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, ⁹⁹mTc-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

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

<table>
<thead>
<tr>
<th>Primary malignant tumor</th>
<th>Incidence of bone metastases (%)</th>
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<tbody>
<tr>
<td>Breast</td>
<td>73</td>
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<tr>
<td>Prostate</td>
<td>68</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>42</td>
</tr>
<tr>
<td>Kidney</td>
<td>35</td>
</tr>
<tr>
<td>Lung</td>
<td>36</td>
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<tr>
<td>Gastrointestinal tract</td>
<td>5</td>
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</tbody>
</table>

The bone seeking agents Strontium-85 (⁴⁰Sr), Strontium-87m (⁴⁰Sr) and Fluorine-18 (¹⁸F) Fluoride were used for bone scanning during the 1960’s and 1970’s. The long-living gamma-emitting radionuclide, ⁴⁰Sr was first described in 1961 by Flemming (2) and was the most commonly used bone imaging tracer until 1970’s. ⁴⁰Sr 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 (⁹⁹mTc) – polyphosphate and pyrophosphates (6). A short time later, other phosphate compounds such as methylene diphosphonate (MDP), hydroxyethylidene diphosphonate (HEDP), and hydroxymethylene dipiphosphonate (HMDP) labeled with ⁹⁹mTc were developed and used for detection of bone metastases (7, 8). Others radionuclide agents, ⁹⁹mTc (9), ⁹⁹mTc-MIBI (10), and ⁹⁹mTc(V) DMSA (11), have been evaluated and used to image bone tumors. At the present time, ⁹⁹mTc-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. 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. Alternatively, 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).
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 hydroxapatite 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.

CONCLUSION

Cortical bone tracers, 99m-Tc-MDP and fluoride (18f) (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 (18F) (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 radiotracer, fluorocholine (18F) (FC) 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.
Conflict of interest
We declare no conflicts of interest.

REFERENCES

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