

DISCUSSIONS IN

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PET



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LEARNING OBJECTIVES

Upon completion of this activity,
participants should be able to:

- Discuss the use of FDG-PET in imaging bone metastases.
- Describe the mechanisms of uptake of radiopharmaceuticals used in PET imaging of bone metastases.
- Discuss the use of fluorine-18 PET in imaging bone metastases.
- Explain the limitations of PET techniques in imaging skeletal metastases.

Dr. Cook is head of the department of nuclear medicine and PET at the Royal Marsden Hospital in London, U.K.

Dr. Cook receives grants/research support from Philips Medical Systems and is a consultant to Alliance Medical Ltd.

PET in the Management of Bone Metastases

By Gary J.R. Cook, M.D.

The skeleton 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.¹ 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.²

Skeletal metastases are predominantly lytic in nature in most cancers, but in some patients, such as those with prostate cancer, skeletal disease tends to be predominantly sclerotic. Lytic metastases are generally associated with an increase in morbidity and reduction in survival compared with

sclerotic disease.

Skeletal metastases are associated with significant morbidity, including pain, hypercalcemia, pathological fracture, and spinal cord compression, as well as bone marrow suppression. Due to the relatively long survival in some patients with skeletal metastases, the management of this problem and its complications represents a major demand on healthcare resources. Accurate noninvasive staging and follow-up of treatment effects of the skeleton by imaging is therefore an important part of clinical oncological management.

PET imaging of the skeleton is possible with two different radiopharmaceuticals: F-18 fluoride ion as a skeletal tracer and F-18 fluo-

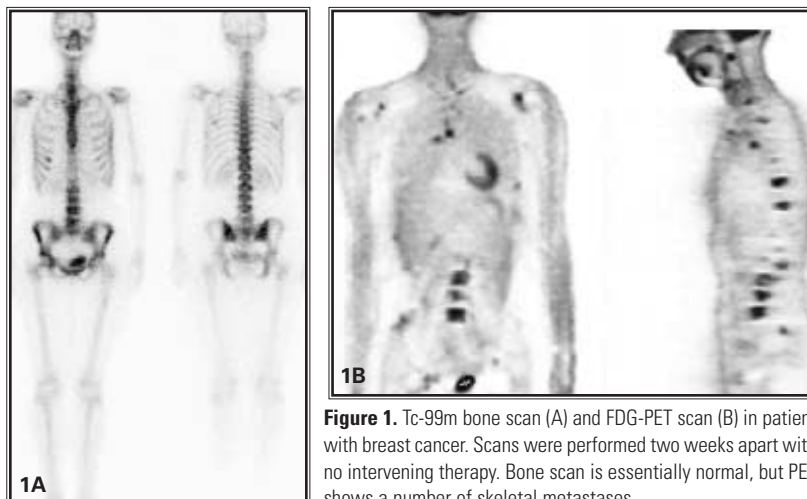


Figure 1. Tc-99m bone scan (A) and FDG-PET scan (B) in patient with breast cancer. Scans were performed two weeks apart with no intervening therapy. Bone scan is essentially normal, but PET shows a number of skeletal metastases.

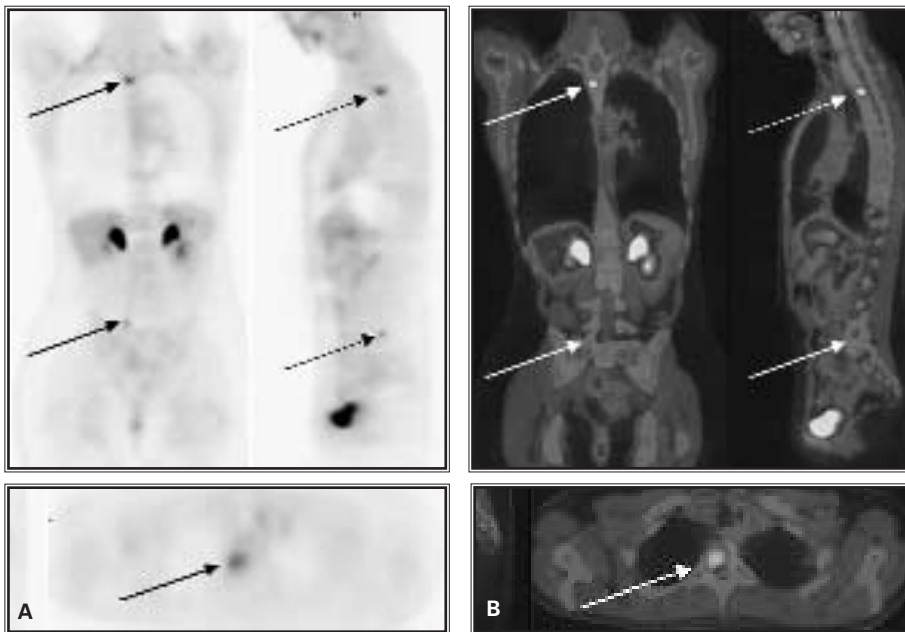


Figure 2. FDG-PET (A) and PET/CT (B) scans in patient with recurrent lymphoma. Abnormal focal uptake is seen on FDG-PET, but it is not possible to confidently localize this to the skeleton. Combined PET/CT scan allows accurate skeletal localization of the lesions, which had been unsuspected and changed management.

rodeoxyglucose as a direct tumor imaging agent. F-18 fluoride was initially described as a bone imaging agent in the early 1960s³ but was difficult to image in view of the high-energy 511-keV gamma rays and relatively unsophisticated scanning hardware of the time. It was soon superseded by the technetium-99m-labeled diphosphonates, and only with the advent of modern, high-quality dedicated PET scanners has there been a resurgence in interest in the use of F-18 fluoride as a skeletal tracer in both benign and malignant conditions.

Its mechanism of uptake is similar to other skeletal imaging agents, including the Tc-99m-labeled diphosphonates, in that it depends on local skeletal blood flow, but more important, on regional osteoblastic activity. It is preferentially deposited at sites of high bone turnover and remodeling, at bone surfaces, exchanging with hydroxyl groups in the hydroxyapatite crystal of bone to form fluoroapatite. It then remains firmly fixed with negligible release of fluoride from bone mineral.^{4,6} Because most bone metastases, even when predominantly osteolytic, are associated with an osteoblastic response, focal uptake of this tracer is seen in most bone metastases. However, in common with Tc-99m-labeled diphosphonates such as Tc-99m-labeled methylene diphosphonate (MDP), metastases that are not accompanied by an osteoblastic reaction may show absent

uptake.⁷ An advantage of F-18 fluoride PET is that good skeletal-to-background ratios can be obtained as quickly as one hour after injection, compared with the two to four hours commonly required with Tc-99m-labeled MDP and other similar diphosphonate compounds.⁸

As F-18 fluoride PET images are of higher spatial resolution than conventional bone scintigraphy and because tomographic images are routinely acquired throughout the skeleton rather than as an additional acquisition of a localized area, the modality offers potential advantages in sensitivity and specificity for detecting bone metastases. A study of 44 patients with prostate, lung, or thyroid cancer compared F-18 fluoride PET with conventional planar bone scintigraphy (Tc-99m-labeled MDP) using CT, MR, or iodine-131 scintigraphy as reference.⁹ F-18 fluoride PET detected all metastases and identified twice as many benign and malignant lesions as Tc-99m-labeled MDP scintigraphy, indicating a higher sensitivity for focal skeletal abnormalities. The higher spatial resolution and 3D information available with PET ensured a higher specificity by allowing correct classification of a larger number of lesions as either benign or malignant (97% compared with 80.5%).

The advantages of F-18 fluoride PET were particularly evident in assessing the vertebral column. Improved accuracy of

skeletal assessment, compared with planar bone scintigraphy, has also been reported in lung cancer^{8,10} and breast cancer.¹¹ It is likely that much of the advantage of F-18 fluoride PET is due to the extra contrast and 3D localization available with tomographic imaging rather than as a result of any differences in uptake mechanisms or excretion between the two types of tracer. No statistically significant difference between F-18 fluoride PET and Tc-99m MDP-SPECT has been reported in a series of patients with lung cancer.⁸ Although the use of F-18 fluoride PET may lead to greater diagnostic accuracy and changes in patient management,^{8,10,11} it is unclear whether the advantages are cost-effective when compared with conventional planar bone scintigraphy augmented with SPECT.¹⁰

F-18 FDG-PET

In contrast to F-18 fluoride, 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 skeletal metastases and has 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



Figure 3. Diffuse increase in uptake of FDG seen in bone marrow two weeks after patient completed chemotherapy is in keeping with reactive changes rather than active lymphoma.

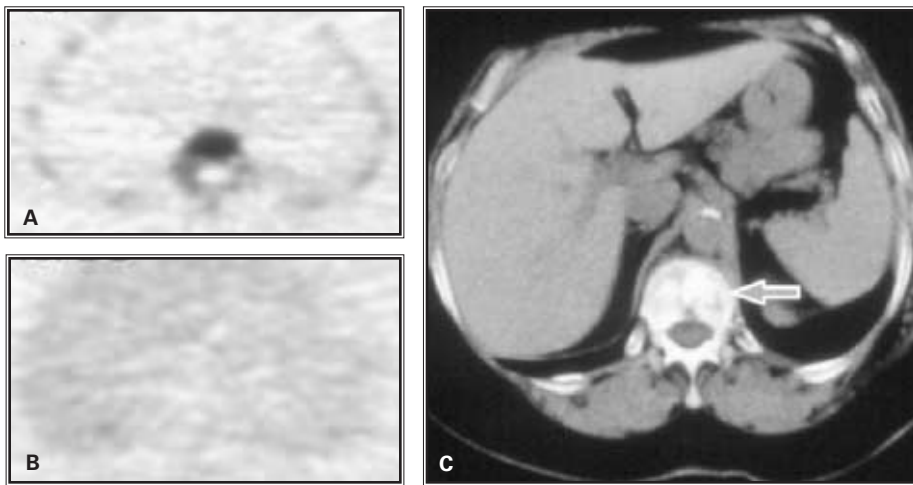


Figure 4. Transaxial F-18 fluoride (A), FDG (B), and CT (C) scans demonstrate focally increased bone turnover in sclerotic metastasis (arrow) but with no abnormal FDG activity.

useful in the assessment of skeletal metastases in a number of different cancers. It is evident that FDG-PET can be more sensitive in detection of 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 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 these tumors compared with bone scintigraphy.^{12,13} 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,¹⁴ Ewing's sarcoma,¹⁵ and lymphoma.¹⁶ In these situations it is possible that the apparent superiority in sensitivity derives from the ability to 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.¹⁶ 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.¹⁷ Increased uptake compared with baseline may persist for four weeks after administration of G-CSF, although it may be possible to obtain diagnostic 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 sen-

sitive than conventional bone scintigraphy and in patients who have predominantly osteoblastic disease.¹⁴ 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.¹⁸ 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.^{12,19-21} 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 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 confirmed 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

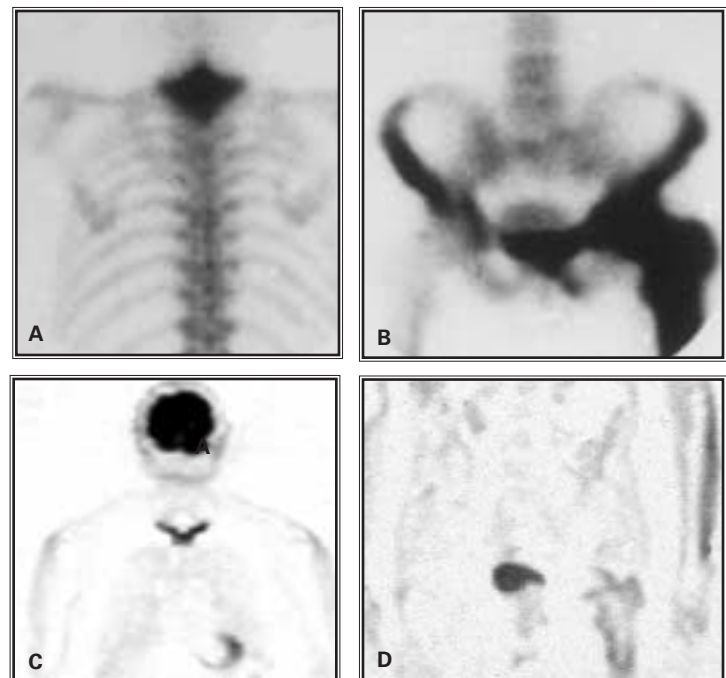


Figure 5. A and B: Tc-99m MDP bone scan demonstrates Paget's disease in left femur and upper thoracic spine. C and D: Avid activity is also seen on FDG-PET scan.

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 is probably not required in most cancers when routine FDG-PET is performed. As combined PET/CT scanners become more commonly available, correct anatomic localization of FDG-avid lesions will likely become much easier in both the skeleton and soft tissues (Figure 2).

Monitoring treatment response in skeletal metastases is notoriously difficult. Radiographs are slow to demonstrate changes, and bone scans can be hampered by the flare phenomenon. Early evidence suggests that serial FDG-PET scans may be a more sensitive and accurate method than conventional modalities in evaluating treatment response, correlating well with clinical response and changes in tumor markers.²² This area requires further research but represents one of the most valuable contributions that PET imaging could potentially make to managing patients with skeletal metastases.

PITFALLS

In common with conventional skeletal scintigraphy, F-18 fluoride PET has the potential for false-positive uptake in coincidental benign skeletal lesions. But this problem is somewhat mitigated by the ability to more confidently differentiate benign from malignant lesions with the tomographic images this imaging technique provides.

With FDG, 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.^{23,24} 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 fluoride 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 fluoride 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 if an FDG-18 PET scan is performed for routine staging, conventional bone scintigraphy is probably not required. A bone scan may be helpful if there is doubt as to whether a lesion is within or adjacent to the skeleton but may not be necessary if combined PET/CT is performed. In osteoblastic predominant disease, conventional bone scintigraphy remains the method of choice for assessing the skeleton.

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