

Early Detection and Accurate Description of Extent of Metastatic Bone Disease in Breast Cancer With Fluoride Ion and Positron Emission Tomography

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Purpose: Previous studies have shown that bone metastases are revealed by magnetic resonance imaging (MRI) or bone marrow scintigraphy several months before they are visible by conventional bone scintigraphy (BS). We present a new approach for detecting bone metastases in patients with breast cancer. We compared findings obtained with fluoride ion (F-18) and positron emission tomography (PET) with those obtained with conventional BS.

Patients and Methods: Thirty-four breast cancer patients were prospectively examined using F-18-PET and conventional BS. F-18-PET and BS were performed within 3 weeks of each other. Metastatic bone disease was previously known to be present in six patients and was suspected (bone pain or increasing levels of tumor markers, Ca²⁺, alkaline phosphatase) in 28 patients. Both imaging modalities were compared by patient-by-patient analysis and lesion-by-lesion analysis, using a five-point scale for receiver operating characteristic (ROC) curve analysis. A panel of reference methods

was used, including MRI (28 patients), planar x-ray (17 patients), and spiral computed tomography (four patients).

Results: With F-18-PET, 64 bone metastases were detected in 17 patients. Only 29 metastases were detected in 11 patients with BS. As a result of F-18-PET imaging, clinical management was changed in four patients (11.7%). For F-18-PET, the area under the ROC curve was 0.99 on a lesion basis (for BS, it was 0.74; $P < .05$) and 1.00 on a patient basis (for BS, it was 0.82; $P < .05$).

Conclusion: F-18-PET demonstrates a very early bone reaction when small bone marrow metastases are present, allowing accurate detection of breast cancer bone metastases. This accurate detection has a significant effect on clinical management, compared with the effect on management brought about by detection with conventional BS.

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CARCINOMA OF THE BREAST is the most prevalent cancer in women in the United States and western Europe and is commonly associated with metastatic bone disease. Although the frequency of bone metastases is 1% to 2% at the time of primary diagnosis,^{1,2} bone metastases are found in one third of all patients with recurrent disease.³ The incidence of bone metastases is significantly higher in well-differentiated and estrogen receptor-positive tumors.⁴⁻⁶ At autopsy, bone metastases were found in 47% to 85% of patients who died from breast cancer.^{7,8} The previous suggestion that bone scans be performed in routine follow-up in patients without clinical evidence of bone metastases⁹⁻¹² is not supported by bone scintigraphy's (BS's) low detection rate, the large number of false-positive results obtained with BS, and BS's poor performance as a prognostic indicator.

Planar BS has been shown clearly to be of value in detecting bone metastases several months before they are revealed by planar radiography.^{1,13} In comparative studies, bone marrow scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) revealed significantly more metastases in the spine that were not detectable with conventional BS.^{8,14-18} Because whole-body MRI is impractical at present, radionuclide bone scanning remains the most suitable technique for whole-body surveys.¹⁸

Uptake of fluoride ion (F-18) into bone is two-fold higher than that of technetium polyphosphonates, and blood clearance of fluoride ion is faster than blood clearance of technetium polyphosphonates.¹⁹⁻²² Therefore, the bone-to-background ratio of F-18 is much higher. Because gamma camera systems respond better in terms of sensitivity and resolution to the 140-keV photons of technetium than to the 511-keV photons of F-18,²¹ Tc-99m-BS has been shown to be superior to planar F-18-BS.^{23,24} With the development of positron emission tomography (PET), it has become possible to perform high-quality whole-body surveys, using F-18-PET.²¹ Because of the superior pharmacologic properties of F-18 and the high-resolution sensitivity and high lesion contrast of PET without superposition of soft tissue,²⁵

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detection of both osteolytic and osteoblastic metastases in patients with solid cancers was expected to be improved with F-18-PET bone imaging.

We devised a prospective study to compare F-18-PET and routine BS in terms of accuracy of diagnosis of osseous metastases in patients with breast cancer and suspected metastatic bone involvement. Because bone metastases in breast cancer patients are mostly located in the spine,⁵ we used MRI or spiral CT of the entire vertebral column as reference methods.

PATIENTS AND METHODS

Patients

This prospective study involved 34 patients with breast cancer (age range, 37 to 75 years; mean age, 52.3 years). Patient characteristics, clinical disease stage, indications for skeletal surveys, and results of

F-18-PET and BS are summarized in Table 1. Bone scanning was carried out for therapy control in six patients with previously diagnosed bone metastases (patient no. 2, paclitaxel therapy; patients no. 1 and 3 through 6, antihormonal therapy) and because of suspected metastatic bone disease in 28 patients (patients no. 7 through 34). Of the 28 patients without previously diagnosed metastatic bone disease, 17 had positive axillary lymph node status in addition to estrogen receptor-positive primary tumors, and five patients had local or distant recurrence. These patients therefore had a high risk of metastatic bone disease.⁴⁻⁶ Nineteen patients were receiving antihormonal therapy, and five patients (patients no. 2, 4, 5, 7, and 10) were being treated with bisphosphonates. All patients gave written consent to participate in this study, which was approved by the ethical committee of the University of Ulm.

Bone Scanning

A double-headed gamma camera (full width at half maximum [FWHM] 4.9 mm, axial field of view 50 cm, low-energy high-resolution

Table 1. Patient Characteristics

Patient No.	UICC Stage*	Receptor Status	Indication for Skeletal Survey	Interval Between Primary Diagnosis and BS (years)	Results (staging)	
					F-18-PET	BS
1	IV	E+/P+	Bone pain (spine/thorax)	4	tp	tp
2	IV	E+/P+	Restaging, suspected liver metastases	9	tp	tp
3	IV	E+/P+	Bone pain (left humerus)	7	tp	tp
4	IV	E+/P-	Bone pain (skull, spine)	3	tp	tp
5	IV	ND	Recurrence in lymph nodes, restaging	15	tp	tp
6	IV	ND	Bone pain (femur)	4	tp	tp
7	IIA	E+/P-	Recurrence in chest wall, restaging	5	tp	tp
8	IIA	E+/P-	Bone pain (lumbar spine)	7	tp	e
9	I	E+/P+	Bone pain (skull, spine)	Staging†	tp	tp
10	IIA	ND	Increased serum calcium levels	Staging	tp	fn
11	IIB	ND	Bone pain (pelvis)	Staging	tp	tp
12	I	ND	Bone pain (spine)	11	tp	fn
13	IIB	E+/P+	Bone pain (femur/spine)	Staging	tn	tn
14	IIA	E-/P-	Increased CEA levels, bone pain (spine)	4	tp	e
15	IIA	ND	Bone pain (thorax)	Staging	tn	tn
16	IIA	E+/P+	Bone pain (spine)	15 months	tn	tn
17	IIIA	E-/P-	Restaging, liver metastases	3	tn	tn
18	IIB	E+/P+	Bone pain (spine)	9 months	e	tn
19	IIB	ND	Bone pain (pelvis)	9	tn	e
20	IIA	ND	Bone pain (spine)	Staging	tn	tn
21	IIB	E+/P+	Bone pain (spine)	Staging	tn	tn
22	I	E-/P+	Bone pain (pelvis, spine, hip)	Staging	tp	tp
23	IIB	E+/P+	Bone pain (humerus, ribs)	Staging	tn	tn
24	IIIA	E-/P-	Bone pain (ribs)	3	tn	tn
25	IIIA	E+/P+	Bone pain (ribs, spine)	2	tp	tp
26	IIA	E+/P+	Bone pain (left hip)	2	tp	tp
27	IIB	E-/P-	Bone pain (ribs)	1	tn	tn
28	I	E+/P+	Restaging, malignant pleural effusion	10	tp	tp
29	IIA	E+/P-	Bone pain (sternum, spine, femur)	2	tn	tn
30	IIB	E+/P+	Restaging, recurrence in lymph nodes	3	tp	fn
31	IIA	E+/P-	Bone pain (femur)	Staging	tn	fp
32	IIB	ND	Restaging, recurrence in lymph node	3	tn	e
33	I	E+/P+	Bone pain (lumbar spine)	4	tn	fp
34	IIIA	ND	Increased CEA levels	6	tn	e

Abbreviations: CEA, carcinoembryonic antigen; E, estrogen; e, equivocal; fp, false-positive; fn, false-negative; ND, not determined; P, progesterone; tn, true-negative; tp, true-positive; UICC, International Union Against Cancer.

*Clinical disease stage before bone survey.

†"Staging" indicates that BS and PET were performed at the time of the primary diagnosis.

collimator, 1,024 × 256 matrix; Bodyscan; Siemens, Erlangen, Germany) was used for planar BS. Data acquisition was started 3 hours after intravenous injection of 740 MBq of 99m-Tc-methylene diphosphonate. One and one half million counts were required for each gamma camera detector. In addition, single photon emission computed tomography (SPECT) was performed in 12 patients with indeterminate vertebral lesions. For SPECT, a double-headed gamma camera (FWHM at the center field of view 8.3 mm, low-energy high-resolution collimator, 64 × 64 matrix, 32 steps, 150,000 to 200,000 counts per step, acquisition time 50 to 70 seconds per step, Butterworth filter, cutoff level 0.8; Multispect 2; Siemens) was used. This procedure for bone scanning was performed according to the guidelines described by Donohoe et al.²⁶

PET

All patients were examined with the use of a whole-body PET camera (FWHM at the center field of view 4.2 mm, field of view 15.5 cm; ECAT EXACT HOUR+; Siemens/CTI, Knoxville, TN). PET scanning of the skeletal trunk (six to seven bed positions, including the skull, neck, arms, thorax, and half of the femora) was performed, without attenuation correction, 1 hour after intravenous injection of 370 MBq of F-18. Acquisition time was 12 minutes per bed position. PET scans were reconstructed using an iterative reconstruction algorithm.²⁷ Coronal, sagittal, and transverse sections as well as projection images were reconstructed and documented on x-rays.

MRI Protocol

MRI of the head and cervical spine, thoracic and lumbar spine, and lumbar spine and pelvis was performed in 28 patients, using MR Vision (Siemens). Each region was imaged in two perpendicular planes with a T1-weighted spin echo sequence (repetition time, 532 msec; echo time, 15 msec; slice thickness, 5 mm; gap, 0.5 mm; Body Array [Siemens]) and a fat-suppressed T2-weighted sequence (repetition time, 5,000 msec; echo time, 60 msec; inversion time, 140 msec; flip angle, 180°; slice thickness, 5 mm; gap, 0.1 mm; Turbo Inversion Recovery TIRM [Siemens]). If the patient had fewer than five lesions, one of the spin echo sequences was repeated after intravenous administration of gadolinium 0.2 mmol/kg of body weight (Magnevist; Schering, Berlin, Germany) to verify typical contrast enhancement of metastasis.

Reference Methods

At present, no whole-body imaging modality offers the high sensitivity and specificity of vertebral MRI. Therefore, in the 28 patients who underwent MRI, MRI of (only) the vertebral column and the pelvis was performed, regardless of BS or PET findings. Spiral CT was performed in four patients with large vertebral metastases detected with BS and 18F-PET, to assess fracture risk. CT scans included the complete vertebral column, to exclude further vertebral metastases probably not detected with BS or F-18-PET. MRI (28 patients) or spiral CT (four patients) of the spine was performed in only 32 patients, because two patients had claustrophobia. Clinical follow-up of ≥ 1 year and planar x-ray were used as gold standards in these two patients (patients no. 5 and 6). Extravertebral lesions detected by PET or BS were confirmed by planar x-ray in 17 patients, by MRI in three patients, and by spiral CT in two patients.

Data Analysis

PET and BS were compared using patient-by-patient analysis and lesion-by-lesion analysis. With most statistical tests used to compare the diagnostic accuracy of imaging modalities, the assumption is that the

results of these imaging techniques must be either negative or positive. However, results are often not definitely positive or negative. For this reason, receiver operating characteristic (ROC) curve analysis was developed.²⁸ For ROC curve analysis, graded levels of positivity must be distinguished. Cutoff levels for positivity were chosen for BS and F-18-PET results. All lesions and all disease were rated using a five-point scale (definitely metastatic, 1; probably metastatic, 2; equivocal, 3; probably not metastatic, 4; and definitely not metastatic, 5). The ROC curve was constructed by considering, in turn, each point on the scale as the cutoff point for the definition of positivity and plotting the sensitivity against 1 – specificity for each point. A smooth curve was drawn through the derived points. Typically, the area under the ROC curve tends to be approximately 0.5 for an inappropriate technique and 1.0 for a perfect technique. For comparison of the areas under the ROC curves, a *P* value of < .05 was considered statistically significant.

Two experienced nuclear medicine physicians interpreted bone scans and two other nuclear medicine physicians interpreted PET scans, independently and blinded to the results of the other imaging modalities. Magnetic resonance images and images produced by the other reference methods were interpreted by two diagnostic radiologists. The locations of lesions as determined by F-18-PET or BS were given to the two readers. If two readers did not agree on the grading of a lesion, they discussed their differences and reached a consensus.

Patients were considered to have no bone metastases when BS, F-18-PET, and the reference methods did not reveal any suspicious lesions. Patients were also considered to have no bone metastases when suspicious lesions revealed by F-18-PET and/or BS were shown to be benign by the reference methods. Lesions were considered metastases when they increased in number or diameter over 1 year, when they appeared osteolytic on spiral CT scans or x-rays, or when there was typical gadolinium enhancement or hyperintense lesions in fat-suppressed T2-weighted magnetic resonance images.

With BS and F-18-PET, lesions were classified as degenerative when they were located at joints or extravertebrally (osteophytes). Lesions were considered traumatic when typical linear tracer uptake of fractured endplates or adjacent lesions of fractured ribs, mostly located at the costochondral joints, were noted. All lesions not having characteristic features of degenerative disease or trauma were considered metastases.

RESULTS

F-18-PET and BS Compared

Focal skeletal tracer accumulation was observed in 33 patients with F-18-PET and in 29 patients with BS. F-18-PET and BS led to correct staging of disease in all of the six patients with previously diagnosed metastatic bone disease. Whereas F-18-PET revealed additional, previously unknown, metastases in five of these patients, BS revealed additional metastases in only two patients.

Of 28 patients with previously unknown bone metastases, F-18-PET led to correct diagnoses of metastatic bone disease in 11 patients and correct diagnoses of no such disease in 16 patients. The disease stage of one patient with degenerative lesions was considered equivocal with F-18-PET. There were no false-negative results and no false-positive results with F-18-PET.

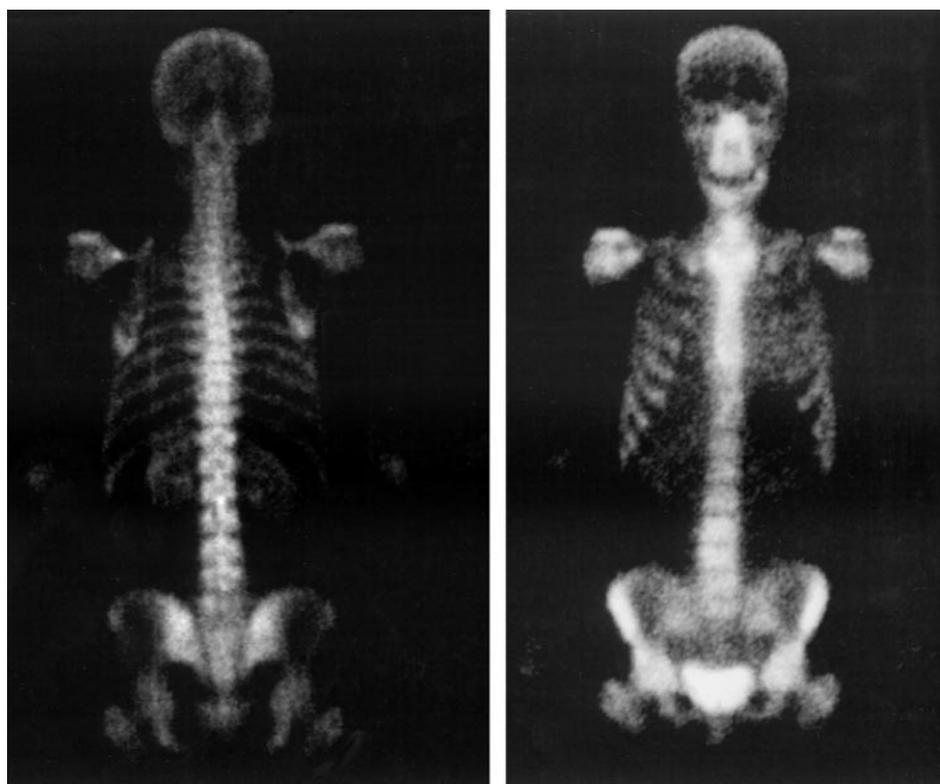


Fig 1. Nonsuspicious bone scan (patient no. 30).

With BS, only five patients were correctly considered to have bone metastases. Disease stage was classified as equivocal in seven patients, of whom three had metastatic bone disease. Eleven patients were correctly considered to be free of bone metastases, and three patients with metastatic bone disease were incorrectly considered to have no metastases (Figs 1 and 2). In two patients, degenerative lesions were incorrectly considered bone metastases.

In the patient group with previously unknown metastases, the full extent of metastatic bone disease was determined correctly in 11 patients with F-18-PET and in four patients with BS.

Bone metastases were located at the pelvis and/or at the vertebral column in 13 patients. Additional metastases were present in the appendicular skeleton in eight of these patients. Bone metastases were present in the peripheral skeleton, without vertebral involvement, in four patients. Therefore, the findings of BS or F-18-PET constituted the data needed to verify the diagnosis of metastatic bone disease made by the reference methods in four patients and to determine the extent of metastatic bone disease in 12 patients.

In summary, 17 patients had metastatic bone disease. Whereas the full extent of metastatic bone disease was described correctly with F-18-PET in all patients, extent

was interpreted correctly in only six patients (35.3%) with BS (Figs 3 and 4). The area under the ROC curve was 1.00 for F-18-PET and 0.82 for BS ($P < .05$) (Fig 5).

F-18-PET revealed a total of 168 osseous lesions. Of these lesions, 96 were judged correctly as benign and 64 were correctly considered metastatic. Eight lesions (seven benign and one metastatic) were classified as equivocal with F-18-PET. Only 89 lesions were detected with BS. Of these lesions, 68 were judged correctly (39 benign and 29 metastatic). Nine lesions were classified incorrectly (seven benign lesions were misinterpreted as metastases and two metastases were classified as benign) and 12 lesions were incorrectly classified as equivocal (five benign and seven metastatic). All lesions detected with BS were also visible on PET scans. The area under the ROC curve was 0.99 for F-18-PET and 0.72 for BS ($P < .05$, Fig 5).

Results of SPECT Imaging

In addition to BS, SPECT was performed in 12 patients, to better locate vertebral lesions. Benign and malignant lesions were differentiated correctly in nine patients. The BS remained indeterminate in one patient and was false-positive in two patients. Compared with planar BS, no additional metastases could be detected with SPECT in our series.

Fig 2. F-18-PET scan (maximum-pixel-intensity projection) showing metastases in the spine and pelvis (patient no. 30).

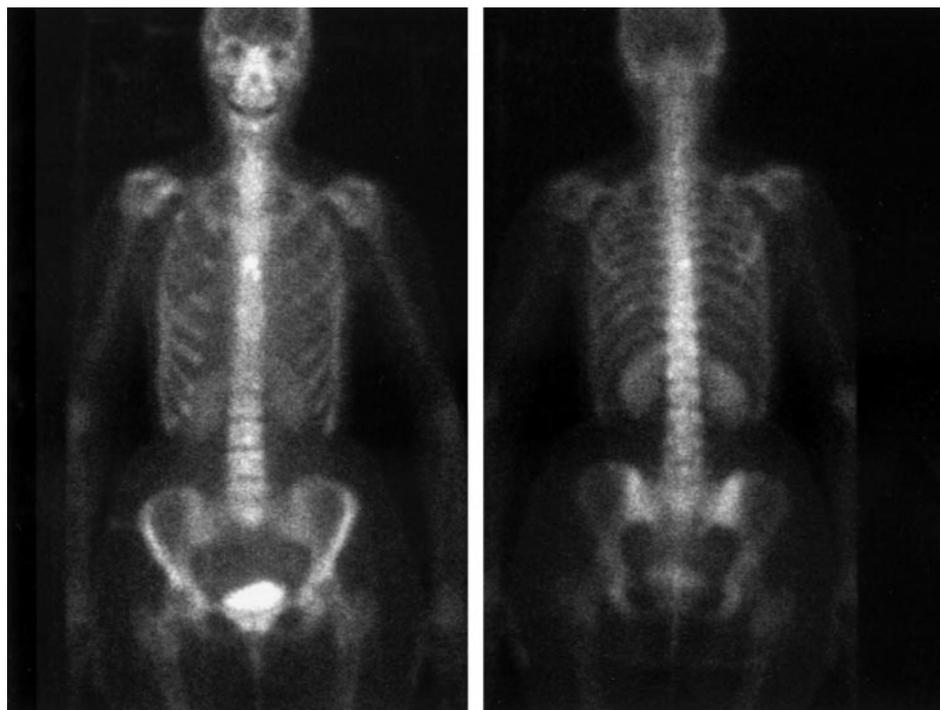
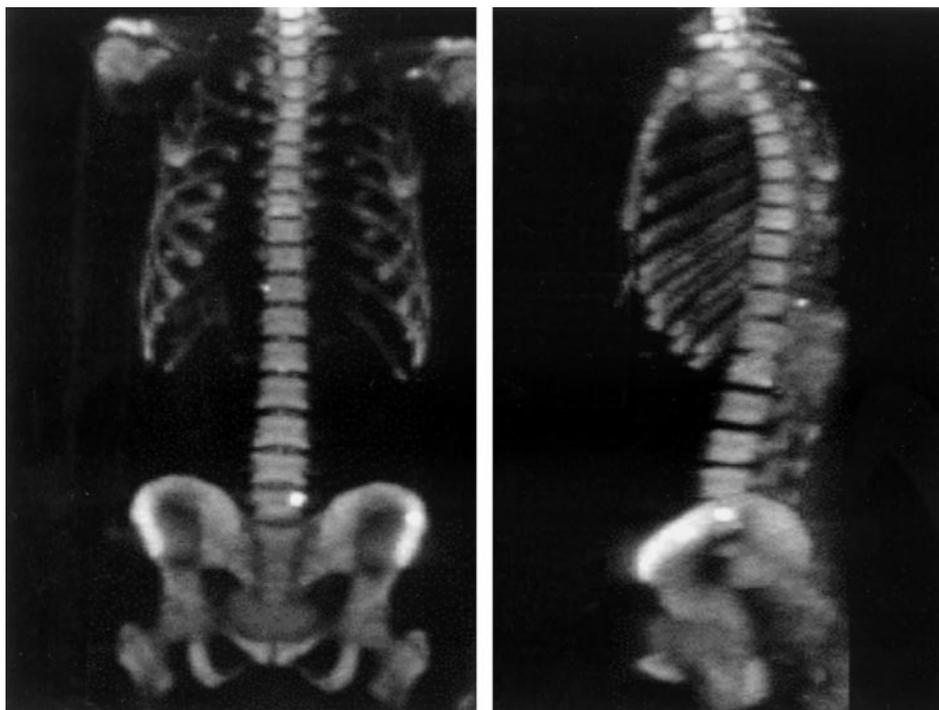


Fig 3. Bone scan showing metastases at the manubrium sterni and the thoracic spine (patient no. 14).

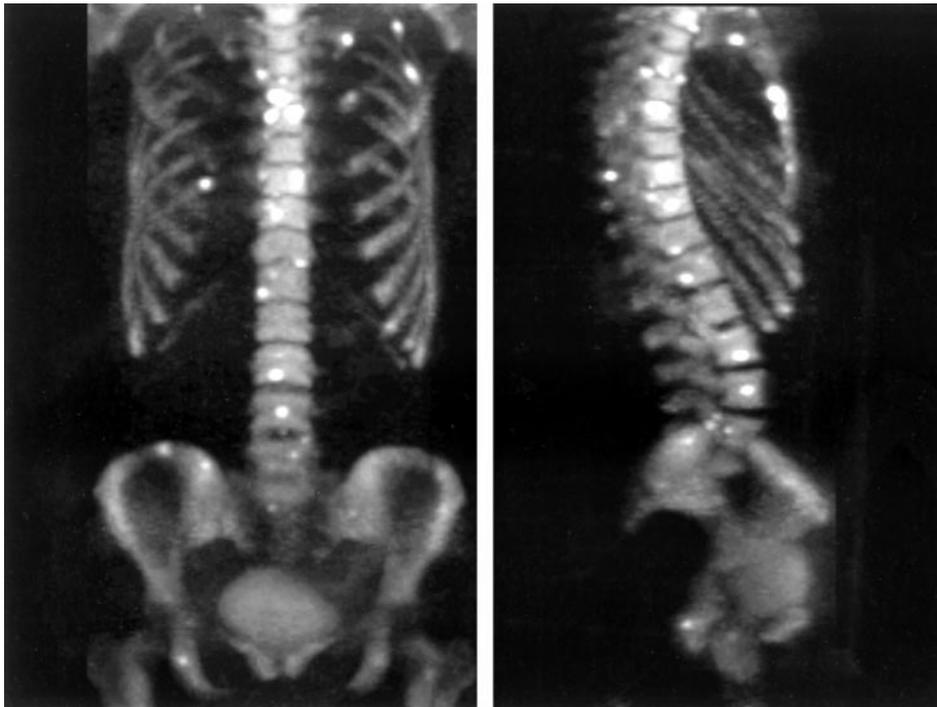


Fig 4. F-18-PET scan (maximum-pixel-intensity projection) showing disseminated metastatic bone disease (patient no. 14).

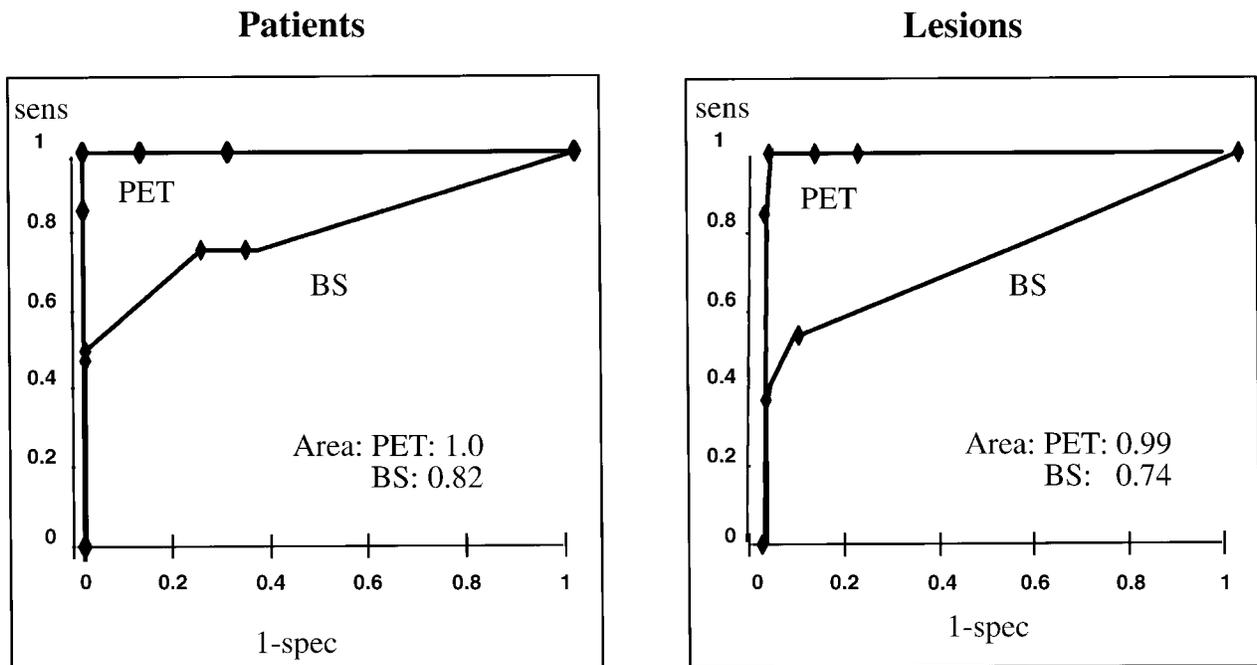


Fig 5. ROC curves for F-18-PET and BS.

Changes in Patient Management

As a result of findings made with the use of F-18-PET, clinical disease stage in three patients with metastatic bone disease and unsuspected bone scans (patients no. 10, 12, and 30) was changed from stage I or II to stage IV. In these three patients, systemic antihormonal and bisphosphonate therapy was initiated. In one patient with known metastatic bone disease (patient no. 1), a large osteolytic metastasis in the thoracic spine that had not been detected with BS was obvious on F-18-PET scans. Because of the risk of fracture, this metastasis was stabilized in surgery.

There was no change in management in two patients who had false-positive results with BS and had F-18-PET and MRI findings of degenerative lesions (patients no. 31 and 33), because they had received no therapy before these examinations. In summary, clinical management was changed in four (11.7%) of 34 patients and was influenced in six patients (17.6%) because of the use of F-18-PET.

DISCUSSION

Detection of metastatic deposits in the skeleton is essential for choosing optimal therapy, and accurate description of their extent is important for avoiding complications associated with pathologic fractures and for therapy control. The results of the present study show that in breast cancer patients who have a high risk of developing, or are suspected of having, bone metastases, F-18-PET enables detection of skeletal metastases that is as accurate as detection by a panel of reference methods and that is significantly earlier and more accurate than detection by conventional BS.

As a result of F-18-PET imaging, clinical management was changed in four patients in our series (11.7%). The extent of metastatic bone disease was strongly underestimated with BS, compared with F-18-PET, in 11 of 17 patients with bone metastases. Additionally performed SPECT was regarded as a part of the bone scanning procedure, and therefore these images were not evaluated separately. Of the 12 bone scans that were complemented by SPECT images, nine were interpreted correctly, one was interpreted as equivocal, and two were interpreted as false-positive. In contrast to recent reports,²⁹ no additional metastases were detected with SPECT in our series. There was no change in patient management in two patients with false-positive results with BS, because the vertebral lesions detected with BS were interpreted as benign with F-18-PET and were confirmed as being benign with MRI. The rate of false-positive results with BS in the present study is in agreement with that reported in the literature.^{10,11} On the other hand, with the introduction of MRI into clinical practice, a number of studies have found an increasing rate of false-negative results with BS and a significant underesti-

mation of metastatic bone disease in patients with various malignant solid tumors.^{14,15,17,18} An early and accurate description of the distribution pattern and extent of metastatic bone disease is required for optimum treatment planning and therapy control.^{30,31} Although MRI is clearly more sensitive than BS, BS remains the examination modality of choice for primary staging and for therapy control because MRI is costly, time-consuming, and impractical for whole-body surveys.^{18,32}

Along with a two-fold-higher sensitivity, there was a two-fold increase in the detection of benign bone lesions with F-18-PET. Because most of the patients reported bone pain, the high incidence of degenerative lesions might be a result of patient selection. False-positive results with BS have been reported more frequently in patients with bone pain.³³ The higher detection rate of degenerative lesions might lead to an increasing rate of false-positive results, because of limited experience in the use of F-18-PET for whole-body skeletal surveys. On the other hand, there is a psychological benefit for both patient and physician when, in a diagnostically unclear situation with unsuspected x-rays and bone scans, PET shows that existing bone pain is due to arthritis. The soft tissue clearance of F-18 is better than that of technetium-labeled polyphosphonates, and therefore there is no prominence of soft tissue in F-18-PET images.²⁵ Even the renal parenchyma is not visible, unlike in conventional bone scans.²⁵ The better pharmacologic properties, combined with the superior spatial resolution of our modern PET scanner, thereby enabled exact pinpointing of osseous lesions, preventing an increasing rate of false-positive results in our series.

Encouraging results concerning surgical treatment of isolated sternal metastases³⁴ as well as systemic treatment of metastatic bone disease by chemotherapy or bisphosphonates³⁵⁻⁴⁰ have recently been reported. However, there are insufficient data in support of the idea that earlier therapy for metastatic bone disease would improve prognosis in patients with osseous metastasized cancers. Therefore, F-18-PET is not suitable for routine skeletal surveys. Further studies are required to assess whether earlier treatment improves the prognosis of patients with bone metastases that were detected early with F-18-PET.

One problem of the present study is that the existence of metastatic bone disease was determined using a gold standard. In our study, gadolinium-enhanced T1-weighted and fat-suppressed T2-weighted images of the entire vertebral column and pelvis were obtained for optimal detection and differentiation between benign and malignant bone lesions. Misidentifications of abnormal bone lesions with MRI could not be excluded, although MRI has been shown to be highly

accurate.⁴¹ There is no sensitive reference method for detecting extravertebral lesions, given that CT and MRI are impracticable for assessing the entire skeleton.^{18,32} Missed extravertebral lesions could not be assessed. The lack of a sensitive whole-body imaging method is well documented by our study, given that four patients had metastatic bone disease without involvement of the vertebral column or the pelvis and that additional peripheral metastases were detected in eight of 13 patients with vertebral metastases. The data needed to assess the extent of metastatic bone disease were therefore dependent on the findings with BS and F-18-PET in 70% of the patients with metastatic bone disease. This means, in effect, that the findings by all of the examination modalities were used as the gold standard in our study, given that histologic confirmation of all osseous lesions is impracticable. Because of these limitations, the results of the ROC curve analysis indicate that the accuracy of F-18-PET is very close to the accuracy of the reference methods, but the conclusion cannot be drawn that F-18-PET

enables detection and differentiation of all osseous lesions that might be revealed at autopsy.

The results of the present study indicate that planar BS is less effective for revealing or excluding metastatic bone disease than is commonly accepted. Because the extent of metastatic bone disease was underestimated in most of the patients, BS is also ineffective for therapy control. In contrast, F-18-PET was optimally accurate in terms of skeletal staging and was clearly superior to BS in terms of describing the extent of metastatic bone disease. F-18-PET is suitable for detection of bone metastases in early tumor stages, resulting in a better selection of patients for promising therapy studies and better monitoring of therapy in such patients. At present, F-18-PET is still costly, time-consuming, and not available for routine use. However, given the increasing number of PET scanners and cyclotrons, F-18-PET may become a cost-effective diagnostic whole-body imaging modality for skeletal surveys in the future.

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