

Prospective Evaluation of the Clinical Value of Planar Bone Scans, SPECT, and ^{18}F -Labeled NaF PET in Newly Diagnosed Lung Cancer

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Previous studies have shown that vertebral bone metastases (BM) not seen on planar bone scintigraphy (BS) might be present on ^{18}F -fluoride PET scans or at MRI. Therefore, we evaluated the effect of SPECT or ^{18}F -labeled NaF PET (^{18}F PET) imaging on the management of patients with newly diagnosed lung cancer. **Methods:** Fifty-three patients with small cell lung cancer or locally advanced non-small cell lung cancer were prospectively examined with planar BS, SPECT of the vertebral column, and ^{18}F PET. MRI and all available imaging methods, as well as the clinical course, were used as reference methods. BS with and without SPECT and ^{18}F PET were compared using a 5-point scale for receiver operating characteristic (ROC) curve analysis. **Results:** Twelve patients had BM. BS produced 6 false-negatives, SPECT produced 1 false-negative, and ^{18}F PET produced no false-negatives. The area under the ROC curve was 0.779 for BS, 0.944 for SPECT, and 0.993 for ^{18}F PET. The areas under the ROC curve of ^{18}F PET and BS complemented by SPECT were not significantly different, and both tomographic methods were significantly more accurate than planar BS. As a result of SPECT or ^{18}F PET imaging, clinical management was changed in 5 patients (9%) or 6 patients (11%), respectively. **Conclusion:** As indicated by the area under the ROC curve analysis, ^{18}F PET is the most accurate whole-body imaging modality for screening for BM. Routinely performed SPECT imaging is practicable, is cost-effective, and improves the accuracy of BS.

Key Words: lung cancer; bone metastases; PET; SPECT

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In lung cancer, bone metastases (BM) are present in 20%–30% of patients at initial diagnosis and in 35%–66% at autopsy (1–3). Non-small cell lung cancer (NSCLC) without distant metastases is potentially curable. Approximately 20%–25% of lung cancers are of the small cell type (SCLC). Although the therapy of SCLC remains palliative, the selection of the appropriate therapy regimen depends on

pretherapeutic staging. Hence, accurate staging of the skeleton is crucial in all patients with lung cancer and increased probability of having BM.

MRI was reported to reveal vertebral BM earlier than does conventional planar bone scintigraphy (BS) (3,4). PET using ^{18}F -labeled NaF (^{18}F PET) has been shown to be significantly more accurate in detecting BM than is BS (5,6). An evaluation of the effect of the superior accuracy of ^{18}F PET or MRI on patient management has not yet been reported. Consequently, ^{18}F PET and MRI are not currently recommended for routine use. Recent studies have suggested that the sensitivity of BS might be improved by the routine performance of additional SPECT imaging (7–9). Hence, complementing planar BS with SPECT imaging of the vertebral column in all patients with increased risk of metastatic bone disease might be an accurate and cost-effective alternative to ^{18}F PET or MRI. The aim of this prospective study was to compare the diagnostic accuracy of ^{18}F PET and BS with and without SPECT at the initial staging of lung cancer and to determine the effect on patient management.

The vertebral column is the most commonly affected region in patients with BM. Although destruction of the pedicles is a common sign of BM on plain films, the disease begins at the vertebral body (10,11). MRI is accepted as the most accurate imaging modality in detecting BM at the vertebral body (12–14). Therefore, MRI of the vertebral column, complemented by the panel of all available imaging methods and the clinical course, was used as the gold standard.

MATERIALS AND METHODS

Patients

Our study consisted of 53 patients. Patients were included when SCLC ($n = 12$) or locally advanced NSCLC (stage III, $n = 41$) were diagnosed through bronchoscopy and CT. We studied 53 patients (42 men, 11 women; age range, 43–78 y; median age, 63 y; mean age, 63.2 y). A history of extrapulmonary cancer, known metastatic bone disease, NSCLC at stages lower than stage III of the Union Internationale Contre le Cancer, pregnancy, or an age of <18 y were exclusion criteria. All patients gave written

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consent to participate in this prospective study. The study was approved by the local ethical committee.

Bone Scanning

Two modern double-head gamma cameras (ECAM and Body-scan; Siemens, Erlangen, Germany) were used. The axial field of view was 40 cm for both cameras. Low-energy, high-resolution collimators ($1,024 \times 256$ matrix) were used for planar BS and for SPECT. Data acquisition was started 3 h after intravenous injection of 740–1,000 MBq ^{99m}Tc -methylene diphosphonate. At least 1.5 million counts were required for each gamma camera detector for planar imaging.

Two additional SPECT acquisitions of the cervicothoracic and thoracolumbar spine were performed on all patients. For SPECT imaging, a double-head gamma camera (ECAM; 128×128 matrix; 64 steps; 150,000–200,000 counts per step; Butterworth filter; cutoff level, 0.5) was used. The total acquisition time ranged from 25 to 35 min for planar BS and from 120 to 150 min for the combination of BS and SPECT. The bone-scanning procedure was performed in accordance with procedure guidelines published by the Society of Nuclear Medicine (15).

^{18}F PET Imaging

^{18}F PET imaging was performed using a modern PET camera (ECAT EXACT HR+; Siemens/CTI, Knoxville, TN). The emission scan was started 75–180 min after intravenous injection of 370–555 MBq ^{18}F -labeled NaF. Attenuation correction was not performed. An iterative algorithm (16) was used for image reconstruction. The ^{18}F PET scans included 6–7 bed positions (12-min acquisition time per bed position; total acquisition time, 72–84 min) covering the skull, neck, arms, thorax, pelvis, and proximal femora. Coronal, transverse, and sagittal sections and maximum intensity projection images were documented in hard-copy form.

MRI Protocol

MRI examinations of the cervicothoracic spine, thoracolumbar spine, and lumbar spine/sacrum (MR Vision; Siemens, Erlangen, Germany) were performed on all patients. Each region was imaged in 2 perpendicular planes with a T1-weighted spin-echo sequence (Body Array [Siemens]; repetition time, 532 ms; echo time, 15 ms; 5-mm slices; gap, 0.5 mm) and a fat-suppressed T2-weighted sequence (Turbo Inversion Recovery TIRM [Siemens]; repetition time, 5,000 ms; echo time, 60 ms; inversion time, 140 ms; flip angle, 180° ; 5-mm slices; gap, 0.1 mm). In lesions indicative of BM, one of the spin-echo sequences was repeated after intravenous application of 0.2 mmol per kilogram of body weight gadolinium (Magnevist; Schering, Berlin, Germany) to verify typical contrast enhancement of BM.

Interpretation of BS, SPECT, and ^{18}F PET

Two nuclear medicine physicians interpreted ^{18}F PET, and 2 other nuclear medicine physicians interpreted BS complemented by SPECT. Planar BS was interpreted without SPECT by 2 other nuclear medicine physicians. The experienced readers of BS, SPECT, and ^{18}F PET were unaware of the findings of each other. The results of all imaging methods were made available to the 2 diagnostic radiologists who interpreted MRI results.

With ^{18}F PET, BS, and SPECT, lesions were classified as arthritis when they were located at joints. Increased tracer uptake on the edge of vertebral bodies adjacent to disk spaces was interpreted as indicating osteophytes. Lesions not located at joints or showing typical linear tracer uptake of fractured endplates were

interpreted as BM. Interpretation of BS and SPECT was performed following the criteria described by Krasnow et al. (17).

Definition of Metastatic Bone Disease

Patients were defined as having no BM when BS, SPECT, ^{18}F PET, or MRI did not show BM. Typical gadolinium enhancement at hyperintense lesions in fat-suppressed, T2-weighted images was defined as BM. Lesions not detectable on planar BS but showing the typical pattern of BM from SPECT or ^{18}F PET and from MRI were defined as metastases. Lesions that were unclear at MRI but negative according to each scintigraphic method were assessed with FDG PET and with spiral CT. In the case of negative FDG PET and spiral CT results, these patients underwent curative surgery and the results of MRI were assessed by autopsy (1 patient) or evaluated by the clinical course (1 patient).

Data Analysis

PET and BS with and without SPECT were compared on a patient basis. All patients were judged on a 5-point scale as definitively having BM (score of 1), probably having BM (score of 2), being equivocal (score of 3), probably not having BM (score of 4), and definitively not having BM (score of 5). Receiver operating characteristic (ROC) curve analysis (18) was performed, and the area under the curve was used to test for statistically significant differences between BS, SPECT, and ^{18}F PET in staging patients to be M1 or M0 on the bone site. A probability value of <0.05 was defined as statistically significant (18).

RESULTS

Accuracy of BS With and Without SPECT and ^{18}F PET Imaging

Twelve patients (23%) had metastatic bone disease. With planar BS, only 5 patients were classified correctly as having BM. Six patients were falsely interpreted as negative and 5 patients as equivocal, 2 of whom had BM. Thirty-five patients were defined correctly as being free of BM. Two patients with degenerative lesions were falsely interpreted as having BM.

The sensitivity in detecting BM was significantly improved by SPECT images because vertebral BM were detected in 5 of the 6 patients that were false-negative according to planar BS. Fifty-two patients were correctly interpreted with ^{18}F PET and 1 patient with a single rib metastasis was interpreted as equivocal with SPECT, BS, and ^{18}F PET. The results of planar BS, BS complemented with SPECT, and ^{18}F PET are summarized in Table 1.

TABLE 1
Results of Planar BS With and Without SPECT and ^{18}F PET

Finding	BS	BS + SPECT	^{18}F PET
True-positive	5	9	11
False-positive	2	0	0
Equivocal	5 (2 BM, 3 benign)	2 (2 BM)	1 (BM)
True-negative	35	41	41
False-negative	6	1	0
Total	53	53	53

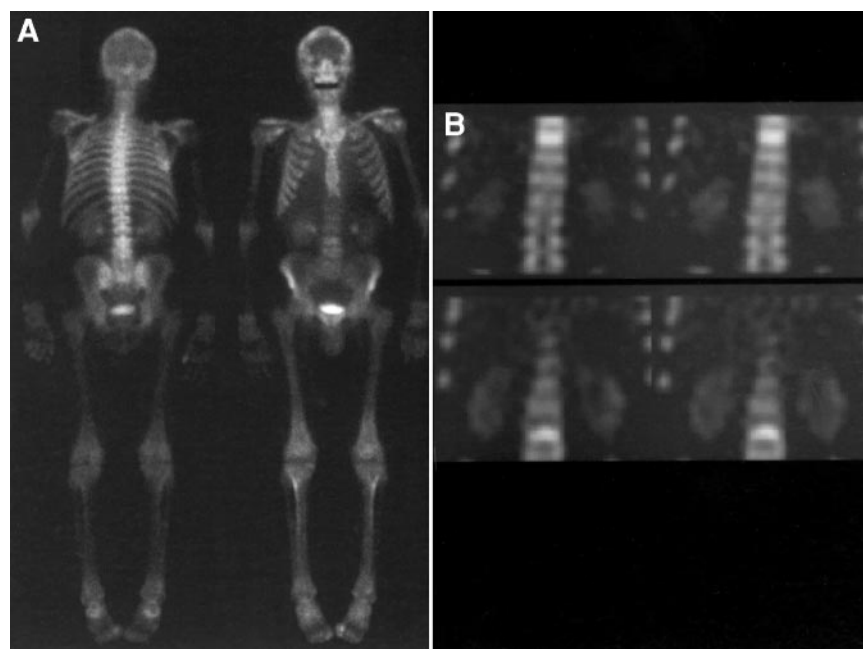


FIGURE 1. A 53-y-old man with NSCLC. (A) Planar BS was interpreted as normal (score 5). (B) Coronal SPECT images presented lesions at lumbar and lower thoracic spine probably indicative of BM (score 2).

The areas under the ROC curve were 0.779 (SD, 0.078) for planar BS, 0.944 (SD, 0.043) for BS complemented with SPECT, and 0.993 (SD, 0.008) for ^{18}F PET. The diagnostic accuracy of both tomographic imaging modalities was significantly higher than that of planar BS alone ($P < 0.05$). The difference between the areas under the ROC curves for ^{18}F PET and for SPECT was statistically not significant.

Changes in Patient Management

As a result of the improved imaging performance of ^{18}F PET and MRI, staging of 3 patients with SCLC and of 3

patients with NSCLC who had BM and normal planar BS was changed (Figs. 1 and 2). Therapy was changed from curative surgery to palliative chemotherapy in the 3 patients with NSCLC. In the 3 patients with SCLC, another chemotherapy regimen was indicated because staging was changed from limited disease to extended disease. Using SPECT instead of ^{18}F PET, BM would have been missed in only 1 of the patients. Compared with the results obtained with ^{18}F PET, the extent of metastatic bone disease was underestimated in 7 of 12 patients (58%) with the combination of BS

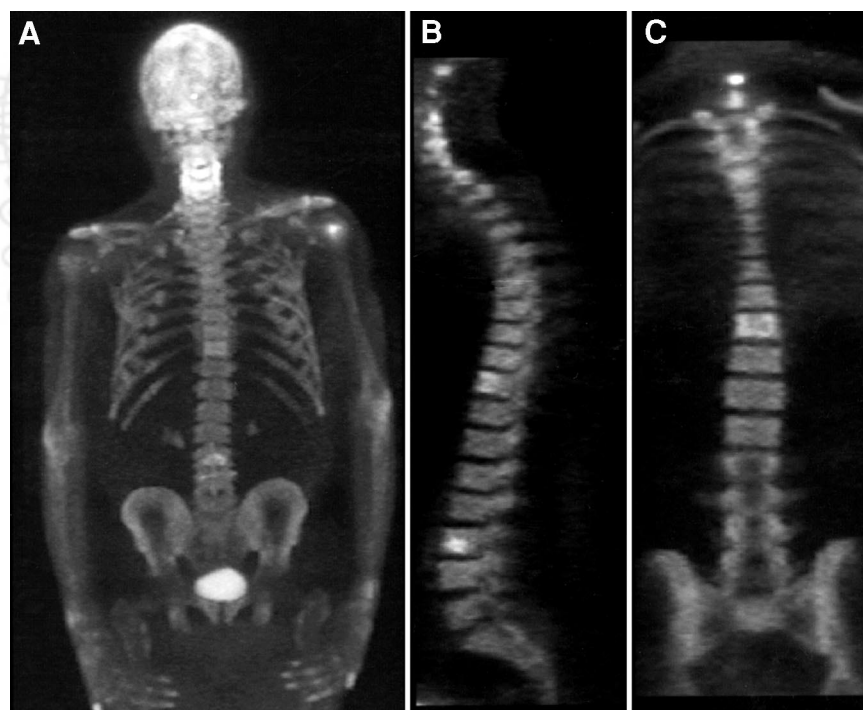


FIGURE 2. Same patient as shown in Figure 1. ^{18}F PET (left, maximum intensity projection images; middle, sagittal; right, coronal) presented BM in vertebral bodies L3 and T10. Both BM were confirmed by MRI.

and SPECT. However, this had no influence on patient management.

In summary, as a result of ^{18}F PET and MRI, the clinical management was changed in 6 of the 12 patients with BM (50%; 11% of all patients). Complementary SPECT imaging of the cervicothoracic and thoracolumbar spine altered patient management in 5 of the 12 patients with BM (42%; 9% of all patients).

DISCUSSION

Radionuclide bone scanning using technetium-labeled polyphosphonates was introduced into clinical practice in the 1970s and was shown to detect BM several months earlier than plain radiographs. Therefore, BS has become one of the most frequently performed nuclear medicine procedures in Europe and the United States. However, the number of BS procedures used in oncology has been reduced because the prevalence of BM in patients with early tumor stages is low and early treatment of metastatic bone disease does not necessarily improve the survival rate. Furthermore, several studies that compared the sensitivity of planar BS with that of MRI have shown that planar BS is less sensitive than previously accepted (3,4,12–14,19).

The limited accuracy of planar BS was confirmed in our study because planar BS produced false-negatives in 50% of the patients with BM. However, complementing BS with routinely performed SPECT images improved the sensitivity of BS significantly (Table 1). This altered treatment in 5 patients. Only 1 patient had BM that were missed with that combination but were present on MRI and ^{18}F PET. Whole-body imaging with ^{18}F PET and the combination of BS with SPECT were significantly more accurate than planar BS, as indicated by the ROC curve analysis. ^{18}F PET and MRI revealed more metastatic lesions than the combination of planar BS and SPECT in 7 patients. However, this had no influence on patient treatment.

Two recent studies indicated that the sensitivity of planar BS depends on the anatomic localization of the BM (5,20). Steinborn et al. (20) reported that whole-body MRI was more sensitive than planar BS in the spine and pelvis, whereas BS revealed more BM in the skull and ribs. A lesion-based comparison with ^{18}F PET indicated that the sensitivity of planar BS in detecting vertebral BM was as low as 40%. In contrast, the sensitivity ranged from 80% to 90% in the skull, thorax, and extremities (5).

Several studies reported a low sensitivity of planar BS in detecting BM when comparing planar BS with MRI of the vertebral column (12–14). However, the interpretation of this finding is limited because a comparison was performed between an anatomic region with the lowest sensitivity using BS and an anatomic region with the highest sensitivity using MRI (5,20).

In our study, SPECT imaging increased the sensitivity of BS significantly by detecting vertebral BM missed by planar BS (Figs. 1 and 2). Because of the low prevalence of BM at

initial diagnosis, the American Society of Clinical Oncology does not recommend BS at initial staging of all asymptomatic patients with lung cancer. In 32 patients with SCLC, the use of MRI at initial staging did not indicate the need for a change in therapy (21). In contrast to that study, our series consisted of patients with increased risk of BM. Furthermore, most of the patients had NSCLC. Hence, detection of BM provided very important information that changed the therapy regimen in 6 patients.

At present, FDG is the most commonly used PET tracer for primary staging of lung cancer. Compared with traditional staging methods, FDG PET can result in more accurate classification of the stage of disease (22). FDG PET has been reported to be as sensitive as planar BS in detecting BM of lung cancer (23). Cook et al. (24) suggested that FDG might be generally less sensitive in detecting osteoblastic metastases but more sensitive in detecting osteolytic metastases. In contrast, ^{18}F PET has been shown to be highly sensitive in detecting both osteolytic and osteoblastic lesions.

The combination of planar BS with SPECT is currently more available and less expensive than ^{18}F PET. However, 2 SPECT acquisitions were necessary for assessment of the entire vertebral column. The total acquisition time was 120–150 min for BS/SPECT, compared with 72–84 min for ^{18}F PET. Along with the 2-fold-longer acquisition time of SPECT, there was lower compliance and an increased risk of movement during acquisition. These factors can cause a spatial localization that is lower with SPECT than with ^{18}F PET. Hence, ^{18}F PET should become more and more attractive in the future, although the accuracies of ^{18}F PET and of SPECT were not statistically significant in our series.

CONCLUSION

The results of this study suggest the use of at least 1 tomographic technique when staging patients with lung cancer and increased risk of metastatic bone disease. ^{18}F PET enables performance of whole-body imaging in a single examination but is costly and not readily available. A practicable and cost-effective strategy that had a significant effect on patient management in our study was the combination of planar BS with SPECT, complemented by MRI in unclear lesions.

REFERENCES

1. Tritz DB, Doll DC, Ringenberg QS, et al. Bone marrow involvement in small cell lung cancer: clinical significance and correlation with routine laboratory variables. *Cancer*. 1989;63:763–766.
2. Bezwoda WR, Lewis D, Livini N. Bone marrow involvement in anaplastic small cell lung cancer: diagnosis, hematologic features, and prognostic implications. *Cancer*. 1986;58:1762–1765.
3. Trillet V, Revel D, Combaret V, et al. Bone marrow metastases in small cell lung cancer: detection with magnetic resonance imaging and monoclonal antibodies. *Br J Cancer*. 1989;60:83–88.
4. Hochstenbag MM, Snoep G, Cobben NA, et al. Detection of bone marrow metastases in small cell lung cancer: comparison of magnetic resonance imaging with standard methods. *Eur J Cancer*. 1996;32A:779–782.
5. Schirrmeister H, Guhlmann A, Elsner K, et al. Sensitivity in detecting osseous

- lesions depends on anatomic localization: planar bone scintigraphy versus ^{18}F PET. *J Nucl Med.* 1999;40:1623–1629.
6. Schirmermeister H, Guhlmann A, Kotzerke J, et al. Early detection and accurate description of extent of metastatic bone disease in breast cancer with fluoride ion and positron emission tomography. *J Clin Oncol.* 1999;17:2381–2389.
 7. Kosuda S, Tatsumi K, Yokoyama H, et al. Does bone SPECT actually have lower sensitivity for detecting vertebral metastases than MRI? *J Nucl Med.* 1996;37:975–978.
 8. Roland J, van den Weygaert D, Krug B, Brans B, Scalliet P, Vandevivere J. Metastases seen on SPECT imaging despite a normal planar bone scan. *Clin Nucl Med.* 1995;20:1052–1054.
 9. Sedonja I, Budihna NV. The benefit of SPECT when added to planar scintigraphy in patients with bone metastases in the spine. *Clin Nucl Med.* 1999;24:407–413.
 10. Algra PR, Heimans JJ, Valk J, Nauta JJ, Lachniet M, Van Kooten B. Do metastases in vertebrae begin in the body or the pedicles? *AJR.* 1992;158:1275–1279.
 11. Asdourian PL, Weidenbaum M, DeWald RL, Hammerberg KW, Ramsey RG. The pattern of vertebral involvement in metastatic breast cancer. *Clin Orthop.* 1990;250:164–170.
 12. Haubold-Reuter BG, Duewell S, Schilcher BR, Marincek B, von Schulthess GK. The value of bone scintigraphy, bone marrow scintigraphy and fast spin-echo magnetic resonance imaging in staging of patients with malignant solid tumors: a prospective study. *Eur J Nucl Med.* 1993;20:1063–1069.
 13. Smoker WRK, Goderski JC, Knutzon RK, Keyes WD, Norman D, Bergman W. The role of MR imaging in evaluating metastatic spinal disease. *AJR.* 1987;149:1241–1248.
 14. Frank JA, Ling A, Patronas NJ, et al. Detection of malignant bone tumors: MR imaging vs. scintigraphy. *AJR.* 1990;55:1043–1048.
 15. Donhoe KJ, Henkin RE, Royal HD, et al. Procedure guidelines for bone scintigraphy 1.0. *J Nucl Med.* 1996;37:1903–1906.
 16. Schmidlin P. Improved iterative reconstruction using variable projection binning and abbreviated convolution. *Eur J Nucl Med.* 1994;21:930–936.
 17. Krasnow AZ, Hellman RS, Timins ME, Collier D, Anderson T, Isitman AT. Diagnostic bone scanning in oncology. *Semin Nucl Med.* 1997;27:107–141.
 18. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curve from the same cases. *Radiology.* 1983;148:839–843.
 19. Horvath LJ, Burtress BA, McCarthy S, Johnson KM. Total-body echo-planar MR imaging in the staging of breast cancer: comparison with conventional methods—early experience. *Radiology.* 1999;211:119–128.
 20. Steinborn MM, Heuck AF, Tiling R, Bruegel M, Laurie G, Reiser M. Whole-body bone marrow MRI in patients with metastatic disease to the skeletal system. *J Comput Assist Tomogr.* 1999;23:123–129.
 21. Milleron BJ, Le Breton C, Carette MF, Cadranet JL, Akoun GM. Assessment of bone marrow involvement by magnetic resonance imaging in small cell lung cancer. *Chest.* 1994;106:1030–1035.
 22. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small cell lung cancer with positron emission tomography. *N Engl J Med.* 2000;343:254–261.
 23. Bury T, Barreto A, Daenen F, Barthelemy N, Ghaye B, Rigo P. Fluorine-18 deoxyglucose positron emission tomography for detection of bone metastases in patients with non-small cell lung cancer. *Eur J Nucl Med.* 1998;25:1244–1247.
 24. Cook GJ, Houston S, Rubens R, Maisey MN, Fogelman I. Detection of bone metastases in breast cancer by ^{18}F FDG PET: differing metabolic activity in osteoblastic and osteolytic lesions. *J Clin Oncol.* 1998;16:3375–3379.





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