

Bone scintigraphy in the evaluation of cancer

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Abstract

Bone scintigraphy being a highly sensitive modality is useful in the detection of skeletal metastases in cancer patients. The procedure does not pose any radiation risks to the patients. To improve the specificity of the modality, proper patient selection is important. This article explores the application of bone scintigraphy in detection of metastatic cancer with an insight about patient selection.

Keywords: Bone Scan, Metastases, Tc99m-MDP, Malignancy

Radionuclide skeletal imaging (popularly called bone scanning or scintigraphy) has contributed significantly to the practice of oncology over the past many decades. The so-called Nuclear Oncology uses radioactive isotopes to detect metastatic disease in cancer patients. This article aims to provide a bird's eye view of role of bone scanning in cancer.

Following the introduction by Subramanian and McAfee in 1971 of phosphate compounds labelled with technetium-99m, methylene diphosphonate (MDP) labelled with this isotope has become well-established for the imaging of bone for metastatic disease [1].

Basic Principles of Nuclear Medicine

During radiological examination like- X-ray or CT, the radiation originating from the x-ray or CT machine passes through the patient's body before being detected and recorded onto a film or by a computer (Transmission Imaging). Whereas, nuclear medicine imaging uses isotopes (called radionuclides, radiopharmaceuticals or radiotracers) that emit photons (gamma rays) which are generated, when to achieve stability the nucleus of an isotope changes from higher energy level to a lower one (called radioactive decay). These gamma rays are similar to x-rays but have a shorter wavelength and can be detected by a special machine called a 'Gamma Camera'. Since in nuclear medicine, the radioactive material is introduced into the patient, and its gamma radiation is then detected by an external detector, it is called as Emission Imaging.

The radionuclide substances used are usually synthetic, like technetium, or radioiodine. The most

commonly used isotope is technetium 99m (99m-Tc). A pharmaceutical which tends to localise in bone is tagged with gamma ray emitting 99m-Tc and injected into the patient. After allowing an appropriate time period for its biological distribution, the pharmaceutical will maximally localise into skeletal system. When 99m-Tc tagged to it decays to 99-Tc, gamma rays are emitted with a characteristic 140-keV energy. Gamma camera is a large scintillation detector which detects gamma rays being emitted from the patient, more specifically from the organ in which the radiopharmaceutical localises.

Scintillation detector converts gamma rays into pulses of light. These are then picked up by photo multiplier tubes and converted to an electric signal which is processed (digitized) by a dedicated computer and reconstructed into an image. These digitized (computerized) images are amenable to manipulation (can be processed). They can be displayed as a map of distribution of radioactivity within the organ/body on a computer monitor. They can be presented in gray scale (shades of black and white) whereby, the regions with relatively more radioactivity are seen brighter than others. It can be transferred to a photographic film, sent over a network to another location, or saved on a disk.

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Rationale behind Bone Scintigraphy

Metastatic disease is a significant cause of morbidity and mortality in cancer patients. For instance, bone metastases affect 8 % of all patients having breast cancer and nearly 70 % in advanced disease. Median survival even when the disease is confined to skeleton is 24 months with only 20 % remaining alive at 5 years [2].

Bone scintigraphy can be an important step in diagnosing the spread and assessing the response to treatment of various kinds of cancer. Tc99m labelled bone seeking agents tend to localise in skeleton are used detect the spread of cancer beyond its primary site to secondary cancer growth (metastasis) in the skeleton. Diphosphonates, the organic analogs of polyphosphate, are bone seeking pharmaceuticals which have P-C-P bonds. It is hypothesised that Methylene Diphosphonate (MDP), has affinity for calcium rich hydroxyapatite crystals of bone. The technetium (Tc) 99m-MDP undergoes 'chemisorption' and gets bound to bone matrix [3]. The hydroxyapatite crystal is most accessible to MDP in exposed bone, such as areas of increased osteogenesis or bone remodelling (i.e. altered metabolism). Old compact bone does not bind MDP as efficiently. In general, any process that results in focally increased osteogenic activity is visualised as an area of increased radioactivity (called a 'hot spot'). Other determinants which lead

to increased uptake are: a) Increased blood flow, b) Increased capillary permeability, and c) Loss of sympathetic tone resulting in capillary dilation [4]. Thus, Scintigraphic images provide a map of the (differential) distribution of osteogenic activity in the skeleton based on differences between normal and diseased osseous tissue. However, replacement of bone by destructive lesion - primary or metastatic (so-called lytic type of metastasis) result in an area of reduced radioactivity (called a 'cold spot' or photopenic bone lesion). Disruption of normal blood flow consequent to radiation can also cause decreased uptake [5].

Any bone pathology, which induces osseous metabolic changes, subsequently leads to delayed osseous morphological changes. Technetium99m-MDP can readily detect these early metabolic changes (Functional imaging). Whereas, radiological procedures can only detect morphological changes, however, they occur very late. Thus, bone scan can detect osseous changes caused by metastatic disease much earlier than radiological procedures.

Figure 1 demonstrates distribution of the radiotracer in the skeletal system in the anterior and posterior projections. There are multiple metastases indicated by white spots especially in multiple vertebrae and head of right femur etc.

Fig. 1

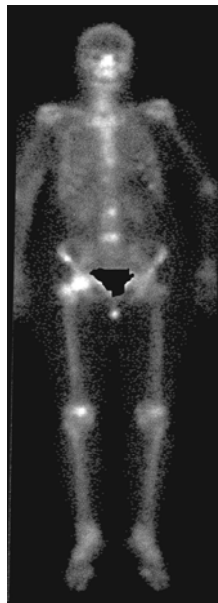


Fig. 2



Image Interpretation

Usually whole body images are acquired as cancer can spread to any bony part, including the pelvis, spine, ribs, skull and extremities. Ideally there should be a uniform and symmetrical distribution of tracer in the skeletal system. Since the skeletal system is symmetrical along longitudinal axis, images of the two halves of the body serve as internal control for comparison and any differential uptake on two sides is easily picked up. Increased bone turnover (remodelling) is normal at the epiphyses in young patients and should not be mistaken for a lesion. Activity seen with degenerative joint disease is variable, depending on the degree of active bone remodelling at that time. Tracer also shows uptake by kidneys and is filtered by glomeruli, therefore, appear in urine and thus accumulate in urinary bladder. Female breasts can be visualized, but accumulation is physiologically symmetrical. These bone scan patterns are generally learned very quickly and become less puzzling as interpreters get familiarised with the technology.

If a lesion is suspected but unclear the resolution can be improved by reducing camera to region distance and to some degree by increasing the duration of per view imaging. To improve overall accuracy multiple views can be used. For instance, to determine position of a focal area of increased uptake in a region, it is important to have lateral or oblique views. A minimum of 2 views should be taken when possible.

Indications

1. Primary or metastatic tumour- Screen for bone metastases in patients with known or suspected cancer.

a) Primary bone tumours e.g. Osteosarcoma, Ewing's sarcoma etc.

For limb salvage surgeries in bone tumour staging is essential to detect metastases and know the extent of tumour [6].

b) To rule out metastatic bone disease following primary carcinoma (ca) e.g. ca breast, ca lung, ca prostate etc.

Nuclear medicine contributes to: diagnosis, staging, location of biopsy site (confirmation, histological grading), planning of radiation portals, evaluate response to therapy (no new lesions appearing and intensity of tracer uptake in previous lesions decreasing on serial imaging).

2. Evaluation of patient with pathological fracture(s) or nonspecific, abnormal roentgenographic appearance of bone which is indicative of metastatic disease.

3. Body pain or Evaluation of nonspecific bone pain.

Radiopharmaceutical

Usually 500 to 800 MBq (15-20 mCi) of Tc-99m Methylene Diphosphonate (MDP) is injected I.V. according to weight. 50% goes to bone in adults and normally 50% of injected dose excreted by kidneys.

Study duration

Imaging is performed at least 2.5 to 3 hours later. The patients should be informed about the waiting period between injection and imaging.

Imaging methods

a) **Planar scintigraphy** - Whole body imaging takes about 30-45 minutes.

b) **Spot views** (oblique or lateral) and/or **SPECT** - a tomographic technique can be used to improve lesion detection/characterisation. The latter is especially useful in joints, spine and pelvis. No any additional tracer injection is required. The patient can be imaged in same imaging session [7,8].

Patient Preparation

1. Should undergo no other Tc-99m imaging study for at least 48 hours prior to bone scanning.

2. There is no risk of allergic reactions and interference from any medication.

3. Fasting is not needed. Patients should be well hydrated. If not contraindicated, the patient should be encouraged to drink 5-6 glasses of water.

4. The radiopharmaceutical is excreted in the urine, hence to minimize radiation exposure to bladder the patient should pass urine frequently to eliminate tracer containing urine from the bladder. The patient should also avoid contact of urine with skin and clothing. The patient should void again just prior to imaging to reduce background interference that may result from accumulation of the tracer in the bladder. If on Foley catheter drainage, urobag should be emptied frequently.

5. Before imaging, the patient should remove any jewelry or personal items like coins, keys etc. that may interfere with the imaging procedure because the gamma rays are attenuated (weakened) by metallic objects.

6. Pregnancy & Lactation: Patients who are pregnant or suspect pregnancy or who are breast feeding baby should inform the physician before undergoing bone scan.

Pregnancy: Technetium-99m (as free pertechnetate) crosses placenta; posing risk to foetus from radiation exposure. Also urinary bladder is near uterus and it contains tracer rich urine, can cause exposure to foetus.

Breast-feeding: May be excreted in breast milk; temporary discontinuation of nursing may be recommended because of risk to infant from radiation exposure.

Radiation Considerations

The levels of radiation involved in most nuclear medicine studies are usually considerably lower than conventional x-ray study or CT scan. If Tc99m is used, the emission is mainly a 140 keV gamma ray. The physical half-life is 6 hours (means after every six hours the level of radioactivity will become half of its previous level). Much of the radiation is eliminated through urine. The result is that the radioactivity inside the patient is only for a short time. There is little absorbed dose to harm the patient, i.e. radiation dose is approximately 0.5 rad to bone and 0.1 rad to whole body per 20 mCi. Critical organ is the bladder; the radiation dose varies with patient hydration and urine voiding frequency, it may be around 0.13 rad/mCi. On the contrary, if whole body survey is done using X-rays to detect metastases, considering per x-ray radiation exposure to be 0.1 rad, the person may be exposed to a radiation of 1 rad or more.

The patients once injected with the tracer can leave and can report back several hours later for the imaging, in the meantime the radionuclide distributes in their body. Further, the radiation doses involved being so low permit the attendant accompanying the patient to stay with him throughout the study.

Scan pattern

a) Focally increased radiopharmaceutical concentration- hot lesion- if seen at multiple sites, is almost specific for multiple metastases. About 90% of patients with skeletal metastases usually have multiple lesions. Nearly 80% of all metastatic lesions are in the axial skeleton and 10 % each in skull and long bones. In patients with a known malignancy, 50 to 60% of solitary lesions in central skeleton are due to metastatic disease [9].

A solitary rib lesion has about a 10% probability of representing a metastasis in a patient with a known malignancy [10].

b) Focally decreased radiopharmaceutical uptake-cold lesion may be seen in so-called lytic metastases, growth of which is very rapid and bony reaction is minimal [5]. 80% of focal cold lesions are metastatic.

c) Super-scan (disseminated malignancies) - diffusely increased uptake throughout the axial skeleton and poor visualization of the kidneys is due to increased bone to soft-tissue ratio. This pattern is caused by very intensive accumulation of tracer when there is diffuse involvement of skeleton by metastatic disease.

d) Soft tissue uptake of MDP can be observed in hypercalcemia or when osteogenic sarcoma metastasises to lung.

e) Flare Phenomenon: It is increased activity in metastatic lesion(s), which is clinically responding. It reflects a favourable response of skeletal metastases to treatment. The phenomenon is typically seen between 2 weeks to 3 months following therapy, but can rarely be seen as late as 6 months after treatment. It is due to increased blood flow consequent to inflammatory response of healing. It peaks at 3 months and resolves by 6 months. The diagnosis of "flare" requires 2 criteria: 1- Increased intensity and/or number of lesions on bone scan (Felt to be secondary to increased osteoblastic activity associated with healing) and, 2- Subsequent decrease uptake in these lesions on repeat exam in 2-3 months. Further, the patients are typically asymptomatic and plain films are not affected and may show sclerosis of the lesions later on. In general, it is prudent to wait about 3 months following completion of a new therapeutic intervention prior to repeating the bone scan. Disappearance of lesions and sclerosis of lytic lesions indicate the adequate response to treatment [11]. Flare response may indicate better prognosis [12].

False Positive Findings

a) Lesions like recent fractures and osteomyelitis can cause intense activity due to osteoblastic response in these conditions. However, correlating with clinical history and most of these lesions being solitary they can be distinguished from metastatic disease most of the times.

b) Tag Breakdown - Free pertechnetate ions tend to localize in thyroid, salivary glands, gastric mucosa.

c) If a hot spot is seen on lower limbs, one should consider urine contamination in differential diagnosis. Oblique or lateral views can help to differentiate superficial dermal activity from true bony pathology.

Pearls & Pitfalls

The advantage of nuclear imaging is that it relies on the body's metabolic function to distribute the radiopharmaceutical. Active lesions are visible whether or not radiographic or gross anatomical changes are seen.

Merick and Merick studied patients with lung cancer and found bone scintigraphy has sensitivity of 89 % and accuracy of 78 % for metastatic cancer [13].

Other group also reported that the presence of skeletal metastatic disease could be predicted with a sensitivity of 80 % and a specificity of 94 % [14].

Bone scan is 50 to 80% more sensitive than radiographs, CT and MRI in detecting skeletal metastases. This is probably because about 50% of the bone mineral content must be lost before a metastasis is evident on a radiograph. Malignant bone lesions - most are metastases, seen on bone scan up to 18 month before can be seen on X-ray [15].

Thus, scintigraphy is a very sensitive modality. However, the specificity of the bone scan in the evaluation of metastatic disease may be somewhat limited simply because resolution can be poor and focal areas of increased uptake can represent anything from abnormal bony remodelling as in degenerative disease to fracture. Radiation and chemotherapy can alter the normal pattern of distribution. Conventional radiography should follow a scintigraphic diagnosis. More sophisticated CT or MRI studies may be needed to arrive at a definitive diagnosis [15].

Further, for myeloma or very lytic aggressive lesions, however, bone scan is less sensitive. Multiple myeloma lesions are detected about 50% of the time on bone scan, as compared to 80 % detection on skeletal survey. Because of this, skeletal scintigraphy is probably not the procedure of choice for evaluating the presence of skeletal involvement in patients with multiple myeloma. However, in multiple myeloma, the bone scintigraphy is useful in detecting alterations in particular locations, i.e. sternum, ribs, scapulae, etc.-which are difficult to demonstrate by plain X-rays; moreover, the recovery of the fractures can be visualized [5].

Nonetheless, given the ease of performing a whole body survey, scintigraphy is an enormously useful tool for the initial evaluation for metastases in patients with cancer. Negative scintigraphic examination can in itself provide a clinical direction by ruling out active bony remodelling, means indicates absence of any active lesion. A negative whole body bone scan would indicate a better prognosis and assure the patient suffering from cancer.

Discretion in using Bone Scan

Bone scan should be used with proper discretion. Bone scan not useful in asymptomatic patients having Stage I and II of breast cancer [16] asymptomatic non-small cell lung cancer [17,18] if serum PSA is 10ng/ml or less in asymptomatic prostate cancer [19,20,21] except those underwent anti-androgen therapy because 35 % of them can have metastases with normal PSA [22].

Conclusion

Scintigraphy which provides a 'functional map' of bone remodelling is a very sensitive technique to detect skeletal metastases in cancer patients. However, case selection is important for optimising its usefulness in diagnosis of cancer. Cancer patients with staging higher than one and those with complaint of bone pain are ideal patients. Bone scintigraphy can also substantiate or refute the significance of radiographic findings, establish the diagnosis much earlier than conventional roentgenic modalities or MRI, help to monitor the response to therapy.

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