced NSCLC patients have bony metastasis accomplished with skeletal-related events (SRE), such as pain, pathological fracture, spinal instability, cord compression, and hypercalcemia [1]. Imaging modalities are powerful tools in assessing malignant bone involvements. Unfortunately, all the imaging modalities in current use have imperfect abilities in detecting bone metastasis. These modalities include plain radiography, CT, MRI, 99 mTc-MDP planar bone scintigraphy (BS), and single photon emission computed tomography (SPECT).

BS is a routine modality in detecting bone involvement and clinical staging of NSCLC at presentation. However, its low spatial resolution and low sensitivity in assessing treatment responses restrict its role [2]. F-18 FDG positron emission tomography (PET) has recently been reported to be valuable in evaluating bone metastasis of NSCLC and has a similar sensitivity as that of BS [3–6]. With tracer accumulation, F-18 FDG PET visualizes regions of enhanced metabolic activity and complements other imaging modalities based on structural anatomic changes [3]. Nevertheless, there are still some discordant evidences that the diagnostic role of F-18 FDG PET in bone metastasis changes with different histological types of tumor cells [7–9]. Intramedullary lesions are easier to detect because of the high glycolysis rate in the red marrow. F-18 FDG PET may perform better in diagnosing lytic lesions but yield inferior values in sclerotic lesions [7,8]. Because of the contradictory reports, F-18 FDG PET is still not a routine staging modality of bone metastasis in NSCLC.

Novel hybrid techniques that allow the acquisition of PET and CT at the same clinical setting and the generation of fused functional–anatomic images have been proven to improve the diagnostic accuracy of malignancies. The hardware hybrid PET/CT can

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provide better anatomic localization of scintigraphic findings and might improve the diagnostic accuracy of PET in detecting malignant bone involvements. Most of the current data on the role of F-18 FDG in bone metastasis come from dedicated PET. Some pilot studies on PET/CT using ^{18}F-fluoride or F-18 FDG have been made [10,11]. To the authors' limited knowledge, few data are available regarding the diagnostic impact of hardware fusion F-18 FDG PET/CT on bone involvement in NSCLC patients. The objective of this study was to evaluate the incremental value of F-18 FDG PET/CT in bone involvement of NSCLC. The study aimed to provide more evidences on bone metastasis detection of F-18 FDG PET/CT and performed a more realistic stratification of those who are actually suffering from the disease.

2. Patients and methods

2.1. Patients

The study population comprised of 362 consecutive pathologically proven NSCLC patients who underwent combined whole-body F-18 FDG PET/CT scanning between October 2002 and December 2007 at Shandong Cancer Hospital. Data sets were retrospectively analyzed. The study excluded those who had bisphosphonate therapy, local therapy approach with external beam radiotherapy or granulocyte colony stimulating factor therapy (less than 1 month). All procedures followed the clinical guidelines of Shandong Cancer Hospital and were approved by the ethical committee.

2.2. F-18 FDG PET/CT procedure

PET and PET/CT scan were performed by a combined PET/CT scanner (Discovery LS, GE Healthcare, USA) with a multislice helical CT. The acquisition of coregistered CT and PET images were performed in one session. Patients were examined in supine position and instructed to fast except for glucose-free hydration for 4–6 h before injection of F-18 FDG. No intravenous contrast agent was given. After intravenous injection of 370.1 ± 38.6 MBq F-18 FDG for 40–60 min, CT scan (parameters: 80 mA, 140 kV, 0.8 s/tube rotation, slice thickness 5 mm, data acquisition time 22.5 s) was performed from the head to the middle thigh without holding one's breath. PET emission scan was then acquired immediately using an acquisition time of 3 min per bed position. CT data were used for attenuation correction and images were reconstructed with the ordered subsets expectation maximization (OSEM) algorithm. The images were viewed on Xeleris workstation (GE Healthcare, USA), which provided multiplanar reformatted images of PET, CT and fused data with linked cursors. The maximum standardized uptake value (SUVmax) was calculated according to the following formula: measured activity concentration [Bq/ml] × body weight [kg]/injected activity [Bq].

2.3. Image analysis

PET and PET/CT images were independently reviewed by two experienced physicians. CT images were analyzed separately by one board-certified radiologist and one double board-certified nuclear medicine physician and radiologist. Each image was performed on 10 separate areas (skull, cervical spine, thoracic spine, lumbar spine, sacrum with coccyx, pelvis, long bone (upper and lower extremities), sternum, ribs, scapula and clavicle) and on each site where an abnormally increased uptake of F-18 FDG was recorded. Suspected focal bone marrow infiltrations by F-18 FDG PET were compared with morphological changes in the corresponding CT scan. The final diagnoses of PET/CT were determined through the following [12]: when the CT component obtained during PET/CT scanning showed that an area of abnormal uptake corresponded to the adjacent tissue rather than to the bone, the suspected lesion was considered to be negative for bone metastasis. If there were definite morphological findings of metastasis in lesions at corresponding CT images suspected of being metastatic at PET, such lesions were considered to be true-positive findings of bone metastasis. When CT depicted the morphologic changes of metastasis in some of the lesions in a patient who was suspected to have multiple bone metastases at PET, the remaining lesions in the same patient that did not show definite morphologic changes were also considered to be positive. If there were major disagreements, the lesion was then reevaluated by both readers together. Patients were monitored for at least 6 months (6.9 ± 3.1 months; 6–14 months) and the medical records were reviewed with an attempt to get a final diagnosis of equivocal lesions. Imaging follow-up was done through biopsy, contemporaneous radiography, diagnostic CT, MRI, and BS. For the CT components, each lesion was further defined as osteolytic, osteoblastic or mixed changes. Osteolytic and mixed lesions were combined into a single group. The locations (cortex, medulla or both) of the metastatic lesions in the bone were also recorded according to the CT images.

2.4. Statistical analysis

Patient-based and segment-based analyses were performed. For each of the modalities, the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Comparison of the detection rates of bone metastases by combined CT, F-18 FDG PET, and F-18 FDG PET/CT were performed using the McNemar test with $p < 0.05$ being statistically significant.

3. Results

3.1. Patient-based analysis

Of the 362 patients, 82 (17–85 years, mean 56.9 ± 14.6 years, M:F = 53:29) were eventually diagnosed to have bone metastasis. Fifty-one patients (159 segments) were newly diagnosed and 31 patients (172 segments) were referred for evaluation of suspected recurrence or progression. In 71 patients, the diagnosis and location of bone metastasis were confirmed by additional imaging studies showing the same findings. These included BS study in 49 patients, separate diagnostic CT scanning 12 patients, MRI examination in 7 patients, radiography in 2 patients and single lesion biopsy in 1 patient. The other 11 patients were confirmed bone metastasis

Table 1
Correlation of SUVmax and histological types of primary tumors.

Characteristics	No.	SUVmax	Compared with SC	Compared with AC	Compared with ASC
SC	39	9.1 ± 2.7			
AC	25	6.2 ± 2.8	$p = 0.000^*$		
ASC	7	6.3 ± 1.9	$p = 0.009^*$	$p = 0.721$	
LC	11	4.4 ± 1.9	$p = 0.000^*$	$p = 0.038^*$	$p = 0.035^*$

SUVmax: the maximum SUVmax of all the bone metastatic lesions in the same patient; SC: squamous cell carcinoma; AC: adenocarcinoma; ASC: adenosquamous carcinoma; LC: large cell carcinoma.

* $p < 0.05$ was considered statistically significant.