

Bone: From planar imaging to SPECT & PET/CT

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SUMMARY

Since its introduction into clinical medicine 50 years ago, the radionuclide bone scan has played a key role in diagnosing a variety of osseous disorders; particularly metastatic disease. Using small diagnostic doses of Strontium-85 in the 1960's, it was rapidly established that the study was much more sensitive than skeletal radiographs. The introduction of Technetium-99m phosphate agents in the early 1970's, offered greatly improved resolution. Whole body imaging became the standard procedure. Interestingly, the positron-emitter, Fluorine 18-sodium fluoride was used by some investigators with the rectilinear scanner. Very recently, this radiotracer has been re-introduced and is witnessing considerable growth using modern PET/CT instrumentation. The cortical bone tracers, ^{99m}Tc-MDP and ¹⁸F-Fluoride assess osteoblastic response to the invading lesion. In the study of metastatic disease, it is superb for sclerotic blastic lesions. Although it detects most lytic lesions, many can be missed. This is due to a lack of osteoblastic response. The tumor may be slow growing, such as myeloma or conversely very rapidly growing and destructive, such as lung or kidney metastases. In these lesions, ¹⁸F-FDG is superior because it is concentrating in the tumor cells and does not depend on osteoblastic response to the tumor. In their early cause, many lytic lesions may be confined to the medullary portion of bone and not yet involve the cortex. Comparative studies of PET and CT have clearly shown the superior sensitivity of FDG in detecting metastatic bone lesions.

Key words: Bone Neoplasms; Neoplasm Metastasis; Diagnostic Imaging; Positron-Emission Tomography and Computed Tomography; Tomography, Emission-Computed, Single-Photon; Fluorodeoxyglucose F18

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INTRODUCTION

Radionuclide bone imaging is useful for detection of bone metastases from malignant neoplasms of many different origins. Breast carcinoma and prostate carcinoma are the most prevalent primary tumors that metastasize to bone at some point during their clinical course. On the contrary, other malignant neoplasms, lung, bladder, kidney, stomach, gastrointestinal, uterus and thyroid carcinomas, develop bone metastases more rarely. The incidence of bone metastases at postmortem examination in different cancers is shown in Table 1 (1).

Table 1. The incidence of bone metastases at postmortem examination in different cancers

Primary malignant tumor	Incidence of bone metastases (%)
Breast	73
Prostate	68
Thyroid gland	42
Kidney	35
Lung	36
Gastrointestinal tract	5

The bone seeking agents Strontium-85 (⁸⁵Sr), Strontium-87m (^{87m}Sr) and Fluorine-18 (¹⁸F) Fluoride were used for bone scanning during the 1960's and 1970's. The long-living gamma-emitting radionuclide, ⁸⁵Sr was first described in 1961 by Flemming (2) and was the most commonly used bone imaging tracer until 1970's. ^{87m}Sr with a 2.8-hour-half-life (3) and the positron emitter, ¹⁸F with the 1.87-hour-half-life were used for a brief period during the 1960's (4, 5). A revolution

in bone scanning occurred in the early 1970's with the introduction of technetium 99m (^{99m}Tc) – polyphosphate and pyrophosphates (6). A short time later, other phosphate compounds such as methylene diphosphonate (MDP), hydroxyethylidene diphosphonate (HEDP), and hydroxymethylene diphosphonate (HMDP) labeled with ^{99m}Tc were developed and used for detection of bone metastases (7, 8). Others radionuclide agents, ²⁰¹Tl (9), ^{99m}Tc-MIBI (10), and ^{99m}Tc(V) DMSA (11), have been evaluated and used to image bone tumors. At the present time, ^{99m}Tc-MDP is the most widely used agent to image bone metastases (6).

BONE SEEKING AGENTS AND MECHANISMS OF UPTAKE

Bone metastases begin as medullary lesions. As the lesion enlarges, the surrounding cortical bone undergoes both osteoclastic and osteoblastic changes. Bone can be destroyed directly by the tumor cells or indirectly by specific mediators which stimulate reabsorption by osteoclasts (12). Depending on the proportion of these clastic and blastic changes, the radiographic appearance will be lytic, blastic or mixed. On one hand, lytic lesions may be associated with a very rapidly growing metastasis so that an osteoblastic repair component is unable to keep pace, such as seen with metastases from lung or kidney carcinoma. Lesions with lytic appearance, however, may also be slowly growing so that an osteoblastic response is only minimally stimulated which is seen in metastases derived from myeloma or thyroid carcinoma. Alternately, tumors like myeloma may release a substance that inhibits the osteoblastic response. On the other hand, sclerotic lesions are seen in bone metastatic tumors with slower, but steady growth (e.g. prostate). Sclerotic lesions may actually be a sign of healing of a lytic process (13).

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IMAGING OF BONE METASTASES

Bone scintigraphy

Either direct visualization of tumor cells or secondary bone reaction to the malignant cells, establishes a basis for detection of malignant bone lesions. The mechanism of visualizing bone metastases is dependent on detection of the reactive (osteoblastic) response to invading tumor. In most of the cases, osteoblasts are stimulated in response to tumor and the new bone mineral formed accumulates the radiotracer ^{99m}Tc -labeled phosphates/phosphonates; consequently producing "hot" spots on a bone scan. In a few cases, tumor may produce a predominantly lytic reaction producing a photopenic area. Radiopharmaceuticals, such as ^{99m}Tc -MDP detect the osteoblastic response to invading tumor (14). Uptake of diphosphonates depends on local blood flow, osteoblastic activity and extraction efficiency. Most likely, the diphosphonates are incorporated into the hydroxyapatite crystal on the bone surface (6).

There are two techniques for bone scintigraphy: either a whole-body scan versus multiple static scans of the entire body. In both cases, if there are some suspicious areas, additional spot views should be done. Regardless of the specific technique, radionuclide bone imaging is able to detect metastases much earlier than conventional plain film radiography (14). During the last decade, single photon emission tomography (SPECT) improved on planar imaging and is being used more and more (15). SPECT is more sensitive than planar scintigraphy; SPECT imaging identifies disease seen on CT but missed on planar scintigraphy in one-third of patients (16). This technique has an important role in patients with chronic low back pain (17), facet syndrome (18), sacroiliitis (19), avascular necrosis (20-23), diagnosis of meniscal tears (24-26), etc. SPECT is useful in the assessment of metastatic disease because of its precise localization of vertebral involvement as well as greater sensitivity for the detection of vertebral metastases. Based on these features, it is able to improve the differentiation between malignant and benign lesions (27, 28) (Figure 1 and Figure 2).

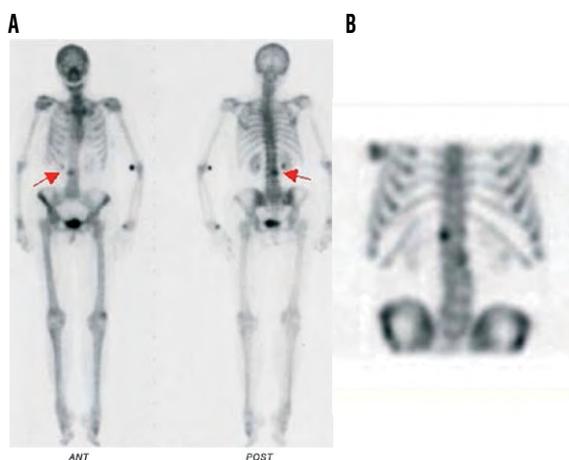


Figure 1. ^{99m}Tc -methylene diphosphonate [MDP] scintigraphy. **A.** Whole body bone scintigraphy, anterior and posterior projections obtained simultaneously on a dual detector system approximately 2 hours after 0.9 GBq of ^{99m}Tc -MDP. Arrows identify a focus in the right side of one of the lumbar vertebrae. It is difficult to be certain about the precise vertebra involved or the location. **B.** Maximal Intensity Projection representing the anterior projection of a volume display assembled from multiple transaxial slices obtained using SPECT. Previously seen focus is identified as spanning the T12-L1 intervertebral space; likely a degenerative process with new bone formation. A 2nd less intense focus is seen in the interspace below on the left.

Positron emission tomography

In recent years, with the availability of positron emission imaging (PET) imaging, the use of ^{18}F as the fluoride ion has increased. In general, PET imaging has better spatial resolution. The mechanism of ^{18}F - Fluoride is similar to that of ^{99m}Tc -MDP and depends on regional blood flow and osteoblastic activity. It is selectively accumulated at sites of high bone turnover and remodeling by chemisorption onto bone surfaces, exchanging with hydroxyl (OH-) groups in hydroxyapatite crystal of bone resulting in forming of the fluoroapatite (29). In general, ^{18}F - Fluoride will be the best for blastic lesions. ^{18}F -Fluoride PET takes advantage of the better pharmacokinetic characteristics of ^{18}F -Fluoride, and the better imaging characteristics of PET technology. Increased ^{18}F -Fluoride uptake may be detected in both sclerotic and lytic metastases. The minimal osteoblastic activity accompanying a lytic lesion, which may not be identified on ^{99m}Tc -MDP bone scan may be readily identified with ^{18}F -Fluoride PET imaging. PET imaging with ^{18}F -fluoro-2-deoxyglucose (^{18}F -FDG) has also been evaluated as a tracer to identify bone metastases. ^{18}F -FDG is directly incorporated into the tumor cells and consequently detects cortical and marrow involvement. This suggests that this radiopharmaceutical will be best for lytic lesions. The fact that ^{18}F -FDG PET has low uptake in normal red marrow, allows for early detection of malignant bone marrow involvement preceding detection of bone metastases by bone scan using bone-specific radiotracers and computed tomography (CT). ^{18}F -FDG PET can detect all three types of skeletal metastases including lytic, blastic and mixed, but preferably ^{18}F -FDG PET is more sensitive for detection of lytic rather than blastic lesions which are often the result of less aggressive lesions (30-32). Cook et al. reported slightly decreased sensitivity for ^{18}F -FDG PET imaging of predominantly osteoblastic lesions but it has higher overall sensitivity due to more frequent occurrence of osteolytic bone metastases (33).

The added values of FDG PET/CT are: better resolution provides localizing bone versus tissue lesions, differentiating benign from malignant sites of bone tracer uptake, providing additional help in identifying sites for biopsy, and enhancing radiotherapy treatment planning (34). If compared to ^{99m}Tc -MDP and ^{18}F -Fluoride, ^{18}F -FDG PET is more sensitive for detection of bone metastases secondary to lung cancer. In breast cancer bone metastases, ^{18}F -FDG appears to be more sensitive for lytic lesions, but less sensitive for sclerotic ones. Conversely, ^{18}F -FDG PET is less sensitive in detection of bone metastases from prostate cancer. Thus, post-treatment studies which often result in sclerotic lesions are negative with ^{18}F -FDG imaging because they have healed and no longer have viable tumor (6) (Figure 3).

CONCLUSION

Cortical bone tracers, ^{99m}Tc -MDP and fluoride (^{18}F) (FNa) PET/CT, have a role in detection of sclerotic blastic lesions of metastatic disease. PET scan has better sensitivity over CT in detecting metastatic bone lesions. Fluorodeoxyglucose (^{18}F) (FDG) PET/CT is more sensitive in detection of lytic lesions, while ^{18}F -fluoride is good for both, sclerotic and lytic metastases. Most recently, a new radioisotope, fluorocholine(^{18}F) (FCH) PET/CT, seems to be promising in detection of bone metastases in patients with prostate cancer. At present, fluorocholine is officially registered for the detection of bone metastases only, but most likely it will find a role in detection of local/locoregional node recurrence in near future.

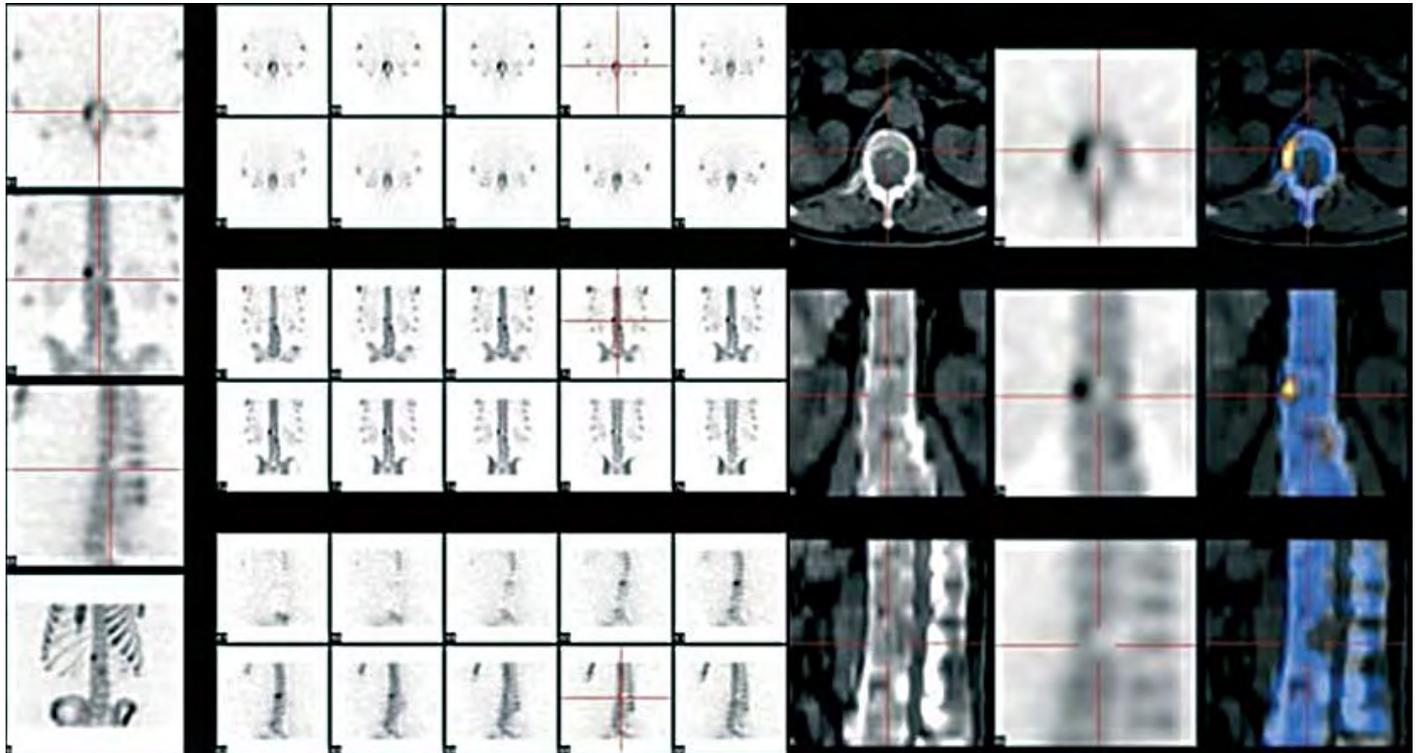


Figure 2: SPECT and SPECT/CT images from same patient as in Figure 1. Left panel, top frame: transaxial slice selected from multiple slices in central panel; 2nd from top frame: coronal slice; 3rd frame: sagittal slice. Note cross hairs is lightly off target and lesion is not seen in selected frame; bottom [4th] image is maximal intensity projection, partially rotated, representing all slices stacked and displayed as a volume. Right panel, CT, SPECT, CT+SPECT fusion image, top to bottom: transaxial, coronal, sagittal. Images demonstrate the advantages of SPECT in terms of better resolution (better definition of individual vertebrae and more clearly defined "lesions" as well as identifying location within the vertebral body itself rather than posterior elements. This location is more likely to represent a benign process such as osseous proliferative reaction secondary to degenerative changes as opposed to metastases. The addition of the CT image (even though less than diagnostic quality) further improves the anatomic localization. [Images courtesy of Stanley J. Goldsmith, MD; New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, USA]

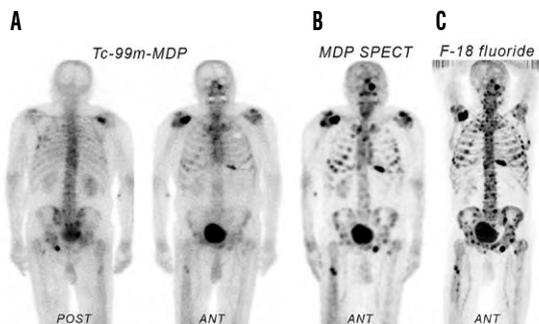


Figure 3. A) Tc-99m-MDP; B) MIP image from SPECT acquisition; and C) F-18 fluoride PET IMAGE. SPECT, even when viewed as an anterior projection, represents an improvement over routine planar imaging. PET provides even better resolution and identifies more lesions. Another demonstration of superior resolution possible with PET tracers and instrumentation. [Source: Enat Evan-Sapi, MD, Icholot Medical Center, Israel]

Conflict of interest

We declare no conflicts of interest.

REFERENCES

- Coleman E. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res*. 2006;12(20 Suppl):6243s-6249s.
- Flemming WH, McClraith JD, King ER. Photoscanning of bone lesions utilizing strontium-87. *Radiology*. 1961;77:635-6.
- Charkes ND, Sklaroff DM, Bierly J. Detection of metastatic cancer to bone by scintiscanning with strontium-87m. *AJR*. 1964;91:1121-7.
- Blau M, Nagler W, Bender MA. Fluorine-18: a new isotope for bone scanning. *J Nucl Med*. 1962;3:332-4.
- Dworkin HJ, Moon NF, Lessard RJ, et al. A study of the metabolism of fluorine-18 in dogs and its suitability for bone scanning. *J Nucl Med*. 1966;7:510-20.
- Gnanasegaran G, Cook G, Fogelman I. Musculoskeletal system. In: Biersac HJ, Freeman LM, eds. *Clinical Nuclear Medicine*. Berlin: Springer-Verlag; 2007. p. 241-62.
- Subramanian G, McAfee JG. A new complex of Tc-99m for skeletal imaging. *Radiology*. 1971;99:192-6.
- Subramanian G, McAfee JG, Bell EG, et al. 99m Tc-labeled polyphosphonate as a skeletal imaging agent. *Radiology*. 1972;102:701-4.
- Elgazzar AH, Malki AA, Abdel-Dayem HM, et al. Role of thallium-201 in the diagnosis of solitary bone lesions. *Nucl Med Commun*. 1989;10:477-85.
- Caner B, Kitapci M, Unlu M, et al. Technetium-99m-MIBI uptake in benign and malignant bone lesions: a comparative study with technetium-99m-MDP. *J Nucl Med*. 1992;33:319-24.
- Lam AS, Kettle AG, O'Doherty MJ, et al. Pentavalent 99Tcm-DMSA imaging in patients with bone metastases. *Nucl Med Commun*. 1997;18:907-14.
- Roodman GD. Mechanism of bone metastasis. *N Engl J Med*. 2004;350:1655-64.
- Padhani A, Husband J. Bone metastases. In: Husband JES, Reznick RH (eds): *Imaging in oncology*. Oxford: Isis medical Media Ltd; 1998. p.765-87.

- 14 Partha S, Freeman LM. Scintigraphy of bone metastases. In: Goldsmith S, eds. p. 525-44.
- 15 Even-Sapir E, Martin RH, Barnes DC, et al. Role of SPECT in differentiating malignant from benign lesions in the lower thoracic and lumbar spine. *Radiology*. 1993;187:193-8.
- 16 Ryan PJ, Evans PA, Gibson T, et al. Chronic low back pain: comparison of bone SPECT with radiography and CT. *Radiology*. 1992;13:497-854.
- 17 Dolan AL, Ryan PJ, Arden NK, et al. The value of SPECT scans in identifying back pain likely to benefit from facet joint injection. *Br J Rheumatol*. 1996;35:1269-73.
- 18 Holder LE, Machin JL, Asdourian PI, et al. Planar and high resolution SPECT bone imaging in the diagnosis of facet syndrome. *J Nucl Med*. 1995;36:37-44.
- 19 Hanly JG, Mitchell MJ, Barnes DC, et al. Early recognition of sacroiliitis by MRI and SPECT. *J Rheumatol*. 1994;21:2088-95.
- 20 Siddiqui AR, Kopecky KK, Wellman HN, et al. Prospective study of MRI and SPECT bone scans in renal allograft recipients: evidence for self-limited subclinical abnormality of the hips. *J Nucl Med*. 1993;34:381-6.
- 21 Stulberg BN, Levine M, Bauer TW, et al. Multimodality approach to osteonecrosis of the femoral head. *Clin Orthop Rel Res*. 1989;240:181-93.
- 22 Collier BD, Carerra GF, Johnson RP, et al. Detection of femoral head avascular necrosis in adults by SPECT. *J Nucl Med*. 1985;26:979-87.
- 23 Kim KY, Lee SH, Moon DH, Nah HY. The diagnostic value of triple head SPECT in avascular necrosis of the femoral head. *Int Orthop*. 1993;17:132-8.
- 24 Murray IPC, Dixon J, Kohan I. SPECT for acute knee pain. *Clin Nucl Med*. 1990;15:828-40.
- 25 Cook GJR, Fogelman I. Lateral collateral ligament tear of the knee: appearances on bone scintigraphy with SPECT. *Eur J Nucl Med*. 1996;23:720-2.
- 26 Ryan PJ, Taylor M, Grevitt M, et al. Bone single-photon emission tomography in recent meniscal tears; an assessment of diagnostic criteria. *Eur J Nucl Med*. 1993;20:703-7.
- 27 Bushnell DL, Kahn D, Huston B, et al. Utility of SPECT imaging for determination of vertebral metastases in patients with known primary tumors. *Skeletal Radiol*. 1995;24:13-6.
- 28 Han LJ, Au-Yong TK, Tong WC, et al. Comparison of bone SPECT and planar imaging in the detection of vertebral metastases in patients with back pain. *Eur J Nucl Med*. 1998;25:635-8.
- 29 Blau M, Ganatra R, Benmder MA. 18F-fluoride for bone imaging. *Semin Nucl Med*. 1972;2:31-7.
- 30 Blake GM, Park-Holohan SJ, Cook GJ, et al. Quantitative studies of bone with the use of 18F-fluoride and 99mTc-methylene diphosphonate. *Semin Nucl Med*. 2001;31:28-49.
- 31 Cook GJ, Fogelman I. The role of positron emission tomography in skeletal disease. *Semin Nucl Med*. 2001;31:50-61.
- 32 Even-Sapir E. Imaging of malignant bone involvement by morphologic, scintigraphic, and hybrid modalities. *J Nucl Med*. 2005;46:1356-67.
- 33 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.
- 34 Even-Sapir E, Flusser G, Blachar A. Malignancy of the bone: Primary tumors, lymphoma, and skeletal metastases. In: Delbeke D, Israel O, eds Hybrid PET/CT and SPECT/CT imaging. A teaching file. Springer: New York; 2010. p. 583-619.