Fluorine-18 deoxyglucose positron emission tomography for the detection of bone metastases in patients with non-small cell lung cancer

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Abstract. Despite advances in morphological imaging, some patients with lung cancer are found to have non resectable disease at surgery or die of recurrence within a year of surgery. At present, metastatic bone involvement is usually assessed using bone scintigraphy, which has a high sensitivity but a poor specificity. We have attempted to evaluate the utility of the fluorine-18 deoxyglucose positron emission tomography (FDG PET) for the detection of bone metastasis. One hundred and ten consecutive patients with histological diagnosis of non-small cell lung cancer (NSCLC) who underwent both FDG PET and bone scintigraphy were selected for this review. In this group, there were 43 patients with metastatic disease (stage IV). Among these, 21 (19% of total group) had one or several bone metastases confirmed by biopsy (n = 8) or radiographic techniques (n = 13). Radionuclide bone scanning correctly identified 54 out of 89 cases without osseous involvement and 19 out of 21 osseous involvements. On the other hand, FDG PET correctly identified the absence of osseous involvement in 87 out of 89 patients and the presence of bone metastasis in 19 out of 21 patients. Thus using PET there were two false-negative and two false-positive cases. PET and bone scanning had, respectively, an accuracy of 96% and 66% in the evaluation of osseous involvement in patients with NSCLC. In conclusion, our data suggest that whole-body FDG PET may be useful in detecting bone metastases in patients with known NSCLC.

Key words: Positron emission tomography – Lung neoplasm – Bone metastasis

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Introduction

The diagnostic work-up of patients with lung cancer remains a difficult clinical challenge. Surgical resection offers the highest probability of cure in those patients. However, the overall 5-year survival rate does not exceed 20% mainly because of presurgical understaging [1]. For this reason, there is a need for the development of new imaging technologies. Positron emission tomography (PET) using fluorine-18 deoxyglucose (FDG) is such a technique.

Malignant tumors have increased metabolic activity and fluorodeoxyglucose accumulates in these lesions. This uptake can be used in PET studies to visualize the tumour with high contrast compared with the surrounding tissue [2–4]. Considerable experience is now available on the diagnostic value of FDG PET in the mediastinal staging of lung cancer [5–9] but analysis of the efficiency of FDG PET for the detection of distant metastasis remains fragmentary [10–12]. This paper reports our current clinical experience in 110 patients with non-small cell lung cancer (NSCLC). We have attempted to evaluate the utility of FDG PET for the detection of bone metastasis.

Materials and methods

One hundred and ten consecutive patients with histological diagnosis of NSCLC, who underwent both FDG PET and bone scintigraphy, were selected for this review. The delay between the two procedures had to be no more than 10 days.

Bone scintigraphy was performed by the intravenous administration of technetium-99m diphosphonate at a dose of 20 mCi. Images were obtained after 4 h on a gamma camera (SMV, Brussels, Belgium). Anterior and posterior views of the whole body were aquired. The bone scan was interpreted by the nuclear medicine staff (agreement between two reviewers). Any localised increase in radionuclide uptake was initially considered as suspicious for skeletal metastases; if no increased uptake was seen, the scan was

considered negative. All positive scans were further assessed by additional radiographs, computed tomography, magnetic resonance imaging, or biopsy, except when the increased uptake was recognised as being due to a benign condition by the nuclear medicine staff (in accordance with a corresponding history, physical findings and/or an imaging pattern of degenerative, osteoarthritic or traumatic changes) [13].

PET was performed using a UGM Penn PET 240H scanner (Philadelphia, USA) 60–90 min following FDG injection. With patients in a fasting state, about 200–250 MBq FDG has been injected via an antecubital vein [8]. The whole-body mode acquires multiple overlapping steps at 64-mm intervals. This acquisition sequence corrects for the uneven interplane sensitivity inherent to three-dimensional data acquisition schemes. Images were reconstructed using a Hanning filter. Ten to 12 steps, extending from the neck to the inguinal regions, were acquired for each patient, with a scanning time of 4–5 min/step. PET data were analysed by visual interpretation of coronal, sagittal and transverse slices alone and in a cross-referenced situation. PET images were read independently by two nuclear physicians who evaluated the presence or absence of FDG uptake in the osseous structures. When the two reviewers did not agree, they reviewed the images together to reach a consensus. In this study, there were two instances of disagreement concerning PET images.

Bone scans and PET images were reported independently as negative (normal) or positive (abnormal). When PET or bone scan demonstrated one or several areas of increased isotope uptake, these areas were further investigated with conventional radiographic techniques (radiography, computed tomography, magnetic resonance imaging) or biopsy. In this study, we defined a true-positive scan as a scan with typical, multiple areas of increased uptake or a single area of increased uptake considered in the final analysis to be of tumoral origin by the clinician in charge; a false-positive scan was defined as one in which the increased uptake was not proved to be tumour. Tumour staging was performed according to the guidelines of the American Thoracic Society [14]. The clinical follow-up period for the study was at least 9 months. Patients were followed regularly every 3 months: routine visit included history, physical examination, chest radiography and further investigations as necessary.

Statistical analysis. Diagnostic specificity and sensitivity of bone scanning and PET imaging have been calculated by the classical method. Positive and negative predictive values (PPV and NPV, respectively) were also evaluated in the same manner. For each parameter, the 95% confidence interval (95% CI) is given.

Results

Clinical data

The medical files of 110 consecutive patients (73 males and 37 females) with a mean age of 66.5 years [41–83] were reviewed. Fifty-four patients had squamous cell carcinoma, 39 had adenocarcinoma, ten had large cell carcinoma and seven had adenosquamous cell carcinoma. The final staging of the disease was: stage I or II in 37 patients, stage IIIA in 19 patients, stage IIIB in 11 patients and stage IV in 43 patients. Among those with stage IV, 21 patients (19%) had one or several bone metastases confirmed by biopsy (n = 8) or radiographic techniques (n = 13).

Imaging findings

Fifty-four of 110 radionuclide bone scans (49%) showed one or more areas of increased uptake. In 15 of these 54 patients no further examinations were done because the area of increased uptake corresponded with a traumatic lesion or a site of degenerative arthritic disease. During the follow-up period, none of these patients developed osseous metastasis. In 31 patients additional conventional radiographic techniques were performed: in 11 of these patients skeletal metastases were confirmed but in the remaining 20 the increased uptake was interpreted as being of degenerative or traumatic origin. In eight other patients, needle biopsy showed malignancy. Thus 35 of the 54 bone scans showing increased uptake were considered to represent false-positive cases. There were also two patients with a false-negative result. These two patients had a squamous cell carcinoma and an osseous metastasis in the vertebral column (dorsal level) confirmed by magnetic resonance imaging and clinical follow-up. Overall, therefore, radionuclide bone scanning correctly identified 54 out of 89 cases without osseous involvement and 19 out of 21 osseous involvements.

Among the 110 cases, evaluation of osseous involvement by FDG PET and bone scanning was similar in 73 cases: this evaluation was correct in 71 cases (53 negative evaluations; 18 positive evaluations), overestimated by the two techniques in one case (traumatic bone disease) and underestimated by the two techniques in one case. In 37 cases, results of imaging evaluation (bone scanning versus FDG PET) were discordant: by comparison to the final diagnosis, FDG PET imaging was correct in 35 cases (34 negative evaluations; 1 positive evaluation) and bone scanning in only two cases.

Osseous involvement was correctly identified by PET in 19 out of 21 patients and the absence of osseous involvement in 87 out of 89 patients. There were two false-negative and two false-positive cases. The false-negative cases were situated in a rib (lesion of 0.7 cm diameter) in one case and in a posterior iliac crest (lesion of 1.3 cm diameter) in the other case. In one of the two cases in which PET was false-positive, scintigraphy was negative and the primary tumour was surgically staged T3 with pleural invasion.

In the evaluation of osseous involvement in patients with NSCLC, FDG PET was found to have a sensitivity of 90% (95% CI: 69%–98%), a specificity of 98% (95% CI: 92%–99%) and an accuracy of 96% (95% CI: 90%–99%). The corresponding positive and negative predictive values were 90% (95% CI: 69%–98%) and 98% (95% CI: 92%–99%) respectively. By contrast bone scanning had a sensitivity of 90% (95%CI: 76%–99%), a specificity of 61% (95% CI: 50%–71%), an accuracy of 66% (95% CI: 57%–75%), a positive predictive value of 35% (95% CI: 23%–49%) and a negative predictive value of 96% (95% CI: 88%–99%).

Discussion

This study suggests that FDG PET imaging is useful in assessing metastatic bone involvement in patients with a recent diagnosis of NSCLC. The accuracy of the method is higher than that of scintigraphy in this indication and its negative predictive value is 98%.

Bone metastases are found at initial presentation in 3.4%–60% of patients with NSCLC (15–17). Bone pain is usually considered as a good indicator of skeletal metastases. However, up to 40% of patients with proven bone metastases are asymptomatic [16, 18]. For this reason, it is probably useful to perform routinely an exploration of the skeletal system in patients with NSCLC. At present, metastatic bone involvement is usually assessed using bone scintigraphy, which has a high sensitivity but a poor specificity.

FDG PET imaging is a non-invasive technique which depends mainly on the metabolic characteristics of a tissue for the diagnosis of disease. 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 [19, 20]. Several studies have evaluated the role of FDG PET for staging lung carcinoma. Most investigators have used focal techniques and concentrated on mediastinal lymph node staging [5–9]. Concerning the detection of distant metastases by whole-body FDG PET, three studies have already been published showing that the technique has excellent accuracy [10–12]. 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. In our study, we compared FDG PET and bone scintigraphy in the pretherapeutic assessment of the skeletal system in patients with NSCLC.

In our series, the rate of patients with bone metastases was 19%. The results suggest that FDG PET could detect metastatic bone involvement more accurately than bone scintigraphy in patients with NSCLC. In particular, PET was more specific, with a higher positive predictive value than bone scintigraphy in this indication. In the present series there were two false-positive cases on PET, both situated in the rib cage. In one of these cases, the primary tumour was peripheral and staged as T3 with pleural invasion; in this case, scintigraphy was negative and PET image interpretation could probably have been improved by anatomical correlation, in particular through the use of image fusion with structural images.

Our results concerning the efficiency of technetium-99m diphosphonate scintigraphy are true to the literature, showing a good sensitivity (90%) but a poor specificity (61%) [21–23]. False-positive cases can be explained by the non-selective uptake of the radionuclide in any area of increased bone turnover (degenerative change, inflammatory processes, mechanical stress, etc.). Two patients with squamous cell carcinoma had negative scintigraphy in spite of the presence of metastasis in dorsal vertebrae. It has previously been reported that false-negative findings may be obtained in a small percentage of patients with purely osteolytic lesions [24] or in patients with slow-growing lesions where reactive bone is not detectable [25].

Ideally, histological confirmation of imaging abnormalities should be available in such a study but practical considerations made acquisition of this information unrealistic. We recognize the non-specific nature of a positive scan, but each abnormality was confirmed or invalidated by conventional radiographic techniques. These techniques are not suitable for screening but the focal lesion appearance can be quite specific. Furthermore, in the absence of suspected osseous lesions, clinical and radiological follow-up was obtained over at least 9 months.

In conclusion, our data suggest that whole-body FDG PET may be useful in detecting bone metastases in patients with known NSCLC. It compares favourably with bone scintigraphy which may have a high rate of false-positive cases, reducing the value of this technique in the preoperative staging of NSCLC. If our preliminary findings are confirmed in prospective and larger clinical trials, whole body FDG PET imaging will have an increasing role in the initial staging of patients with NSCLC as it will replace the need for concomitant bone scanning. An appropriate cost-benefit study should be carried out.

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