PET IN THE MANAGEMENT OF BONE METASTASES

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PET is one of the most common metastatic sites in patients with malignancy. It has been estimated that approximately 70% of patients with breast and prostate cancer have skeletal metastases during the late stages of the disease. Other cancers commonly associated with bone metastases include lung, renal, thyroid, and primary bone sarcomas.

Survival with bone metastases may be prolonged in some cancers, including breast and prostate, where the median survival is as long as two years. In comparison, the median survival in lung cancer with skeletal disease is only three months.

Skeletal metastases are predominiantly lytic in nature in most cancers, but in some patients, such as those with prostate cancer, skeletal disease tends to be predominantly sclerotic.

PET imaging of the skeleton is possible with two different radiopharmaceuticals: F-18 fluorodeoxyglucose (FDG) and 18F-fluoride ion (NaF). This article will discuss the use of FDG-PET in imaging bone metastases.
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FDG-PET

In contrast to F-18 fluorodeoxyglucose (FDG) uptake, which is more directly related to tumor metabolic activity than to a local bone osteoblastic reaction to tumor, the major factors affecting accumulation of FDG in tumor cells include glycolysis and membrane glucose transporters, both of which are known to be increased in many malignant tumors. Uptake of FDG is obviously not restricted to skeletal metastases, and the advantage of demonstrating all metastatic sites, whether in soft tissue or bone, is reasonably large. Too little evidence is available in these tumor types, compared with bone scintigraphy, to draw any conclusions.1,2,15 This has potential implications for patient management, for example, the detection of multiple lesions in a solitary plasmacytoma or FDG-PET leads to a change in diagnosis to multiple myeloma with concomitant changes in therapy. An increase in sensitivity has also been reported in a number of cancers where bone scintigraphy has been regarded as one of the most sensitive methods of skeletal involvement. These include breast cancer (especially of the “sparing of bone” type),25 lymphoma,26 and soft tissue sarcoma.27 In these situations it is possible that the apparent superiority of FDG-PET in the demonstration of tumor activity while small metastases have undergone systemic chemotherapy or have been released granulocyte colony-stimulating factors (G-CSF) that can cause false positives on bone scintigraphy. When FDG-PET was compared with bone scintigraphy in 110 patients with non-small cell lung cancer, both methods identified 19 out of 21 patients with skeletal metastases. PET, however, correctly identified the absence of bone metastases in a much larger proportion of patients than bone scintigraphy (87% compared with 54%).

On occasion, it can be difficult to determine whether FDG-avid lesions are caused by the ability to detect in skeletal metastases than conventional bone scintigraphy with Tc-99m MDP in some cancers for which Tc-99m MDP bone scintigraphy performs relatively poorly. Examples include renal cell cancer and plasmacytoma/myeloma, which tend to be predominantly osteolytic and have little or no local osteoblastic skeletal reaction to cause uptake of bone tracers. Direct visualization of tumor metabolic activity with FDG has been shown to have advantages in bone metastases compared with bone scintigraphy.16 This has potential implications for patient management, for example, the detection of multiple lesions in assumed solitary plasmacytoma with FDG-PET leads to a change in diagnosis to multiple myeloma with concomitant changes in therapy. An increase in sensitivity has also been reported in a number of cancers where bone scintigraphy has been regarded as one of the most sensitive methods of skeletal involvement. These include breast cancer (especially of the “sparing of bone” type),25 lymphoma,26 and soft tissue sarcoma.27 In these situations it is possible that the apparent superiority of FDG-PET in the demonstration of tumor activity while small metastases lie within the bone marrow rather than in an iliac crest bone marrow sample has proven negative.28 A complicating factor in patients who have undergone systemic chemotherapy or have received granulocyte colony-stimulating factors (G-CSF) is that a dif fuse increase in activity can occur in the bone marrow after treatment (Figure 3). FDG-PET scans remain useful, however, in evaluating response to therapy in nodal sites; for example, in patients with evidence of bone marrow involvement at initial staging. But PET is likely to be of more limited utility unless appropriately timed for assessing bone marrow response.29 Increased uptake compared with baseline may persist for four weeks after administration of G-CSF, although it may be possible to distinguish it from d i a g n o s t i c results earlier. It is of interest that purely sclerotic skeletal metastases tend to be less avid for FDG, and PET is likely to be less sensitive than conventional bone scintigraphy and in patients who have predominantly osteoblastic disease.30 This phenomenon has been seen in patients with sclerotic metastases from breast cancer (Figure 4), but it also probably explains the lower sensitivities reported for skeletal evaluation in prostate cancer.30 It is possible that this type of skeletal metastasis tends to have relatively low glycolytic activity, but it is also known that this type of metastasis is relatively acellular, so it is possible that low volumes of viable tumor tissue within a lesion may influence the degree of uptake of FDG, resulting in apparent low activity. Although a higher sensitivity has been reported for FDG-PET in a number of cancers, a higher specificity compared with bone scintigraphy is also a common finding.31 This is to be expected as there is no significant uptake of FDG in most benign skeletal lesions, e.g., osteoarthritis, that can cause false positives on bone scintigraphy. When PET compared with bone scintigraphy in 110 patients with nonsmall cell lung cancer, both methods identified 19 out of 21 patients with skeletal metastases. PET, however, correctly identified the absence of bone metastases in a much larger proportion of patients than bone scintigraphy (87% compared with 54%). On occasion, it can be difficult to determine whether FDG-avid lesions are caused by...
FDG-PET (A) and PET/CT (B) scans in patient with recurrent lymphoma. Abnormal focal uptake is seen on FDG-PET, but it is not possible to confidently localize this to the skeleton. Combined PET/CT scan allows accurate skeletal localization of the lesions, which had been unsuspected and changed management.

FDG-PET in contrast to F-18 fluorodeoxyglucose (FDG) uptake relies more directly on tumor metabolic activity than on a local bone osteoblastic reaction to tumor. The major factors affecting accumulation of FDG in tumor cells include glycolysis and membrane glucose transporters, both of which are known to be increased in many malignant tumors. Uptake of FDG is obviously not restricted to regions of bone metastases and the advantage of demonstrating all metastatic sites whether in soft tissue or bone.

A reasonably large body of evidence indicates that FDG-PET may be clinically useful in the assessment of skeletal metastases in a number of different cancers. It is evident that FDG-PET is more sensitive in detection of skeletal metastases than conventional bone scintigraphy with Tc-99m MDP in some cancers for which F-18 fluoride PET bone scintigraphy performs relatively poorly. Examples include renal cell cancer and plasmacytoma/myeloma, which tend to be predominantly osteolytic with little or no local osteoblastic skeletal reaction to cause uptake of bone tracers. Direct visualization of tumor metabolic activity with FDG has been shown to have advantages in both of these tumors compared with bone scintigraphy.

This has potential implications for patient management; for example, the detection of multiple lesions in assumed solitary plasmacytoma with FDG-PET leads to a change in diagnosis to multiple myeloma with concomitant changes in therapy.

An increase in sensitivity has also been reported in a number of cancers where bone scintigraphy has been regarded as one of the most sensitive measures of skeletal involvement. These include breast cancer (‘bone-sauna’), and lymphoma. In these situations it is possible that the apparent superimposition of benign processes may demonstrate tumor activity while small metastases lie within the bone marrow and before a significant skeletal reaction has taken place, which would be required for bone scintigraphy to become positive. (Figures 1 and 2)

Although FDG-PET probably cannot replace bone marrow biopsies in patients with lymphoma, it is commonly regarded as a complementary procedure as it provides accurate staging information in nodal and extranodal sites but on occasion will show sites of skeletal involvement when an iliac crest bone marrow sample has proven negative. A complicating factor in patients who have undergone systemic chemotherapy or have received granulocyte colony stimulating factors (G-CSF) is that a diffuse increase in activity can occur in the bone marrow after treatment (Figure 3). FDG-PET scans remain useful for evaluating response to therapy in nodal sites; for example, in patients without evidence of bone marrow involvement at initial staging. But FDG-PET is likely to be of more limited utility unless appropriately timed for assessing bone marrow response.57 Increased uptake compared with baseline may persist for four weeks after administration of G-CSF although it may be possible to detect d i a g n o s t i c responses earlier.

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sitive than conventional bone scintigraphy and in patients who have predominantly osteoblastic disease. This phenomenon has been seen in patients with sclerotic metastases from breast cancer (Figure 4), but it also probably explains the lower sensitivities reported for skeletal evaluation in prostate cancer.8 It is possible that this type of skeletal metastasis tends to have relatively low glycolytic activity, but it is also known that this type of metastasis is relatively acellular, so it is possible that low volumes of viable tumor tissue within a lesion may influence the degree of uptake of FDG, resulting in apparent low activity.

Although a higher sensitivity has been reported for FDG-PET in a number of cancers, a higher specificity compared with bone scintigraphy is also a common finding. This is to be expected as there is no significant uptake of FDG in most benign skeletal lesions, e.g., osteoarthritis, that can cause false positives on bone scintigraphy. When PET was compared with bone scintigraphy in 110 patients with non-small cell lung cancer, both methods identified 19 out of 21 patients with skeletal metastases. PET, however, correctly identified the absence of bone metastases in a much larger proportion of patients than bone scintigraphy (87/89 compared with 54/89).

On occasion, it can be difficult to determine whether FDG-avid lesions are...
located within or adjacent to the skeleton, and including bone scintigraphy in the diagnostic workup can be helpful in these situations. If skeletal localization is not an issue, bone scintigraphy probably not required in most cancers when routine FDG-PET is performed. As combined PET/CT scanners become more available, conventional modalities in evaluating treatment response, correlating well with clinical response, may become less cost-effective.

Further correlative investigations may be required in these cases, particularly if unexpected solitary lesions are encountered. Uptake of FDG has also been reported following acute fractures, but activity normalizes by approximately two to three months following trauma unless the fracture is complicated by infection or is a pathological fracture associated with malignancy.22 When there is a recent history of trauma, radiographic correlation of focal skeletal abnormalities on FDG-PET may be advisable to avoid this potential pitfall.

PITFALLS

In common with conventional skeletal scintigraphy, F-18 fluorodeoxyglucose (FDG) PET has the potential for false-negative or positive uptake in coincidental benign skeletal lesions. This problem is somewhat mitigated by the ability to more confidently differentiate benign from malignant lesions when combined with the tomographic images this imaging technique provides.

With FDG-PET, apart from potential false-negative scans in patients with sclerotic bone metastases, a number of nonmalignant pathologies can mimic metastases. Examples include Paget’s disease (Figure 5), fibrous dysplasia, and osteomyelitis. Further correlative investigations may be required in these cases, particularly if unexpected solitary lesions are encountered. Uptake of FDG has also been reported following acute fractures, but activity normalizes by approximately two to three months following trauma unless the fracture is complicated by infection or is a pathological fracture associated with malignancy.22 When there is a recent history of trauma, radiographic correlation of focal skeletal abnormalities on FDG-PET may be advisable to avoid this potential pitfall.

CONCLUSION

F-18 fluorodeoxyglucose (FDG) PET is a technique that enhances diagnostic accuracy when compared with conventional bone scintigraphy, although the advantages are less marked when bone scintigraphy is augmented with SPECT. However, there is evidence of enhanced sensitivity and specificity in a number of cancers when compared with planar bone scintigraphy suggesting that F-18 fluorodeoxyglucose PET imaging of metastases is an effective diagnostic technique. It can be concluded that in the majority of cancers, excluding those associated with predominantly sclerotic skeletal metastases, that an FDG-PET scan is performed for routine staging, conventional scintigraphy is probably not required. A bone scan may be helpful if there is doubt as to whether a lesion is static or adjacent to the skeleton but may not be necessary if combined PET/CT is performed. In osteoblastic predominant disease, conventional scintigraphy remains the method of choice for assessing the skeleton.

References
6. Minnich JW, et al. Planar bone scintigraphy suggesting that F-18 NaF PET is a technique that can enhance diagnostic accuracy when compared with conventional bone scintigraphy, although the advantages are less marked when bone scintigraphy is augmented with SPECT. However, there is evidence of enhanced sensitivity and specificity in a number of cancers when compared with planar bone scintigraphy suggesting that F-18 fluorodeoxyglucose PET imaging of metastases is an effective diagnostic technique. It can be concluded that in the majority of cancers, excluding those associated with predominantly sclerotic skeletal metastases, that an FDG-PET scan is performed for routine staging, conventional scintigraphy is probably not required. A bone scan may be helpful if there is doubt as to whether a lesion is static or adjacent to the skeleton but may not be necessary if combined PET/CT is performed. In osteoblastic predominant disease, conventional scintigraphy remains the method of choice for assessing the skeleton.