Eur J Nucl Med Mol Imaging (2008) 35:465–471
DOI 10.1007/s00259-007-0593-0

EDITORIAL

Evolving concept of imaging bone marrow metastasis in the twenty-first century: critical role of FDG-PET

Sandip Basu · Drew Torigian · Abass Alavi

Published online: 23 October 2007

Keywords Skeletal metastasis · Bone marrow · Red marrow · Bone marrow scintigraphy · Bone scintigraphy · FDG-PET · MRI · CT

Introduction

In this communication, we have explored the role of modern imaging modalities in investigating skeletal involvement by cancer. Obviously, detecting and characterizing disease sites at early stages are most desirable for the early and accurate assessment of disease activity. Based on the differences in physical and biological principles of each of these imaging modalities, they can be broadly categorized into two groups: those that detect the disease sites at the "bone marrow" (BM) level and those that rely on indirect evidence including osteoblastic reaction after invasion of the surrounding bone by the pathologic process. We further subclassify the first group of methodologies into two categories: those that visualize lesions as negative focal marrow defects as seen on BM scintigraphy (BMS) or MRI, and those that are based on targeting of abnormal tissue directly such as with fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging. The emergence of the latter method combined with whole-body tomographic imaging has truly revolutionized diagnosis and staging of patients with cancer and other serious disorders. This is particularly true for FDG-PET imaging, which is now commonly employed. It is imperative to understand the significance and implications of the osseous abnormalities visualized by FDG-PET as opposed to those seen by either structural (CT or MRI) or other functional imaging modalities (bone scintigraphy). Inappropriate interpretation of the results from these distinctly different types of imaging studies has resulted in misunderstanding of the optimal utility of different approaches. In this communication, we shall make an effort to clarify the underlying concepts that are related to this subject and the controversies that are reported in the literature.

For years, functional imaging with bone scintigraphy has been utilized as the initial imaging modality to screen the skeleton for metastatic disease. Because of its widespread availability, low cost, relatively high sensitivity, and ability to evaluate the entire skeleton in a single examination, this technique has been quite effective in many settings. However, as the role of FDG-PET in the management of patients with cancer and other disorders is becoming well established, the role of conventional bone scintigraphy and similar imaging techniques is being questioned in this setting [1, 2]. The principles by which these modalities

S. Basu · A. Alavi (✉)
Division of Nuclear Medicine, University of Pennsylvania School of Medicine, Hospital of the University of Pennsylvania,
3400 Spruce Street,
Philadelphia, PA 19104, USA
e-mail: abass.alavi@uphs.upenn.edu

D. Torigian
Department of Radiology, University of Pennsylvania School of Medicine, Hospital of the University of Pennsylvania,
Philadelphia, PA, USA

S. Basu
Radiation Medicine Center (BARC),
Tata Memorial Hospital Annexe,
Parel,
Mumbai 400012, India

visualize sites of abnormalities in the skeletal structure should be taken into consideration in this context. The same is also applicable to other tests such as BMS, ^{18}F-Fluoride PET, CT, and MRI. Therefore, understanding the strengths and weaknesses of these imaging modalities is critical for their optimal utilization in the evaluation of patients with skeletal disease. In this scientific exchange, we will focus our discussion mainly on the comparative results in the literature and the relevant issues related to bone scintigraphy, BMS, and FDG-PET with regard to the assessment of osseous metastatic disease. The roles of CT and MRI will also be briefly discussed in this commentary.

Pathophysiology of skeletal metastasis and its implications for imaging skeletal involvement

Skeletal metastasis usually occurs by seeding of tumor emboli through the bloodstream, but can also occur via retrograde venous flow [3] or direct extension. Seeding via the hematogenous route takes place in the red marrow, which accounts for the distribution of skeletal metastases in red marrow-predominant sites in patients with cancer. After seeding of the malignant cells in the red marrow, the surrounding bone is remodeled by both osteoblasts and osteoclasts. The relative degree of resultant osteoclastic and osteoblastic remodeling is highly variable (depending on the tumor biology and local homeostasis) and determines whether a predominantly lytic, sclerotic, or mixed pattern will be noted on radiographic studies. Therefore, bone scintigraphy or radiological studies only provide indirect evidence for tumor activity, which is mainly dependent upon local osteoblastic/osteoclastic remodeling. In contrast, FDG-PET directly images tumor cells based on their metabolic activity. Hence, in theory, metastatic disease foci should be detectable by FDG-PET earlier than by conventional bone scintigraphy. In addition, FDG-PET has the advantage of providing information about the primary tumor site, the state of lymph nodes, and metastases to other organs during a single whole-body study.

It is important to recognize the patterns of hematopoietic red marrow vs fatty yellow marrow distribution at different age groups and the changes that take place with different disease states [4]. At birth, virtually all marrow is hematopoietic. Conversion of red marrow to yellow marrow with advancing age begins in the distal bones and eventually leads to substantial disappearance of hematopoietic tissues from the extremities. In adults, hematopoietic BM is confined to the axial skeleton (skull, vertebrae, ribs, sternum, and pelvis) and proximal portions of the humeri and femora. By now, it has been established that more than 90% of skeletal metastases are noted in the distribution of hematopoietic BM [5, 6]. Therefore, in adults, the axial skeleton is the most common site of early metastatic disease. In contrast, the extremities, which mainly contain yellow marrow, are typically spared.

Disseminated tumor cells in the BM have been shown to be present in a significant proportion of patients with early-stage malignancies. Recent literature [7] demonstrates that disseminated tumor cells in the BM usually evolve from circulating tumor stem cells, which adhere to the endothelial cells lining the blood vessels in the BM and subsequently extravasate into the BM space. The expression of CD44, a hyaluronic acid (HA) cell surface receptor has been implicated in this process. Only when the cancer cells secrete proteolytic enzymes at the endosteal surface or within the bone matrix, the degradation of bone matrix ensues. A study by Hill et al. [8] demonstrated the fact that HA-induced CD44 signaling in breast cancer cells activates the transcription of genes for proteolytic enzymes (e.g., matrix metalloproteinase-9 and cathepsin K). The release of tumor growth factor-beta (TGF-β) and other growth factors from the bone matrix further increases the growth and colonization of the malignant cells. In addition to this, TGF-β also enhances the production and release of other growth factors (e.g., parathyroid hormone-related protein) from the cancer cells, which plays an important role in stimulating osteoclasts and thereby leads to further degradation of the bone matrix.

Comparison among different imaging approaches designed for detecting bone marrow metastasis vs osseous abnormalities after metastatic spread

Bone scan and bone marrow scintigraphy

Bone scintigraphy has commonly been used for evaluation of skeletal metastases. However, metastases that are associated with minimal reactive bone formation because of poor blood supply or are confined to the BM only can be missed with this approach. Therefore, over the past three decades, a number of investigators have assessed the utility of BMS (in addition to bone scanning) for depicting skeletal metastases. Images generated by BMS using large colloid particles are suboptimal for this purpose, but those acquired by utilizing ^{99m}Tc-nanocolloid (^{99m}Tc-NC) or ^{99m}Tc-antigranulocyte antibody (^{99m}Tc-AGAb) with substantially smaller particle size are reported to be superior to bone scintigraphy for depicting a variety of metastases. Most investigators agree that BMS, using either ^{99m}Tc-NC or ^{99m}Tc-AGAb [9, 10], reveals more lesions than bone scans in patients with lung [11–13], breast [14], renal, or bladder cancer [13].

Focal marrow defects are regarded as the major evidence for detecting a metastatic lesion with BMS [13, 15]. As a

result of the nonspecificity of this criterion, false-negative findings have been seen in patients with cancer in locations that are devoid of hematopoietic marrow after irradiation or at the peripheral skeleton, which contain minimal red marrow. In addition, there is superimposition of sites of ^{99m}Tc-NC uptake in the red marrow with that of the reticuloendothelial system in the liver and spleen. Moreover, BM defects on BMS are not specific for metastases, as benign disorders can result in identical imaging findings to those from malignant diseases. Such benign disorders include focal fatty degeneration of the marrow, Paget's disease, BM infarction, and some benign tumors including hemangioma or lipoma [15–18]. Detection of marrow defects without concordant abnormalities on bone scintigraphy resulted in a false-positive rate of 21% [19]. No significant scintigraphic differences have been observed on BMS between patients who have received chemotherapy and those who have not [20]. This suggests that chemotherapy-induced marrow suppression is unlikely to cause focal marrow defects on BMS in patients with lymphoma.

The red marrow activity expands peripherally into the appendicular skeleton as the extent of metastatic disease in the axial skeleton increases with advancing disease. Again, this phenomenon alone does not appear to be a reliable indicator of widespread metastases in the axial skeleton. This type of marrow expansion is observed in 50% of patients without metastases, while only 75% of patients with metastases demonstrate this pattern. This may also be observed after chemotherapy and the administration of marrow-stimulating drugs in such settings. Although the efficacy of BMS has been reported several times in various studies in the literature, it has never been practically incorporated into routine clinical practice because of the shortcomings enumerated above.

Magnetic resonance imaging

MRI has been described as a promising imaging modality to assess BM disease before bone remodeling ensues. With MRI, metastatic seeding in the BM is typically characterized by long T1 relaxation and variably increased T2 relaxation times, depending on tumor composition. Metastases typically appear as focal or diffuse areas of hypointensity on T1-weighted images and areas of intermediate to high signal intensity on T2-weighted images. Furthermore, metastatic deposits typically appear hyperintense against a dark background of suppressed fat signal intensity on short-tau inversion recovery (STIR) images. MRI can also be used to characterize the nature of abnormal findings detected on BMS such as degenerative changes, hemangioma, or lipoma. In recent years, several reports have documented that MRI is more sensitive than bone scintigraphy in the detection of metastases [21–25] as it can depict early hematogenous dissemination of tumor to the BM before reactive bone formation is detected by scintigraphy. However, the imaging features of metastases on MRI is not always specific for metastases, which may limit the utility of MRI to screen for the presence of BM metastases [26, 27]. The use of whole-body MRI to screen the skeleton has long been regarded as impractical, although in the recent past, Steinborn et al. [28] reported that this is feasible by using a whole-body MRI protocol consisting of T1-weighted and T2-weighted STIR sequences applied in different anatomical positions to cover the whole skeleton. This study reported sensitivities of 91.4 and 84.8% for MRI and skeletal scintigraphy, respectively, for the detection of skeletal involvement. Similar results were reported by Eustace et al. [21] who reported superior results with MRI (sensitivity, 96.5%, specificity, 100%; positive predictive value, 100%) compared to bone scintigraphy (sensitivity, 72%; specificity, 98%; positive predictive value, 95%).

CT scan

CT has been typically used to characterize focal abnormalities seen on bone scintigraphy that cannot be detected by planar radiographs. It has also been useful to guide needle biopsies for lesions in the vertebrae and to plan therapeutic interventions. However, the utility of CT to detect early metastatic deposits in the BM is limited. Furthermore, CT delivers a relatively high radiation dose to the marrow and reproductive organs, which makes it unsuitable as a whole-body screening examination for the detection of metastatic lesions. In addition to its relatively low sensitivity for small intramedullary lesions, some more advanced destructive lesions of the cancellous bone may not always be visible on CT images, particularly in the absence of reactive bone formation or cortical destruction. In one study [29] that retrospectively evaluated lesions by CT performed as part of a combined PET/CT examination in patients with suspected osseous metastatic lesions, morphologic changes on CT were observed in just half of the cases of true-positive BM metastases seen with FDG-PET. It was also noted that subtle changes on CT were common but presented a definitive diagnosis of a metastasis in only two thirds of suspected lesions seen on FDG-PET.

Therefore, the role and shortcomings of various imaging modalities in assessing malignant skeletal involvement should be reassessed by taking into account successes that have been achieved by employing FDG-PET imaging over the past decade. However, in light of recent developments with regard to whole-body imaging with MRI, the role of PET-CT needs to be further assessed in the future. In addition, the introduction of PET-MRI as an option for screening the whole body may further enhance the role of combined use of these two powerful modalities.

Emergence of FDG-PET as a powerful modality for assessing skeletal involvement by metastatic disease

Tumor cells have a higher rate of glycolysis due to increased activity of glycolytic enzymes and increased membrane glucose transport. PET with FDG detects lesions directly based on their degree of metabolic activity rather than by altered anatomy. This is in contrast to BMS using other tracers, where the normally functioning BM is visualized and the diseased sites are seen as negative defects without clear-cut evidence for disease activity. Compared to conventional planar BMS, FDG-PET also provides precise anatomic localization, higher spatial and contrast resolution images of normal and abnormal sites, and accurate quantification of metabolic activity of imaged tissues [30–34].

FDG-PET provides high target-to-background contrast ratios and therefore allows for detection of lesions with high sensitivity. The uptake of FDG in the skeleton represents active hematopoietic marrow, and the pattern and degree of uptake can vary depending on the patient age and level of marrow function at the time of examination [35]. FDG-PET has shown efficacy for the detection of BM metastases from several malignancies including lung carcinoma, breast carcinoma, and lymphoma [31, 36–42]. In one study which included 145 patients with a variety of malignancies, FDG-PET was found to be more sensitive and specific compared with bone scintigraphy [38]. In another report which describes the role of this technique for detecting BM metastases in 257 patients with newly diagnosed lung cancer, the accuracy, sensitivity and specificity of FDG-PET and bone scintigraphy were 94% vs 85%, 91% vs 75%, and 96% vs 95%, respectively [31]. Recent studies suggest that FDG-PET can provide information regarding appropriate biopsy sites, improve staging, increase accuracy for the assessment of therapeutic response, and allow for optimal restaging in patients with aggressive lymphomas [37, 39–41]. It also allows for measurement of standardized uptake values (SUV), which reflect the rate of glucose metabolism in lesions. This can provide information regarding the degree of aggressiveness of a malignant process and is useful for treatment planning and treatment monitoring. The implications of FDG-PET to assess disease burden have been extremely promising in multiple myeloma [43–45], the most common primary BM malignancy in adults. In one report, FDG-PET imaging, influenced clinical management in 14.0% of patients with multiple myeloma. The positive predictive value for active disease based on FDG uptake was 100% in patients with focal or mixed focal/diffuse disease, and 75% in patients with a diffuse uptake pattern. Depending on the interpretation of the PET scans in patients with diffuse BM uptake, the sensitivity ranged from 83.8% to 91.9% and the specificity ranged from 83.3% to 100%. FDG-PET thus proved highly accurate in detecting active sites of disease in multiple myeloma, and revealed a greater extent of disease than that provided by radiography in 60.9% patients who had osteolytic bone lesions. Thus, FDG-PET might contribute to the diagnostic performance of initial staging for solitary plasmacytoma [43, 44].

In a comparative study of 3 modalities (whole body MRI, FDG-PET and skeletal scintigraphy) for detecting skeletal metastasis, Daldrup-Link et al. [25] found sensitivities of 90% for FDG-PET, 82% for whole-body MRI, and 71% for bone scintigraphy. FDG-PET appears to be particularly useful when MRI is unable to differentiate between changes that are related to treatment from those of residual or recurrent tumor in a variety of malignancies.

With the emergence of ^{18}F-fluoride as an optimal PET tracer for imaging osseous abnormalities, it is likely that the role of conventional skeletal scintigraphy with ^{99m}Tc labeled phosphonates will diminish in the future. This tracer is readily extracted from the target in the cyclotron and can be used for clinical purposes with minimal quality assurance efforts. The cost of producing ^{18}F-fluoride is markedly lower than that of other PET tracers, and will be competititve with conventional bone imaging agents. While ^{18}F-fluoride PET is superior to conventional planar skeletal scintigraphy due to its superior high spatial resolution and tomographic approach, it theoretically suffers from certain shortcomings when compared to FDG-PET. FDG-PET is highly effective in identifying disease at an earlier stage when only the BM is involved and before bone remodeling has occurred. FDG-PET also allows for accurate quantification of metabolic activity of disease sites. Therefore, FDG-PET may obviate the need for bone scintigraphy with either single emitting or positron emitting radiopharmaceuticals.

Shortcomings of FDG-PET to evaluate skeletal involvement by metastatic disease: the current status

In spite of its strengths, FDG-PET has shortcomings that need to be addressed. Cytokines employed for BM stimulation may induce diffusely increased uptake in the BM, which can mimic generalized marrow metastasis or mask focal metastases on FDG-PET [46, 47]. However, the timing of FDG-PET studies is critical in differentiating between metastatic disease and stimulated BM. In general, the metabolic activity of BM rapidly decreases 3 to 5 days after cessation of cytokine therapy, although FDG uptake in tumor sites may remain elevated for up to 4 weeks [46–48]. It has been suggested that FDG-PET should be delayed for at least 2 weeks after completion of cytokine therapy.

It is interesting to note that a lower sensitivity of FDG-PET is reported for sclerotic skeletal metastases, particularly in prostate cancer, which predominantly produces this type of skeletal metastasis. The reason for this is still unclear,

although a plausible explanation is that sclerotic metastases are relatively acellular and harbor only small amounts of viable tumor cells, and therefore have low FDG uptake [49–51]. It is well known that evidence for response to therapy with bone scintigraphy in sclerotic bone lesions is nonspecific, and therefore, active and inactive processes involving bone remodeling may have the same degree of increased radiotracer uptake. It is important to determine whether the apparent lower sensitivity of FDG-PET in such clinical settings is due to lack of disease activity at these sites. It will be worthwhile to investigate the clinical significance of FDG-PET-negative and bone scan-positive lesions in patients with prostate cancer. Morris et al. [51] studied the performance of FDG-PET imaging in progressive metastatic prostate cancer and noted that all positive lesions represented active disease sites on subsequent studies. They concluded that FDG-PET can discriminate between active osseous disease sites and scintigraphically quiescent lesions in these patients. Post-treatment changes based on the SUV measured on FDG-PET scans correlated well with the serum prostate-specific antigen level. We believe that a head-to-head comparison of FDG and radiolabeled positron-emitting amino acids (e.g., choline) or acetate (which has been shown to accumulate in prostate cancer) should be carried out to clarify the role of these radiotracers for the evaluation of metastatic prostate cancer.

Similar observations have been made in breast cancer [50] but to a lesser extent. For example, osteolytic breast cancer metastases show increased FDG uptake, while osteoblastic metastases show low FDG uptake and may even be undetectable on PET images. The performance of FDG-PET may therefore vary depending on the tumor type and tumor biology. Increased FDG uptake may reflect hypoxia-induced increased glycolysis in aggressive and highly destructive lesions with an inadequate blood supply [52, 53]. Future well-designed prospective studies are necessary to provide some insight into tumor biology and discrepancies noted among reports that have appeared in the literature. It is conceivable that in patients with osteoblastic lesions, who have responded well to treatment, low or no FDG uptake truly reflects response to treatment, and bone scintigraphic abnormalities represent false-positive results. The lower sensitivity of FDG-PET for sclerotic metastases, such as in prostate cancer, is likely a reflection of low glycolytic metabolism of viable tumor tissue within the lesions [52, 53].

Overall implications of FDG-PET imaging of bone marrow lesions for patient management

FDG-PET has recently emerged as a potentially useful modality for the evaluation of BM involvement by various malignancies. Before tumor invasion of the bone matrix occurs, there are usually a substantial number of metabolically active tumor cells in the BM, representing the initial phase of skeletal metastases. This accounts for the superior sensitivities of FDG-PET and MRI compared to skeletal scintigraphy and CT in detecting early skeletal involvement by metastatic disease. It is important to differentiate the nature of lesions observed on FDG-PET and other tumor-targeting agents from those seen with bone-seeking compounds. As noted above, the mechanisms of localization of these tracers are quite different, and therefore findings from the diverse group of imaging techniques will have important implications for patient management. A recent study [54] investigating the BM status in 112 breast cancer patients with N0 or N1 disease (who had undergone BM aspiration twice) demonstrated that tumor cells are present in the BM in 83% of the cases at the time of primary surgery, and this was reduced to 24%, 12 months after initiation of adjuvant systemic therapy. This supports the concept that systemic treatment is effective in reducing the number of tumor cells in the BM. The results from other large-scale studies also suggest that systemic treatment can lead to survival benefit by eradicating occult metastases when they are confined to BM. In contrast, overt bone matrix involvement has been usually considered as incurable. Further studies are warranted to investigate this differential response to systemic therapy when metastases are mainly confined to the BM compared to those that involve the bone matrix. This would further enhance the role of metabolic imaging of BM metastases by FDG-PET in various malignant disorders.

In conclusion, the principles of diagnosis of skeletal involvement by cancer and related pathologies need to be clearly defined based on the observations that have been made with modern molecular techniques such as PET and possibly MRI in recent years. It is clear that red marrow is the primary site of initial spread of cancer to the skeleton and with time, and in advanced stages of the disease, the bony structures will be affected. Therefore, relying on imaging techniques that are designed to detect osseous abnormalities including conventional scintigraphy and CT will no longer provide a state-of-the-art approach for managing patients with suspected skeletal metastases. Although whole-body MRI with recent advances may allow screening the entire body for marrow lesions, it may not provide an advantage over FDG-PET. FDG-PET imaging also appears to be superior to MRI and CT for detecting lesions outside the skeletal system. Further studies may be required to confirm this impression in the near future.

Acknowledgment This work was supported in part by the International Union against Cancer (UICC), Geneva, Switzerland, under the ACSBI fellowship.

References

1. Basu S, Alavi A. Bone marrow and not bone is the primary site for skeletal metastasis: critical role of [^{18}F]fluorodeoxyglucose positron emission tomography in this setting. J Clin Oncol. 2007; 25(10):1297, Apr 1.
2. Lucignani G. Bone and marrow imaging: do we know what we see and do we see what we want to know. Eur J Nucl Med Mol Imaging. 2007;34(7):1123–6, Jul.
3. Morgan-Parkes JH. Metastases: mechanisms, pathways, and cascades. Am J Roentgenol. 1995;164(5):1075–82, May.
4. Blebea JS, Houseni M, Torigian DA, Fan C, Mavi A, Zhuge Y, et al. Structural and functional imaging of normal bone marrow and evaluation of its age-related changes. Semin Nucl Med. 2007;37(3):185–94, May.
5. Bonner H. The blood and the lymphoid organs. In: Rubin E, Farber JL, Rubin E, Farber JL, editors. Pathology. Philadelphia: Lipincott William and Wilkins; 1988. p. 1079–83.
6. Kamby C, Guldhammer B, Vejborg I, et al. The presence of tumor cells in bone marrow at the time of first recurrence of breast cancer. Cancer. 1987;60(6):1306–12.
7. Draffin JE, McFarlane S, Hill A, et al. CD44 potentiates the adherence of metastatic prostate and breast cancer cells to bone marrow endothelial cells. Cancer Res. 2004;64:5702–11.
8. Hill A, McFarlane S, Johnston PG, et al. The emerging role of CD44 in regulating skeletal micrometastasis. Cancer Lett. 2006; 237:1–9.
9. Duncker CM, Carrio I, Berna L, et al. Radioimmune imaging of bone marrow in patients with suspected bone metastases from primary breast cancer. J Nucl Med. 1990;31(9):1450–5.
10. Reske SN, Karstens JH, Gloeckner W, et al. Radioimmunoimaging for diagnosis of bone marrow involvement in breast cancer and malignant lymphoma. Lancet. 1989;1(8633):299–301.
11. Bourgeois P, Thimpont J, Feremans W, et al. Bone marrow scintigraphy in lung carcinomas using nanosized colloids: when is it useful and how useful is it. Nucl Med Commun. 1992;13(6): 421–8.
12. Widding A, Stilbo I, Hansen SW, et al. Scintigraphy with nanocolloid Tc 99m in patients with small cell lung cancer, with special reference to bone marrow and hepatic metastasis. Eur J Nucl Med. 1990;16(8–10):717–9.
13. Reske S, Kartsens J, Sohn M, et al. Bone marrow immunoscintigraphy compared with conventional bone scintigraphy for the detection of bone metastases. Acta Oncol. 1993;32(7–8):753–61.
14. Bourgeois P, Gassavelis C, Malarme M, et al. Bone marrow scintigraphy in breast cancer. Nucl Med Commun. 1989;10(6):389–400.
15. Haubold-Reuter BG, Duewell S, Schilcher BR, et al. The value of bone scintigraphy, bone marrow scintigraphy and fast spin-echo magnetic resonance imaging in staging of patients with malignant solid tumours: a prospective study. Eur J Nucl Med. 1993;20(11): 1063–9.
16. Cooper M, Miles KA, Wraight EP, et al. Degenerative disc disease in the lumbar spine: another cause for focally reduced activity on marrow scintigraphy. Skelet Radiol. 1992;21(4):247–9.
17. Palestro CJ, Kim CK, Swyer AJ, et al. Radionuclide diagnosis of vertebral osteomyelitis: indium-111-leukocyte and technetium-99m-methylene diphosphonate bone scintigraphy. J Nucl Med. 1991;32(10):1861–5.
18. Rudberg U, Ahlback SO, Uden R. Bone marrow scintigraphy in Paget's disease of bone. Acta Radiol. 1990;31(2):141–4.
19. Lee KH, Chung JK, Choi CW, et al. Technetium-99m-labeled antigranulocyte antibody bone marrow scintigraphy. J Nucl Med. 1995;36(10):1800–5.
20. Linden A, Zankovich R, Theissen P, et al. Malignant lymphoma: bone marrow imaging versus biopsy. Radiology. 1989;173(2):335–9.
21. Eustace S, Tello R, DeCarvalho V, et al. A comparison of whole-body turbo STIR MR imaging and planar 99mTc-methylene diphosphonate scintigraphy in the examination of patients with suspected skeletal metastases. Am J Roentgenol. 1997;169(6):1655–61, Dec.
22. Flickinger FW, Sanal SM. Bone marrow MRI: techniques and accuracy for detecting breast cancer metastases. Magn Reson Imaging. 1994;12(6):829–35.
23. Frank JA, Ling A, Patronas NJ, et al. Detection of malignant bone tumors: MR imaging vs scintigraphy. Am J Roentgenol. 1990;155 (5):1043–48, Nov.
24. Evans AJ, Robertson JF. Magnetic resonance imaging versus radionuclide scintigraphy for screening in bone metastases. Clin Radiol. 2000;55(8):653discussion 653–4, Aug.
25. Daldrup-Link HE, Franzius C, Link TM, et al. Whole-body MR imaging for detection of bone metastases in children and young adults: comparison with skeletal scintigraphy and FDG PET. Am J Roentgenol. 2001;177(1):229–36, Jul.
26. Altehoefer C, Blum U, Bathmann J, et al. Comparative diagnostic accuracy of magnetic resonance imaging and immunoscintigraphy for detection of bone marrow involvement in patients with malignant lymphoma. J Clin Oncol. 1997;15(5):1754–60.
27. Federico M, Magin RL, Swartz HM, et al. Detection of bone marrow involvement in patients with cancer. Tumori. 1989;75(2):90–6.
28. Steinborn MM, Heuck AF, Tiling R, et al. Whole-body bone marrow MRI in patients with metastatic disease to the skeletal system. J Comput Assist Tomogr. 1999;23(1):123–9, Jan–Feb.
29. Nakamoto Y, Cohade C, Tatsumi M, Hammoud D, Wahl RL. CT appearance of bone metastases detected with FDG PET as part of the same PET/CT examination. Radiology. 2005;237(2):627, Nov.
30. Alavi A, Lakhani P, Mavi A, et al. PET: a revolution in medical imaging. Radiol Clin North Am. 2004;42(6):983–1001.
31. Cheran SK, Herndon JE 2nd, Patz EF Jr. Comparison of whole-body FDG-PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer. Lung Cancer. 2004; 44(3):317–25.
32. El-Haddad G, Zhuang H, Gupta N, et al. Evolving role of positron emission tomography in the management of patients with inflammatory and other benign disorders. Semin Nucl Med. 2004;34 (4):313–29.
33. Durski JM, Srinivas S, Segall G. Comparison of FDG-PET and bone scans for detecting skeletal metastases in patients with Non-small cell lung cancer. Clin Positron Imaging. 2000;3(3):97–105.
34. Basu S, Zaidi H, Houseni M, Bural G, Udupa J, Acton P, et al. Novel quantitative techniques for assessing regional and global function and structure based on modern imaging modalities: implications for normal variation, aging and diseased states. Semin Nucl Med. 2007;37(3):223–39, May.
35. Shreve PD, Anzai Y, Wahl RL. Pitfalls in oncologic diagnosis with FDG PET imaging: physiologic and benign variants. Radiographics. 1999;19(1):61–77.
36. Mavi A, Lakhani P, Zhuang H, et al. Fluorodeoxyglucose-PET in characterizing solitary pulmonary nodules, assessing pleural diseases, and the initial staging, restaging, therapy planning, and monitoring response of lung cancer. Radiol Clin North Am. 2005; 43(1):1–21.
37. Moog F, Bangerter M, Kotzerke J, et al. 18-F-Fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. J Clin Oncol. 1998;16(2):603–609.
38. Chung J, Kim Y, Yoon J. Diagnostic usefulness of F-18 FDG whole body PET in detection of bony metastases compared to 99mTc MDP bone scan. J Nucl Med. 1999;40:96.
39. Kasamon YL, Wahl RL, Swinnen LJ. FDG PET and high-dose therapy for aggressive lymphomas: toward a risk-adapted strategy. Curr Opin Oncol. 2004;16(2):100–5.
40. Kumar R, Alavi A. Fluorodeoxyglucose-PET in the management of breast cancer. Radiol Clin North Am. 2004;42(6):1113–22.

41. Kumar R, Maillard I, Schuster SJ, et al. Utility of fluorodeoxyglucose-PET imaging in the management of patients with Hodgkin's and non-Hodgkin's lymphomas. Radiol Clin North Am. 2004;42(6):1083–100.
42. Schirrmeister H, Guhlmann A, Elsner K, Kotzerke J, Glatting G, Rentschler M, et al. Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus 18F PET. J Nucl Med. 1999;40(10):1623–39, Oct.
43. Schirrmeister H, Bommer M, Buck AK, et al. Initial results in the assessment of multiple myeloma using 18F-FDG PET. Eur J Nucl Med Mol Imaging. 2002;29(3):361–6.
44. Schirrmeister H, Buck AK, Bergmann L, Reske SN, Bommer M. Positron emission tomography (PET) for staging of solitary plasmacytoma. Cancer Biother Radiopharm. 2003;18(5):841–5, Oct.
45. Mileshkin L, Blum R, Seymour JF, Patrikeos A, Hicks RJ, Prince HM. A comparison of fluorine-18 fluoro-deoxyglucose PET and technetium-99m sestamibi in assessing patients with multiple myeloma. Eur J Haematol. 2004;72(1):32–7, Jan.
46. Sugawara Y, Fisher SJ, Zasadny KR, Kison PV, Baker LH, Wahl RL. Preclinical and clinical studies of bone marrow uptake of fluorine-1-fluorodeoxyglucose with or without granulocyte colony-stimulating factor during chemotherapy. J Clin Oncol. 1998;16 (1):173–80, Jan.
47. Hollinger EF, Alibazoglu H, Ali A, Green A, Lamonica G. Hematopoietic cytokine-mediated FDG uptake simulates the appearance of diffuse metastatic disease on whole-body PET imaging. Clin Nucl Med. 1998;23(2):93–8, Feb.
48. Gundlapalli S, Ojha B, Mountz JM. Granulocyte colony-stimulating factor: confounding F-18 FDG uptake in outpatient positron emission tomographic facilities for patients receiving ongoing treatment of lymphoma. Clin Nucl Med. 2002;27(2):140–1, Feb.
49. 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;199:751–6.
50. Cook GJ, Houston S, Rubens R, et al. Detection of bone metastases in breast cancer by ^{18}FDG PET Differing metabolic activity in osteoblastic and osteolytic lesions. J Clin Oncol. 1998;16:3375–9.
51. Morris MJ, Akhurst T, Osman I, et al. Fluorinated deoxyglucose positron emission tomography imaging in progressive metastatic prostate cancer. Urology. 2002;59:913–8.
52. Cook GJ, Fogelman I. The role of positron emission tomography in the management of bone metastases. Cancer. 2000;88(12 Suppl): 2927–33.
53. Cook GJ, Fogelman I. The role of positron emission tomography in skeletal disease. Semin Nucl Med. 2001;31(1):50–61.
54. Becker S, Becker-Pergola G, Wallwiener D, et al. Detection of cytokeratin-positive cells in the bone marrow of breast cancer patients undergoing adjuvant therapy. Breast Cancer Res Treat. 2006;97:91–96.