FDG PET Can Replace Bone Scintigraphy in Primary Staging of Malignant Lymphoma

Florian Moog, Jörg Kotzerke and Sven N. Reske

Department of Nuclear Medicine, University of Ulm, Ulm, Germany

Recent studies indicated that ^{18}F-fluorodeoxyglucose (FDG) PET may be more accurate than CT in staging nodal and extranodal malignant lymphoma. The objective of this study was to compare conventional bone scintigraphy as an established skeletal staging procedure with PET using FDG in the detection of osseous involvement in malignant lymphoma. **Methods:** Whole-body PET-based staging studies of 56 consecutive patients with proven Hodgkin's disease (n = 34) or non-Hodgkin's lymphoma (n = 22) were compared with the results of bone scintigraphy. Positive PET or bone scintigraphic findings were confirmed, if possible, by biopsy, MRI, CT or radiographic investigations. **Results:** Of the 56 patients studied, 12 were found to have skeletal involvement on both studies (PET, 30 regions; bone scintigraphy, 20 regions). Findings were confirmed in all 12 patients. FDG PET detected an additional 12 involved regions in 5 patients. This was subsequently verified in 3 patients, although the other 2 cases remained unresolved. Conversely, bone scintigraphy revealed five abnormalities compatible with lymphoma in 5 patients. Three of these lesions were found to be erroneous; final evaluation of the remaining two findings was not possible. **Conclusion:** FDG PET is suitable for identifying osseous involvement in malignant lymphoma with a high positive predictive value and is thereby more sensitive and specific than bone scintigraphy.

Key Words: lymphoma; ^{18}F-fluorodeoxyglucose PET; bone scintigraphy; skeletal involvement; staging

J Nucl Med 1999; 40:1407–1413

Several clinical characteristics of diphosphonate molecules make methylene diphosphonate or dicarboxymethylene diphosphonate the bone-seeking tracer of choice. The sensitivity in detecting bone metastases results from the very early osteoblastic reaction that occurs even when microscopic tumor is present (*1*). This stimulates regional osteoclasts, which erode nearby trabeculae, and a significant proliferation of osteoblasts occurs on the opposite side of the same trabeculae. The early phase of tracer deposition occurs at this rapid calcifying front of immature bone formation, where the calcium-to-phosphorus molar ratio is low (*2*).

Received Jul. 7, 1998; revision accepted Mar. 5, 1999.

For correspondence or reprints contact: Florian Moog, MD, Department of Nuclear Medicine, Ludwig-Maximilian-Universität München, Marchionini-Str. 15, D-81366 München, Germany.

Bone scanning has been used traditionally in the evaluation of bone involvement in lymphoma (*3–5*). Findings are characterized by relatively discrete uptake of tracer (*3*); osteolytic lesions, which are commonly encountered in non-Hodgkin's lymphoma (NHL) (*6,7*), routinely escape scintigraphic detection (*8*). The fact that bone scintigraphy remains a routine method in the work-up of malignant lymphoma is due not only to its low cost and its capability for rapid visualization of the entire skeleton but to the lack of viable alternatives.

Despite its limitations, bone scintigraphy is more sensitive than radiography in the detection of lymphoma (*4*). With conventional radiography, destruction of nearly 50% of bone mass is necessary before osteolytic lesions can be identified (*9*). Furthermore, examination of the entire skeleton is not feasible. Hence, radiography is mostly used to exclude false-positive findings on ^{99m}Tc bone scintigraphy. ^{67}Ga imaging is widely used for the evaluation of lymphoma but is of limited usefulness in detecting skeletal involvement (*3,10*). The use of modern equipment such as dual-head cameras, SPECT technique and high tracer dose may represent improvements, but none of these is superior to bone scintigraphy for whole-skeleton diagnostics (*11,12*).

The introduction of PET has resulted in several diagnostic advances in recent years. In terms of sensitivity and resolution, modern PET cameras display nearly optimal response to photons from positron emitters, compared with most generally available techniques in standard nuclear medicine. The capacity for accurately visualizing regional metabolic processes represents a fundamental advantage over other currently available imaging modalities.

^{18}F-fluorodeoxyglucose (FDG) PET has been used successfully in the evaluation of musculoskeletal (*13,14*) and strictly intraosseous tumors (*15*), as well as in the detection of osseous metastasis of breast carcinoma (*16*). Although results with prostatic carcinoma were disappointing in comparison with conventional bone scintigraphy (*17*), Sasaki et al. (*18*) have reported other osseous tumors with high FDG uptake and negative bone scintigraphy.

The high accuracy of FDG PET in the evaluation of nodal and extranodal involvement in lymphoma was first demonstrated by Newman et al. (*19*) and was confirmed by our findings (*20,21*). The results were superior to those of classic

staging methods, such as CT or bone marrow biopsy (*22*). For patients suffering from lymphoma, Hoh et al. (*23*) found that FDG PET-based staging may offer enhanced cost effectiveness, compared with conventional diagnostic tools including CT. Of great interest, both clinically and financially, is the capacity of FDG PET to accurately stage the entire body in a single imaging study.

The objective of this study was to evaluate the hypothesis that the diagnostic capabilities of FDG PET may equal or even exceed those of bone scintigraphy in the staging of malignant lymphoma.

MATERIALS AND METHODS

Between July 1992 and February 1997, 56 consecutive patients (25 males, 31 females; age range 13–72 y; mean age 36.0 y) suffering from untreated Hodgkin's disease (HD) or NHL were inducted into this study. Of 34 patients with HD, 18 showed histology with nodular sclerosis, 13 showed histology with mixed cellularity and 3 showed histology with lymphocytic predominance. Of the 22 patients with NHL, 3 had low-grade and 19 had high-grade disease according to the Kiel Classification (*24*). All patients gave their informed consent before being enrolled in the study. Patients underwent both FDG PET and bone scintigraphy within 4 wk (median 7 d) before the start of therapy.

PET studies were first obtained using a Siemens-CTI-ECAT scanner 931/08/12 (Siemens, Knoxville, TN) (40 patients). Since October 1995, a Siemens-ECAT-Exact HR+ scanner has been used (16 patients). The scanners simultaneously acquire either 15 or 63 contiguous transverse sections (6.75 or 2.46 mm, respectively) covering 10.1 and 15.5 cm, respectively, of the long axis of the patient (one bed position). Patients fasted for at least 8 h before examination. FDG, synthesized according to standard procedures (*25*), was injected intravenously at a dose of 250–350 MBq (mean 270 MBq) (6.75–9.45 mCi). Static emission scans from the base of the skull to the lower pelvis, covering the proximal femora in most of the patients and the lower legs in 1 patient, were obtained 50–60 min after FDG administration. To obtain these scans, we measured five to eight bed positions with an aquisition time of 10–15 min each. For attenuation correction, which was performed in 40 of 56 patients (71.4%), we acquired transmission scans by using a ^{68}Ge external ring source before FDG injection. We then obtained 10-min emission scans per bed position in six to eight bed positions. Between transmission and emission scans, patients were allowed to move, if desired. Patients were repositioned carefully using laser-guided landmarks to ensure an identical field of view for emission and transmission scanning. Furosemide (20 mg) was given intravenously before scanning to reduce artifacts due to the high level of radioactivity in the renal collecting system. Images were reconstructed with an iterative reconstruction algorithm (*26*). The in-plane resolution (full width at half maximum) for iterative reconstruction was 7 mm in the center of the field of view.

Bone scans were obtained using a Siemens gamma camera (Bodyscan; Siemens AG, Erlangen, Germany) with a high-resolution, low-energy collimator. Three to 4 h after intravenous application of 450–850 MBq (median 720 MBq) (19.45 mCi) ^{99m}Tc-marked methylene diphosphoniacide (Amerscan ^{99m}Tc; Amersham Healthcare, Braunschweig, Germany) and subsequent oral hydration, static whole-body scans with a minimum of 1.5 million counts per view were obtained. In the case of ambiguous findings, static images of individual regions of interest were obtained in addition to the whole-body scans.

PET studies were evaluated by both visual and blinded interpretation, as well as independent interpretation by two nuclear medicine physicians. Transaxial, coronal and sagittal sections were reviewed on film, and additional evaluation on the monitor was performed with alteration of the gray scale. Any foci with increased FDG uptake in comparison with contralateral bone tissue for midline structures with adjacent bone tissue were considered suggestive of lymphoma. In the case of diffuse or multifocal uptake patterns, the point of most intense uptake was used for evaluation. These visual findings were graded on a three-point scale as slight, moderate or marked. Quantitative analysis of FDG uptake was not performed.

Bone scintigraphy studies were interpreted in the same manner as the PET studies on analog data film by another experienced nuclear medicine physician. These visual findings were also graded from slight to marked, although the determination of intensity was in relation to adjacent osseous structures. In comparison with PET interpretation, however, the intensity of tracer uptake was not used as the main diagnostic criterion. Other important factors were configuration and localization of findings and historical data (trauma and history of degenerative osseous disease). Scans were judged to be positive if the abnormalities observed were most consistent with neoplastic involvement.

Bone scintigraphy and FDG PET images were evaluated blinded to each other. Only those skeletal regions that were examined with both bone scintigraphy and PET were compared, whereas suspicious findings detected in body regions that were examined exclusively with one method were not evaluated in this study. The following skeletal regions were compared: the bony thorax (ribs, sternum, scapulae, clavicles); humeri; the cervical, thoracic, lumbar and sacral spine; left and right bony pelvis; and femora and distal extremities.

To confirm concordant positive findings or to clarify discrepant PET and scintigraphic findings, 4 patients underwent selective second biopsies, while MRI, CT, bone marrow scintigraphy or conventional radiographic examinations were performed in 9, 4, 1 and 6 patients, respectively. Independent of this protocol, 47 of 56 patients (83.9%) underwent bone marrow biopsies of both iliac crests. In individual cases, biopsy material was obtained from only one iliac crest.

RESULTS

Concordant Results

In 34 patients (60.7%), both bone scintigraphy and PET visualized normal skeletal structures (Table 1). These results showed excellent correlation with findings of bone marrow biopsy (all negative), which were conducted in 27 of these 34 patients.

Conversely, in 12 other patients (21.4%), both methods identified at least one affected skeletal region (HD, 4 patients; NHL, 8 patients). In 4 of these 12 patients, guided second biopsies provided direct, histologic confirmation of lymphomatous involvement at sites with pathologic FDG and methylene diphosphonate uptake (thoracic vertebrae, 3 patients; tibia, 1 patient). It is of interest that biopsy material obtained from the iliac crest showed no evidence of bone marrow infiltration in any of these 4 patients. In the

TABLE 1
Number of Patients with FDG PET and Bone Scintigraphy in 56 Patients with Lymphoma

Bone scintigraphy	FDG PET	
	Positive	Negative
Positive	12 (30,* 20†)	5 (5)
Negative	5 (12)	34

*PET.
†Bone scintigraphy.
FDG = fluorodeoxyglucose.
Numbers in parentheses represent number of affected regions.

remaining 8 patients, skeletal involvement was confirmed by MRI, CT or radiography in 5, 1 and 2 patients, respectively. Thus, in each of these patients, concordant findings of PET and bone scintigraphy were confirmed by at least one other imaging method (Table 2). Only 5 of these 12 patients also exhibited positive findings on histologic examination of biopsy material derived from the iliac crest.

In these 12 patients, bone scintigraphy detected a total of 20 affected skeletal regions suggestive of lymphomatous infiltration (1.7 lesions per patient), 18 of which were also visualized on PET (Table 1). The 2 remaining sites were visualized as enhanced focal lesions projecting into the iliosacral joint. Because bilateral iliac crest biopsies had already been performed in both patients, definitive determination of the malignancy of the lesions was not possible. FDG PET scans in these same 12 patients showed 30 skeletal regions of increased tracer uptake that were suggestive of lymphoma (2.5 per patient) (Fig. 1).

On bone scintigraphy, these findings were visualized in 3 cases as slight, in 11 cases as moderate and in 6 cases as marked in contrast to adjacent, normal bone. Of 30 lesions visualized on PET, 2 showed slight, 1 showed moderate and 27 showed marked tracer uptake (Table 3). No difference in individual lesion intensity was seen between HD and NHL.

Discordant Results

In 5 additional patients with normal findings on bone scintigraphy, PET scanning revealed areas of tracer uptake typical of lymphomatous infiltration, which represents an increase of 41.7% over the number of patients with concordant positive PET and bone scan findings (Fig. 2). Four of these patients suffered from HD, whereas the fifth had been diagnosed with high-grade NHL. A total of 12 skeletal regions were affected, including the thorax (1 case), thoracic spine (3 cases), femora (2 cases), lumbar spine (1 case), pelvis (4 cases) and sacrum (1 case). Of these lesions, 2 showed moderate and 10 showed marked FDG uptake. In 3

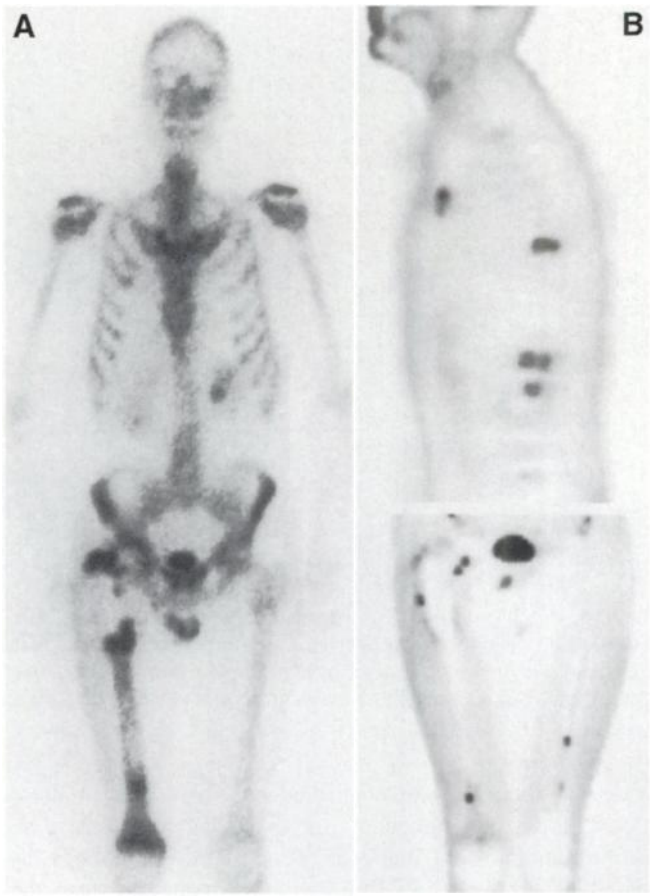

FIGURE 1. Highly malignant NHL. First manifestation was pathological fracture of right femur. (A) Bone scan conducted 8 d after surgical treatment of fracture demonstrated intense marker uptake in entire femur and adjacent areas of pelvis. It is not possible to differentiate between postsurgical changes and lymphomatous involvement. Remainder of study provided no additional relevant data. (B) FDG PET, however, detected multiple, circumscribed areas of metabolic activity typical of lymphoma, both within area affected by surgery and in pelvis, spine, sternum and contralateral femur.

TABLE 2
Evaluation of FDG PET and Bone Scintigraphy Findings

Results	No. of patients		
	PET and BS	PET only	BS only
True-positive	12	3	—
False-positive	—	—	3
Unconfirmed	—	2	2
Total	12	5	5

FDG = fluorodeoxyglucose; BS = bone scintigraphy.

TABLE 3
Uptake Intensity of Individual Lesions at FDG PET (n = 42) and Bone Scintigraphy (n = 25)

Results	PET			BS		
	Slight	Moderate	Marked	Slight	Moderate	Marked
No. of lesions	2	3	37	5	13	7
Percentage	4.8	7.1	88.1	20.0	52.0	28

FDG = fluorodeoxyglucose; BS = bone scintigraphy.

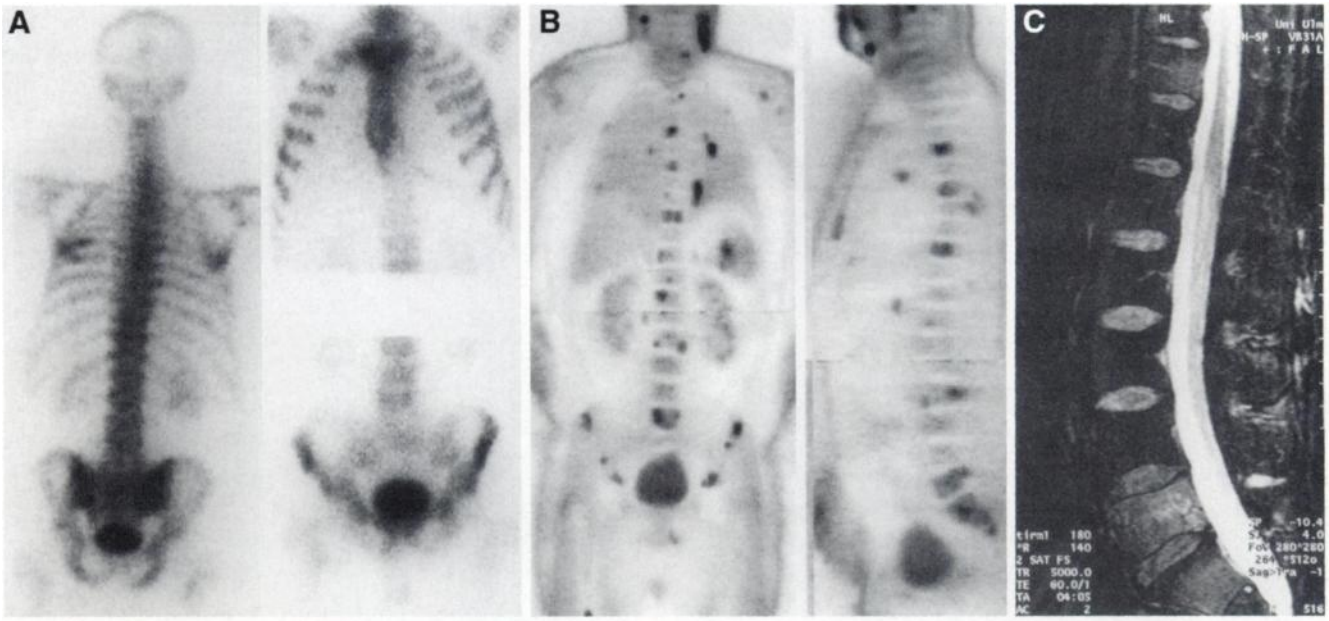

FIGURE 2. Highly malignant NHL. (A) There is no suspicious tracer uptake at bone scintigraphy, but (B) FDG PET shows enhanced FDG uptake in multiple axial and peripheral skeletal regions typical of malignant disease. (C) Lymphomatous infiltration was confirmed by MRI using short inversion-time inversion recovery sequence.

patients, findings were confirmed on MRI. In 2 of these cases, biopsy material taken from the iliac crest was normal. In the remaining 2 patients, no definitive confirmation was possible, although bone marrow biopsy sample from the iliac crest was positive in one.

Conversely, 5 patients with normal findings on PET showed one suspicious lesion each on skeletal scintigraphy (pelvis, 1 patient; forehand, 1 patient; bony thorax, 3 patients). Two of these areas showed slight, two showed intermediate and one showed marked uptake patterns (Table 3). Further work-up in these cases yielded, in 1 patient, a benign tumor originating in the iliac crest (Fig. 3); in 2 other patients, an old fracture and a thickened pleural membrane, respectively, were found to be responsible for the increased tracer uptake. In the remaining 2 patients, radiographic target views showed normal osseous structures. Bone marrow biopsies from the iliac crest were conducted in 4 of these patients and returned negative findings in all.

Confirming reports by other authors (*3*), our findings indicated more frequent involvement of axial than peripheral skeletal segments in both HD and NHL (Table 4). We also observed that vertebral lesions occur most frequently in the thoracic and lumbar spine and occur least commonly in the cervical spine (*7,27*).

The studies that were attenuation corrected (40 patients) clearly showed all skeletal lesions; there were no true differences between the images with and without attenuation correction.

DISCUSSION

Compared with PET, bone scintigraphy is a simple imaging method. However, because it is suitable mainly for the evaluation of osseous structures, it is no more than a single building block in the entire clinical staging process for lymphomatous diseases. The advantage of PET over other imaging methods is that all organ systems can be visualized in a single examination session. Furthermore, disease may be detected long before anatomic changes become apparent, because biochemical changes in a tumor occur before gross morphological alterations.

Recent studies have provided evidence of an important potential role for FDG PET in the detection of nodal and extranodal lymphomatous infiltration. Data from these studies even suggest that PET may, in fact, be superior to established staging methods, such as conventional CT or bone marrow biopsy (*20–22*). Findings of this study demonstrate advantages of PET over bone scintigraphy, another established imaging method. Investigations by Hoh et al. (*23*) postulate that clinical staging strategies for malignant lymphomas may be altered fundamentally by the introduction of this sensitive imaging method. Their findings also indicate that whole-body FDG PET may be more cost effective than current conventional staging algorithms. Most lymphomas are amenable to curative therapy. This, coupled with the fact that younger individuals with higher life expectancies are affected more frequently, underscores the need for optimal staging.

Lymphomatous infiltration of skeletal structures may occur as a result of both hematogenous spread of the disease and direct invasion from adjacent involved tissues (*28*). Because both bone and bone marrow are usually supplied by the same vascular system, infiltration of the marrow often becomes clinically apparent before involvement of the bone itself. However, tumor cells may primarily reach osseous

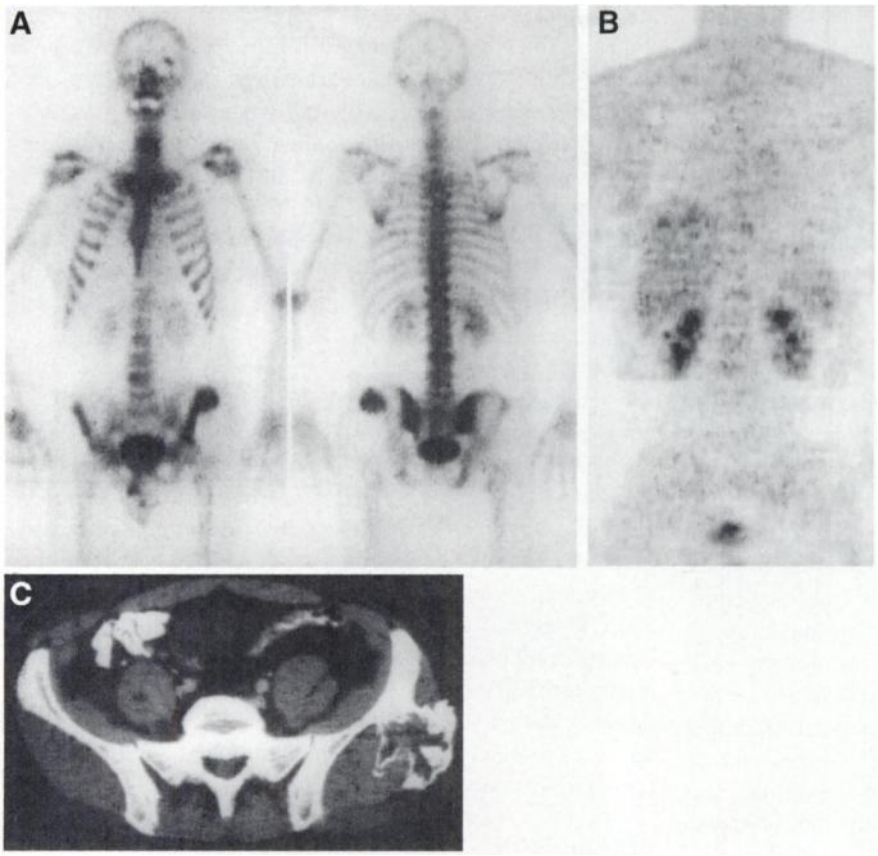

FIGURE 3. (A) ^{99m}Tc-diphosphonate scintigrams show intense and eccentric lesion in left ilium and (B) normal glucose metabolism on FDG PET. (C) Unchanged visualization on CT follow-up examination confirmed benign nature of this lesion.

structures by way of periosteal vessels and only reach the marrow once penetration of cortical bone has been achieved (*5*). The functional interfaces between both compartments have received insufficient clinical attention. For example, histological confirmation of even localized lymphomatous infiltration of bone marrow is considered evidence of generalized disease, whereas scintigraphic or radiologic findings of isolated osseous lesions are held to be compatible with focal disease. It is well known that certain more aggressive forms may be associated with early osseous destruction but remain circumscribed in the marrow over prolonged periods of time, whereas less aggressive forms may not affect the trabecular structure of the bone at all yet spread extensively in the marrow (*29*).

TABLE 4
Distribution of Skeletal Findings with FDG PET (n = 42) and Bone Scintigraphy (n = 25)

Skeletal finding	FDG PET	BS
Cervical spine	1	—
Thoracic spine	7	4
Lumbar spine	5	2
Sacral spine	3	—
Thorax	5	7
Pelvis	11	6
Femora	7	2
Humeri	2	2
Distal extremities	1	2

FDG = fluorodeoxyglucose; BS = bone scintigraphy.

Corresponding to this biologically and clinically heterogeneous pattern of behavior, it would seem that the presence or absence of abnormalities in bone scans in patients with bone marrow involvement depends on a number of factors, such as the extent of lymphomatous involvement within the cavity, the degree of associated destruction of normal bone architecture and the intensity of osteoblastic-stimulating mediator systems. For example, Ferrant et al. (*5*) have shown that, in patients with HD, local accelerated osseous turnover and, thus, increased uptake of bone-seeking radionuclide were due to local involvement of bone marrow, without concommitant destruction of osseous structures or disseminated bone marrow involvement. Conversely, Munker et al. (*30*) found that only 21.4% of patients with HD with confirmed bone marrow involvement showed pathologic findings on skeletal scintigraphy. This would indicate that confirmation of bone marrow involvement should not necessarily be considered evidence of generalized disease and that localized osseous findings may be associated with varying degrees of bone marrow infiltration.

Traditionally, various diagnostic methods have been used in the work-up of lymphomatous involvement of intra- and extramedullar skeletal bone. At present, biopsy of tissue obtained from the iliac crest is the most widely accepted method for determining bone marrow involvement. However, false-negative results are often obtained with this

technique, because a focal pattern of infiltration makes the method subject to sampling error (*31*). In addition to MRI, which is able to detect focal disease before diffuse infiltration (*32*), bone marrow scintigraphy has been shown to be a sensitive tool for detection of bone marrow involvement (*33*). Osseous skeletal structures are accessible to scintigraphic techniques and to radiologic or CT modalities. None of these imaging techniques, however, is capable of simultaneous examination of both intra- and extramedullar bone and of larger skeletal segments with a sufficient degree of sensitivity and specificity.

Today, FDG PET has been shown to be capable of demonstrating both these functional and anatomic relationships and the true extent of the disease with a high degree of sensitivity. In another study, we showed FDG PET's potential for determining local bone marrow involvement at sites that were inaccessible to local biopsy (*22*). The findings of this study of FDG PET's usefulness in evaluating osseous skeletal structures suggest that an integrated examination of the entire skeleton with a single imaging modality is feasible. The excellent local resolution of modern PET scanners using appropriate image reconstruction (*26*) allows differentiation of intra- and extramedullar skeletal structures of marrow-containing long bones, of the sternum and of central areas of the pelvis. Under normal conditions, the vertebrae are well delineated from adjacent intervertebral spaces.

A potential limitation of FDG for assessing malignant osseous lesions may be its physiologic accumulation in bone marrow. In untreated patients, at least, this accumulation is generally quite homogeneous and, at standardized uptake value (SUV) levels of 0.7–1.3, is comparatively low (*34*). On the other hand, in areas of lymphomatous involvement, despite large differences depending on the degree of malignancy, with SUV values of 3.5–31.0 (median 8.5), Lapela et al. (*35*) found a significantly higher glucose metabolism. Although at this level it is not characteristic for all malignancies (*17*), this intense FDG uptake provides adequate contrast in most cases of malignant lymphoma to permit differentiation from benign processes. Thus, in this study, although we did not perform quantitative uptake measurements, there were no false-positive findings at FDG PET.

One advantage of attenuation-corrected images might be a better delineation of the lungs to the hili. Furthermore, an intense representation of the skin in uncorrected images might influence the detectability of small lesions near the body surface. Despite changes in attenuation correction in this study, all skeletal lesions were clearly recognizable on both nonattenuation-corrected and, if conducted, (40 patients) attenuation-corrected images. Recently, the accuracy of FDG PET nonattenuation-corrected images was systematically compared with that of attenuation-corrected images in patients with malignant lymphoma, regarding detection of nodal and extranodal lesions (*36*). In only 5 of 225 lesions with increased FDG uptake (2.2%) were there true differences between the images with and without attenuation correction. This relevant lesion contrast was found in lymph nodes in the liver and spleen hilus, whereas all skeletal manifestations were clearly shown on both image sets because of similar lesion contrast. Therefore, we conclude that for primary staging of malignant lymphoma the attenuation correction can be neglected. In concordance with our own findings, Hoffman et al. (*37*) observed a statistically significant difference in quantitative FDG uptake between cerebral lymphoma and infection; but even their data would confirm that there is no substantial difference between semiquantitative analysis and the results of visual interpretation.

This study compared a tomographic imaging technique with one that, for the most part, is performed in planar fashion. This is certainly a conceptual weak point in the study design; however, these represent the only routinely feasible measurement methods. PET scanning is a tomographic method, per se; on the other hand, the routine scintigraphic examination of larger skeletal segments using SPECT technology has yet to become established. Our departmental practice has been to conduct SPECT measurements primarily in cases of ambiguous findings on planar imaging. A fundamental advantage of PET technology is its ability to routinely provide optimal tomographic representation of all data obtained.

CONCLUSION

Bone scintigraphy is a sensitive but nonspecific method for visualizing the activity of osseous metabolism and is typically used for exclusion of skeletal involvement in malignant disease. Because of the increased level of glycolysis in malignant cells, uptake of FDG is increased and can thus serve as a tracer for direct identification of malignant lesions. On the basis of its measurement technique and the intense biologic signal, PET is superior to skeletal scintigraphy for detecting lymphomatous cells in the skeletal system.

In this study, all confirmed malignant lesions were also detected by FDG PET. Conversely, skeletal scintigraphy identified fewer malignant but more nonspecific changes, delivering no additional clinically relevant information. This suggests that it may be appropriate to defer skeletal scintigraphy in patients undergoing FDG PET. A reduction in costs (primarily due to deferring scintigraphy and secondarily due to avoidance of follow-up radiography) may also be an advantage of the method.

REFERENCES

1. Guillemart A, Besnard JC, Pape AL, et al. Skeletal uptake of pyrophosphate labeled with technetium-95m and technetium-96, as evaluated by autoradiography. *J Nucl Med.* 1978;19:895–899.
2. Wilson AW. Musculoskeletal system. In: Wilson MA, ed. *Textbook of Nuclear Medicine.* Philadelphia, PA: Lippincott-Raven Publishers; 1998:3–32.
3. Orzel J, Sawaf NW, Richardson ML. Lymphoma of the skeleton: scintigraphic evaluation. *Am J Rehabil.* 1988;150:1095–1099.
4. Schechter JP, Jones SE, Woolfenden JM, et al. Bone scanning in lymphoma. *Cancer.* 1976;38:1142–1146.
5. Ferrant A, Rodhain J, Michaux JL, Piret L, Maldague B, Sokal G. Detection of skeletal involvement in Hodgkin's disease: a comparison of radiography, bone scanning, and bone marrow biopsy in 38 patients. *Cancer.* 1975;35:1346–1353.

6. Malloy PC, Fishman EK, Magid D. Lymphoma of bone, muscle, and skin: CT findings. *Am J Rehabil.* 1992;159:805–809.
7. Edeiken-Monroe B, Edeiken J, Kim E. Radiologic concepts of lymphoma of bone. *Radiol Clin North Am.* 1990;28:841–864.
8. Jânoskuti L, Szilvôsi I, Papp G, Rona E, Benedek S, Fekete S. Bone scanning and radiography in the evaluation of patients with malignant lymphoma. *Fortschr Röntgenstr.* 1988;149:427–428.
9. Edelstyn GA, Gillespie PJ, Grebbbell FS. The radiological demonstration of osseous metastasis. Experimental observations. *Clin Radiol.*1967;18:158–162.
10. Moon TY, Kim EE, Kim YC, et al. Comparison of nuclear bone and gallium scans in the therapeutic evaluation of bone lymphoma. *Clin Nucl Med.* 1995;20:721–724.
11. Bar-Shalom R, Israel O, Epelbaum R, et al. Gallium-67 scintigraphy in lymphoma with bone involvement. *J Nucl Med.* 1995;36:446–450.
12. Mouratidis B, Gilday DL, Ash JM. Comparison of bone and ^{67}Ga scintigraphy in the initial diagnosis of bone involvement in children with malignant lymphoma. *Nucl Med Commun.* 1994;15:144–147.
13. Kern KA, Brunetti A, Norton JA, et al. Metabolic imaging of human extremity musculoskeletal tumors by PET. *J Nucl Med.* 1988;29:181–188.
14. Adler LP, Blair HF, Makley JT, et al. Non-invasive grading of musculoskeletal tumors using PET. *J Nucl Med.* 1991;32:1508–1512.
15. Dehdashti F, Siegel BA, Griffeth LK, et al. Benign versus malignant intraosseous lesions: discrimination by means of PET with 2-[F-18]fluoro-2-deoxy-D-glucose. *Radiology.* 1996;200:243–247.
16. Wahl RL, Cody RL, Hutchins GD, et al. Primary and metastatic breast carcinoma: initial clinical evaluation with PET with radiolabeled glucose analogue 2-(F-18)-fluoro-2-deoxy-D-glucose. *Radiology.* 1991;179:765–770.
17. Shreve PD, Grossman HB, Gross MD, et al. Metastatic prostate cancer: initial findings of PET with 2-deoxy-2-(F-18)fluoro-D-glucose. *Radiology.* 1996;199:751–756.
18. Sasaki M, Ichiya Y, Kuwabara Y, et al. Fluorine-18-fluorodeoxyglucose positron emission tomography in technetium-99m-hydroxymethylenediphosphate negative bone tumors. *J Nucl Med.* 1992;34:288–290.
19. Newman JS, Francis IR, Kaminski MS, et al. Imaging of lymphoma with PET with 2-(F-18)-fluoro-2-deoxy-d-glucose: correlation with CT. *Radiology.* 1994;190:111–116.
20. Moog F, Bangerter M, Diederichs C, et al. Lymphoma: role of whole-body FDG-PET in nodal staging. *Radiology.* 1997;203:795–800.
21. Moog F, Bangerter M, Diederichs C, et al. Malignant lymphoma: detection with F-18-FDG PET versus CT. *Radiology.* 1998;206:475–481.
22. Moog F, Bangerter M, Kotzerke J, et al. FDG PET as a new approach to detect lymphomatous bone marrow. *J Clin Oncol.* 1998;16:603–609.
23. Hoh CK, Glaspy J, Rosen P, et al. Whole-body FDG PET imaging for staging of Hodgkin's disease and lymphoma. *J Nucl Med.* 1997;38:343–348.
24. Stansfeld AG. Updated Kiel Classification for lymphomas. *Lancet.* 1988;6:292–293.
25. Hamacher K, Coenen HH, Stoecklin G. Efficient stereospecific synthesis of no-carrier-added 2-(^{18}F)-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J Nucl Med.* 1987;27:235–238.
26. Schmidlin P. Improved iterative image reconstruction using variable projection binning and abbreviated convolution. *Eur J Nucl Med.* 1994;21:930–936.
27. Harder J. Knochengranulomatose. *Fortschr Röntgenstr.* 1960;63:445–450.
28. Vieta JO, Friedell HL, Craver LF. A survey of Hodgkin's disease and lymphosarcoma in bone. *Radiology.* 1942;39:1–15.
29. Braunstein EM, White SJ. Non-Hodgkin lymphoma of bone. *Radiology.* 1980;135:59–63.
30. Munker R, Hasenclever D, Brosteanu O, et al. Bone marrow involvement in Hodgkin's disease: an analysis of 135 consecutive cases. *J Clin Oncol.* 1995;13:403–409.
31. Ellis ME, Diehl LF, Granger E, et al. Trephine needle bone marrow biopsy in the initial staging of Hodgkin's disease: sensitivity and specificity of the Ann Arbor staging procedure criteria. *Am J Hematol.* 1989;30:115–120.
32. Tsunoda S, Takagi S, Tanaka O, Miura Y. Clinical and prognostic significance of femoral marrow magnetic resonance imaging in patients with malignant lymphoma. *Blood.* 1997;89:286–290.
33. Reske SN, Karstens JH, Gloeckner W, et al. Radioimmunoimaging for diagnosis of bone marrow involvement in breast cancer and malignant lymphoma. *Lancet.* 1989;2:299–301.
34. Zasadny K, Wahl RL. Standardized uptake values of normal tissues at PET with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose: variations with body weight and a method for correction. *Radiology.* 1993;189:847–850.
35. Lapela M, Leskinen S, Minn H, et al. Increased glucose metabolism in untreated non-Hodgkin's lymphoma: a study with positron emission tomography and fluorine-18-fluorodeoxyglucose. *Blood.* 1995;9:3522–3527.
36. Kotzerke J, Guhlmann A, Moog F, et al. Role of attenuation correction for FDG-PET in the primary staging of malignant lymphoma. *Eur J Nucl Med.* 1999;26:31–38.
37. Hoffman JM, Waskin HA, Hanson MW, et al. FDG PET in differentiating lymphoma from nonmalignant central nervous system lesions in patients with AIDS. *J Nucl Med.* 1993;34:567–575.