

Skeletal System Imaging With F-18 NaF And Tc-99m Phosphates

1. OVERVIEW

- a) Bone scintigraphy is a diagnostic study used to evaluate the distribution of active bone formation in the body.
- b) Whole-body bone scintigraphy produces planar images of the skeleton, including anterior and posterior views of the axial skeleton. Anterior and/or posterior views of the appendicular skeleton also are obtained. Additional views are obtained as needed.
- c) Limited bone scintigraphy records images of only a portion of the skeleton.
- d) Bone single-photon emission computed tomography (SPECT) produces a tomographic image of a portion of the skeleton.
- e) Multiphase bone scintigraphy usually includes blood flow images, immediate images, and delayed images. The blood flow images are a dynamic sequence of planar images of the area of greatest interest obtained as the tracer is injected.
- f) The immediate (blood pool or soft tissue phase) images include 1 or more static planar images of the areas of interest, obtained immediately after the flow portion of the study and completed within 10 min after injection of the tracer. Delayed images may be limited to the areas of interest or may include the whole body, may be planar or tomographic, and are usually acquired 2–5 h after injection. If necessary, additional delayed images may be obtained up to 24 h after tracer injection.

2. RADIOPHARMACEUTICALS UTILIZED

- a) Commercially available kits are available for the preparation of Tc 99m labeled phosphate-based skeletal imaging agents. They are all multi-dose reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Tc 99m compounds for diagnostic use by intravenous injection.
- b) Each 10 mL multi-dose vial contains the phosphate based compound, stannous chloride (serves as the reducing agent), and often an antioxidant such as ascorbic acid or gentisic acid. The pH is typically adjusted to 5.0-5.5 with sodium hydroxide and/or hydrochloric

acid prior to lyophilization. No bacteriostatic preservative is present and the vial is sealed under nitrogen.

- c) The four bone-imaging radiopharmaceuticals available in the US are listed in the chart below along with their typically prescribed doses. The two most commonly used drugs are Tc-99m MDP and Tc-99m HDP; their molecular formulas differ by one O atom (refer to diagram in section 5 below).

IMAGING PROCEDURE	RADIOPHARMACEUTICAL ADMINISTERED	INJECTED DOSE (mCi)
BONE SCAN	¹⁸ F Na fluoride	10-15
	^{99m} Tc MDP	20-30
	^{99m} Tc HDP	20-30
	^{99m} Tc PYP	20-30
MDP = methylenediphosphonate HDP = hydroxymethylenediphosphonate PYP = pyrophosphate		

- d) Tc-pyrophosphate (PYP) is no longer used for bone scintigraphy. It was the first phosphate-based bone agent (introduced in 1972), followed by Tc-99m MDP (1978) and Tc-99m HDP (several years later). Although Tc-PYP is a good bone agent, both Tc-MDP and Tc-HDP produce higher quality scans as their blood clearance is more rapid.
- e) F-18 NaF is also not commonly used for bone scanning, most likely because Medicare and other insurers reimburse the same amount regardless of whether a \$1,000.00 bone scan or a \$5,000.00 PET bone scan is performed.

3. CHARACTERISTICS OF THE RADIONUCLIDE

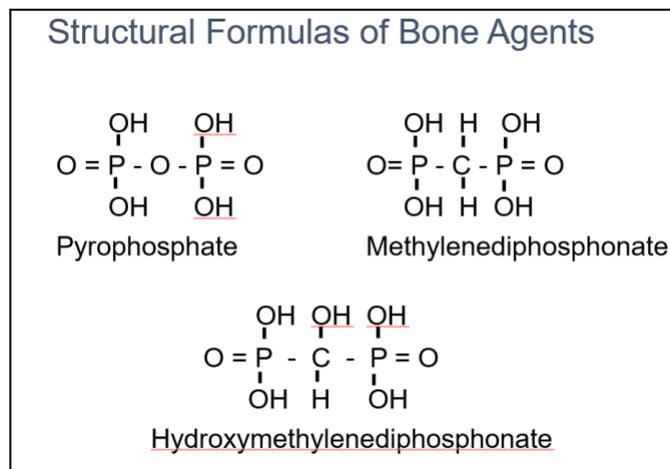
- a) Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging studies has a percent abundance of 89.07 % and the energy is 140.5 KeV.
- b) The specific gamma ray constant for Tc 99m is 0.78 R/millicurie-hr at 1 cm.
- c) The first half-value layer is 0.017 cm of lead (Pb) and the first tenth value layer is 0.08 cm of Pb.

4. DRUG AVAILABILITY

- The three phosphate based drugs listed in the chart above are readily available in the US in the form of unit doses calibrated for a particular patient as well as a “cold kit” that must be reconstituted with Tc-99m pertechnetate prior to use.
- F-18 NaF is available on a more limited basis from central pharmacies which make this chemical form as a precursor to F-18 FDG preparation.

5. MOLECULAR STRUCTURES

As indicated in the diagram below, there is little difference between the phosphate-based bone agents. The central backbones are P-O-P, P-CH₂-P, and P-CH(OH)-P.



6. DRUG PREPARATION

- Waterproof gloves should be worn during the preparation procedure.
- With a sterile shielded syringe, aseptically add 1-8 mL of oxidant free, sterile and non-pyrogenic Tc 99m Pertechnetate containing no more than 11.1 GBq (300 millicuries) to the vial.
- Swirl the contents of the vial for one minute, and let stand for at least 10 minutes. Record time and date of preparation.
- The radiochemical purity of the prepared radiopharmaceutical should be checked prior to patient administration.

- e) Aseptically withdraw material with a sterile shielded syringe for use within six hours of preparation.
- f) The patient dose should be measured in a suitable dose calibration system immediately prior to administration.

7. QUALITY CONTROL PROCEDURES

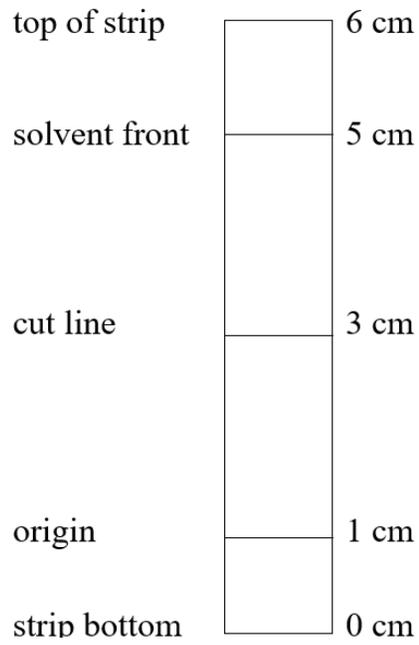
- a) A small drop of the Tc-99m bone agent no wider in diameter than 1/3 the width of the chromatography strip should be placed on the origin line and the strip should be immediately placed in the vial containing the solvent.
- b) Once the solvent has migrated to the line marked “solvent front”, the strip is removed, cut on the “cut line”, and the two halves of the strip are placed in labeled test tubes for counting.

THIN LAYER CHROMATOGRAPHY SYSTEMS OF Tc-99m BONE AGENTS

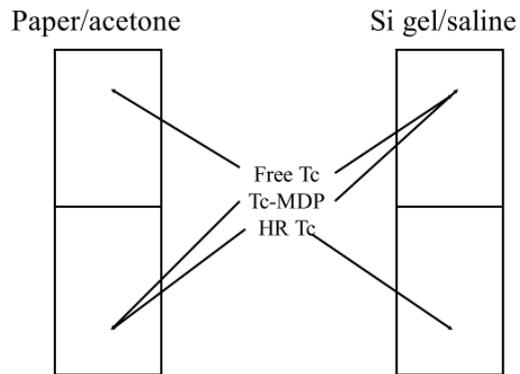
Tc-99m HDP, MDP, PYP

SYSTEM	IMPURITY MEASURED
1. Silica Gel/0.9% saline	Hydrolyzed Reduced Tc
2. Paper/acetone	Free Tc (Pertechnetate)

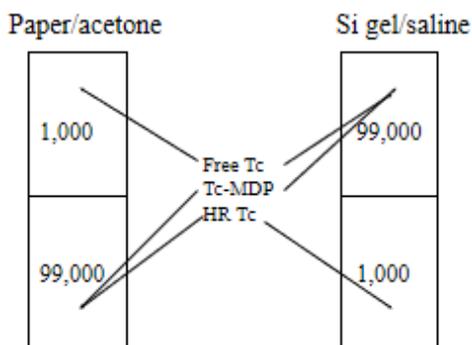
STRIP DESIGN



Migration Patterns of Tc-MDP



What is Radiochemical Purity of Tc-MDP?



Results

$$\% \text{ free Tc} = 1,000 / (1,000 + 99,000) = 1 \%$$

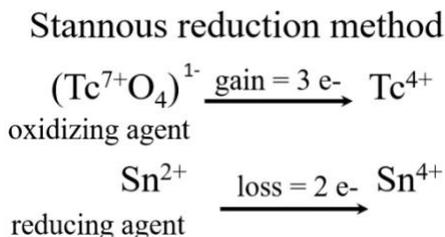
$$\% \text{ HR Tc} = 1,000 / (1,000 + 99,000) = 1 \%$$

therefore,

$$\% \text{ Tc-MDP} = 100 \% - 2 \% = 98 \%$$

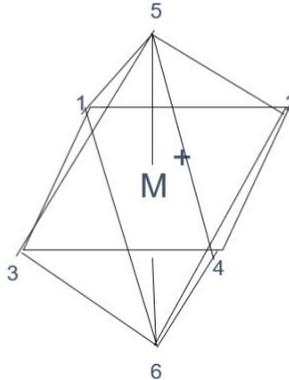
8. RADIOCHEMICAL REACTION

- a) It is necessary to convert the electronegative pertechnetate to an electropositive form as it is unable to react with the electronegative phosphonate compound due to repulsion of 2 negative ions. That conversion of pertechnetate takes place via a reduction/oxidation reaction as shown below.



- b) Tc^{4+} then reacts with the electronegative methylenediphosphonate to form the Tc-MDP complex, which has an octahedral structure illustrated in the diagram below.

Hexa-coordinated Compound Octahedral Structure



9. CLINICAL PHARMACOLOGY

- a) During the initial 24 hours following intravenous injection of Tc 99m MDP, about 50% of each dose is retained in the skeleton, and about 50% is excreted into the bladder. Upon intravenous injection, Tc 99m MDP exhibits a specific affinity for areas of altered osteogenesis. In humans, blood levels fall to 4-10% of the injected dose by two hours post-injection and to 3-5% by three hours.
- b) Uptake of Tc 99m MDP in bone appears to be related to osteogenic activity and to skeletal blood perfusion. The deposition in the skeleton is bilaterally symmetrical, with increased accumulation in the axial structure as compared to the appendicular skeleton. There is increased activity in the distal aspect of long bones as compared to the diaphyses.

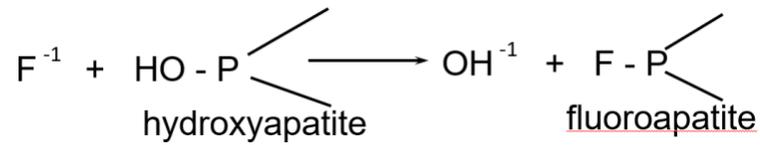
10. MECHANISM OF LOCALIZATION OF RADIOPHARMACEUTICAL:

Skeletal imaging with phosphate-based compounds

- a) Mechanism: physicochemical adsorption or **chemisorption**. The phosphate or phosphonate groups on currently used bone agents bind instantaneously, avidly, and essentially irreversibly to the hydroxyapatite structure of bone tissue. In addition, by the same mechanism, they localize in lesions metastatic to bone.

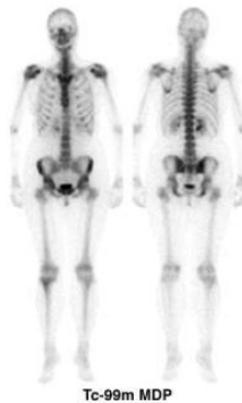
Skeletal imaging with F-18 NaF

- a) By the process called **exchange diffusion**, fluoride ion diffuses into bone tissue and exchanges with hydroxide ion, an integral part of the hydroxyapatite structure, to form fluoroapatite. Binding is essentially irreversible



11. NORMAL DISTRIBUTION OF DRUG

Normal Bone Scan



- Tracer uptake greatest in axial skeleton
- Background activity of soft tissue
- Kidneys routinely visualized
- Skull can appear uneven (variations in calvarial thickness)
- Sites of persistently increased symmetric uptake are- Acromial and Coracoid processes of the scapulae, Medial ends of the clavicles, Junction of the body and manubrium of the sternum and the sacral alae

Normal Bone Scan-Pediatrics

- Growth Center
most intense: distal femur-proximal tibia-proximal humerus (which is also the order of relative occurrence of osteosarcoma in children)
- Costochondral junctions



12. INDICATIONS FOR CLINICAL STUDIES

**(Society of Nuclear Medicine Procedure Guideline for Bone Scintigraphy
version 3.0, approved June 20, 2003)**

- a) Neoplastic disease
- b) Occult fracture
- c) Osteomyelitis
- d) Stress reaction/stress fracture
- e) Avascular necrosis
- f) Arthritides
- g) Reflex sympathetic dystrophy
- h) Bone infarcts
- i) Bone graft viability
- j) Otherwise unexplained bone pain
- k) Distribution of osteoblastic activity before radionuclide therapy for bone pain

13. TYPICAL ADMINISTERED DOSE FOR ADULTS

- a) The usual administered activity for adult patients is 740–1,110 MBq (20–30 mCi) injected intravenously.
- b) For markedly obese adult patients, the administered activity may be increased to 30–40 mCi.
- c) For pediatric patients, the administered activity is 9–11 MBq/kg (250–300 μ Ci/kg), with a minimum of 20–40 MBq (0.54–1.08 mCi).
- d) The maximum administered activity for pediatric patients should not exceed the administered activity for an adult.

14. PATIENT PREPARATION FOR BONE IMAGING

- a) The rationale for performing the procedure and the details of the procedure itself should be explained to the patient in advance.
- b) Unless contraindicated, patients should be well hydrated and instructed to drink 2 or more 8-oz glasses of water between the time of injection and the time of delayed imaging. The patient should be asked to urinate immediately before delayed imaging and to drink plenty of fluids for at least 24 h after radiopharmaceutical administration

15. DRUG ADMINISTRATION PROCEDURE

- a) The injection is performed intravenously over a period of a few seconds.
- b) A small volume of blood is drawn back into the syringe and then re-injected to insure complete delivery of the bone agent.
- c) Hemostasis is accomplished using a gauze pad and pressure.
- d) The gauze pad at the injection site is covered with a Band-Aid or tape.

16. IMAGING PROTOCOLS

(adapted from Society of Nuclear Medicine Procedure Guideline for Bone Scintigraphy, version 3.0) and reprinted from http://snmmi.files.cms-plus.com/docs/pg_ch34_0403.pdf, © SNMMI Inc.

Image Acquisition

- a) **Flow images:** If flow images are acquired, the camera should be positioned over the region of interest before tracer injection. The acquisition computer should be programmed to acquire approximately 30 frames. When digital images are acquired, blood flow images may be obtained in a $64 \times 64 \times 16$ or greater matrix at 1–3 s/frame. If film is used, 3–5 s/frame may be used. 2. Blood pool (tissue phase) images
- b) **Blood pool images** should be acquired immediately after the flow portion of the study and completed within 10 min of tracer injection, for approximately 3–5 min/image. After 10 min, some activity may be apparent in the skeleton. Blood pool images are usually obtained in a $128 \times 128 \times 16$ or greater matrix, with count density of approximately 300,000 counts/image (150,000–200,000 counts/image may be adequate for extremities).
- c) **Delayed (skeletal phase) images** Routine delayed images are usually obtained from 2–5 h after injection. Whole-body bone scintigraphy can be accomplished with multiple overlapping images (i.e., spot imaging) or with continuous images (i.e., whole-body scan) obtained in anterior and posterior views with a high-resolution or ultrahigh-resolution collimator. When spot views are used as the primary method of acquiring bone images, the areas of bony skeleton covered by the spot views must overlap to avoid missing regions of the skeleton. The first spot view of the axial skeleton, usually the chest, is acquired for approximately 500,000–1 million counts. The remaining spot views are then acquired for the same time as the first view. Spot images may be obtained using a $128 \times 128 \times 16$ or $256 \times 256 \times 16$ matrix. Whole-body views are usually obtained in a $256 \times 1024 \times 16$ or greater matrix. Computer acquisition, processing, and display of images are very helpful and particularly so in

pediatric populations because of extreme ranges of normal uptake. Films of scintigrams photographed with different intensities also may be helpful when digital processing and review are not available. When whole-body scanning is used, the count rate (usually of the anterior chest) should be determined before image acquisition. The scanning speed should be adjusted so that routine delayed (obtained 2–5 h after injection) anterior or posterior whole-body images contain >1.5 million counts. If the scanner electronically joins multiple passes, care must be taken to avoid having the “zipper” superimposed on the spine. When the probability of disseminated disease is small, a limited study is reasonable. When disseminated disease is more likely, spot views limited to the area of interest may be a source of error if distant disease is present.

- d) **SPECT imaging** In some patients, SPECT imaging is helpful to better characterize the presence, location, and extent of disease. SPECT imaging should be performed as recommended by the camera manufacturer. Typical acquisition and processing parameters are 360° circular orbit, 60–120 stops, 64 × 64 × 16 or greater matrix, and 10–40 s/stop. An equivalent total number of counts should be acquired if continuous acquisition is used.
- e) **Other imaging** Additional delayed (6–24-h) images will result in a higher target-to-background ratio and may permit better evaluation of the pelvis if it was obscured by bladder activity on the routine delayed images. Six- to twenty-four-h delayed imaging may be particularly helpful in patients with renal insufficiency or urinary retention. A pinhole collimator may be used if very high-resolution images of a specific area are necessary. Approximately 75,000–100,000 counts should be obtained for pinhole collimator views. Zoom magnification or a converging collimator also may be used to improve resolution, particularly when small structures or pediatric patients are being imaged. The physician interpreting the image should be notified when collimators that introduce distortion (e.g., a pinhole collimator) are used. Other views (e.g., lateral, oblique, or tangential) and special views (e.g., frog-leg views of the hips or sitting-on-detector [caudal] views of the pelvis) may be obtained when necessary.

17. MEDICATIONS THAT AFFECT BONE SCAN QUALITY

The following drugs may interfere with the quality of scintigraphic images:

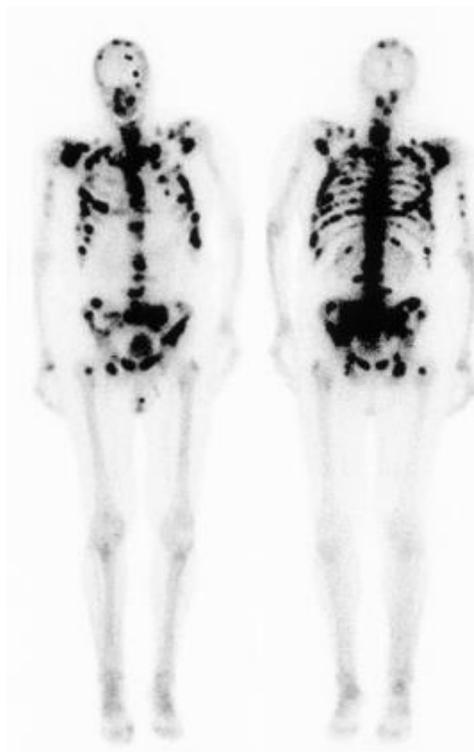
- a) Aluminum: reduced skeletal tracer uptake, diffuse hepatic tracer uptake, increased renal tracer uptake. Common source: antacids
- b) Androgen deprivation therapy for prostate cancer (bicalutamide, estrogens): increased mammary tracer uptake in case of gynecomastia
- c) Bone-modifying agents (including bisphosphonates and denosumab) or agents interfering with osteoblast function (e.g. cabozantinib): reduced skeletal tracer uptake

- d) Corticosteroids: reduced skeletal tracer uptake, reduced tracer uptake at fracture sites
- e) Hematopoietic growth factors: increased spinal tracer uptake, possible increased tracer uptake in the appendicular skeleton
- f) Iron: increased renal tracer uptake, increased tracer uptake at site of intramuscular injection, diffuse hepatic tracer uptake
- g) Methotrexate: diffuse hepatic tracer uptake
- h) Nephrotoxic chemotherapy: increased renal tracer uptake; reduced skeletal tracer uptake
- i) Nifedipine: reduced skeletal tracer uptake

18. ADVERSE REACTIONS FOLLOWING IV INJECTION OF Tc-LABELED PHOSPHATE BASED BONE AGENTS

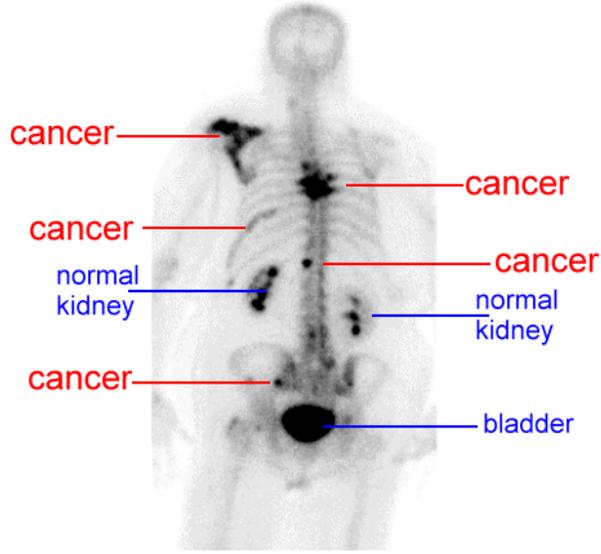
Several adverse reactions have been reported. These were usually hypersensitivity reactions characterized by itching, various skin rashes, hypotension, chills, nausea and vomiting. They are very rare.

19. TYPICAL BONE SCANS IN VARIOUS DISEASES



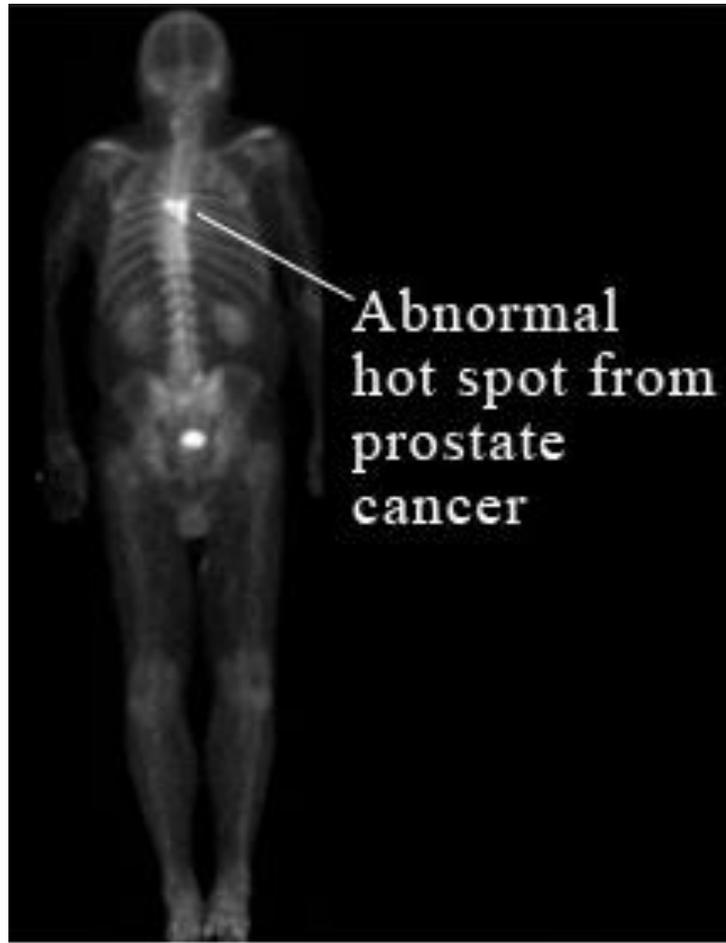
nuclear medicine bone scan showing multiple bony metastases (black areas)

Bone Scan

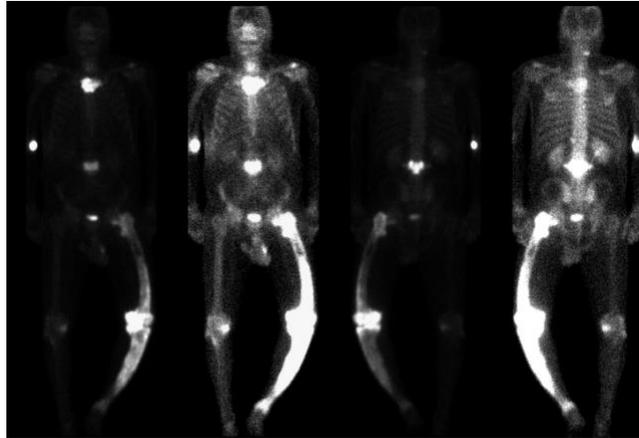


collects in
kidney and bladder

**Tracer collects in
kidney and bladder**



Abnormal
hot spot from
prostate
cancer

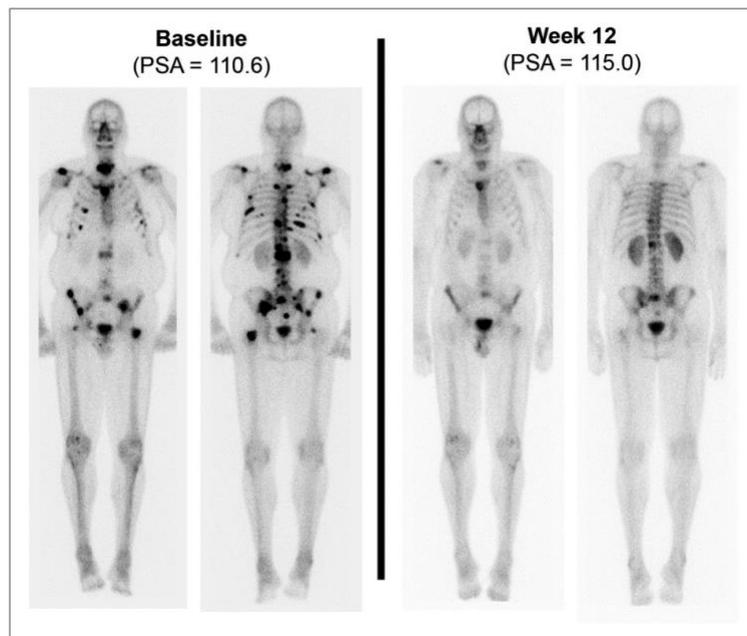


Diagnosis: Paget's Disease

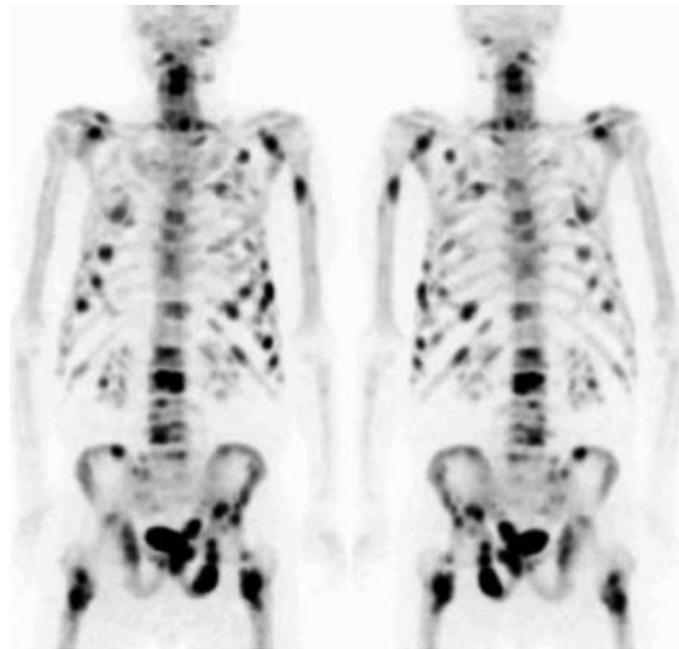
History: The patient is a 65-year-old man with known Paget's Disease, who was recently diagnosed with prostate cancer. He is being evaluated for metastatic disease.

Findings:

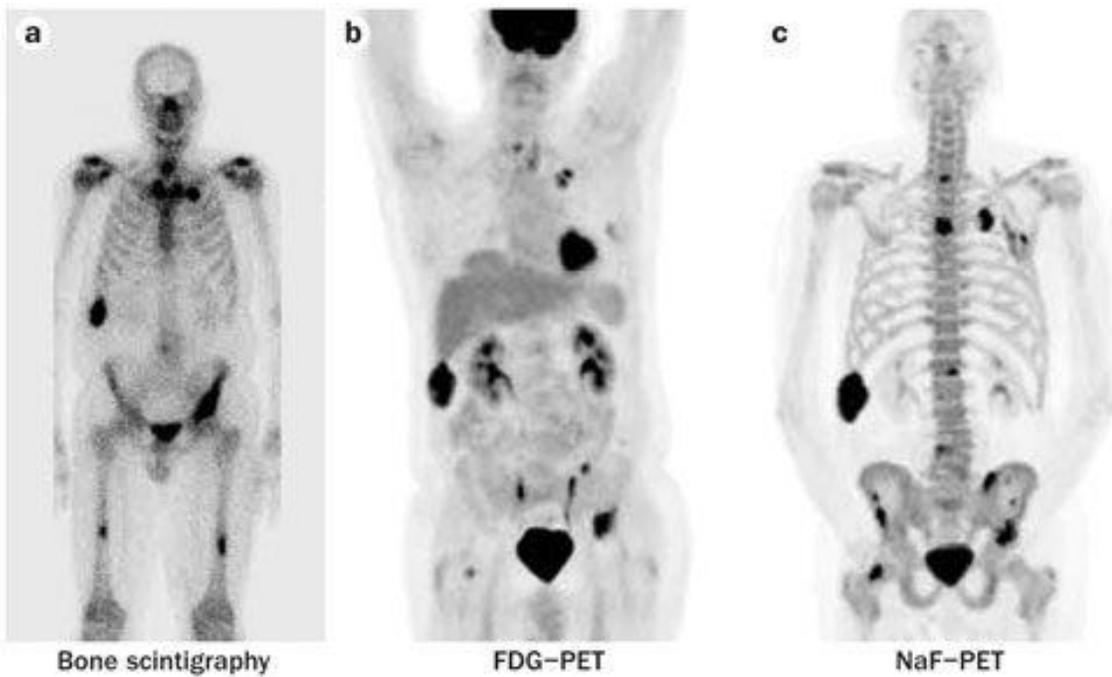
- (1) **Markedly increased activity is noted throughout an expanded, deformed left lower extremity. In addition, markedly increased activity is noted in the third lumbar vertebrae and in the manubrium.**
- (2) **Moderately increased activity is noted in the right knee, and shoulders bilaterally in a pattern characteristic of degenerative changes.**



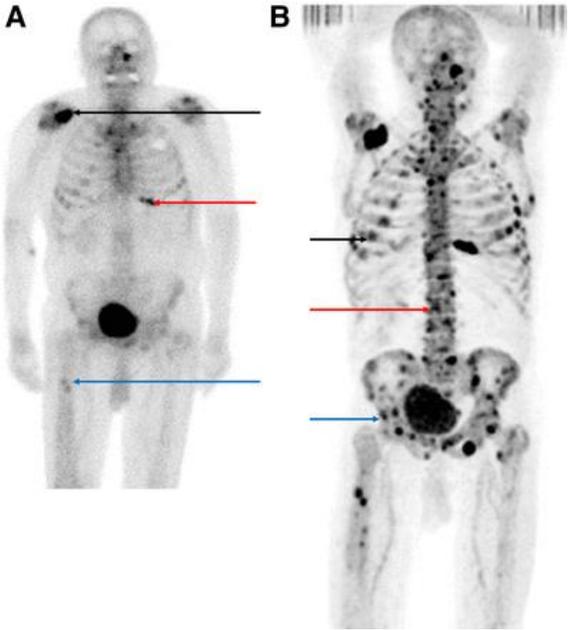
Bone Scan before and after treatment for prostate cancer



Superscan= widespread metastatic disease with minimal appearance of kidneys

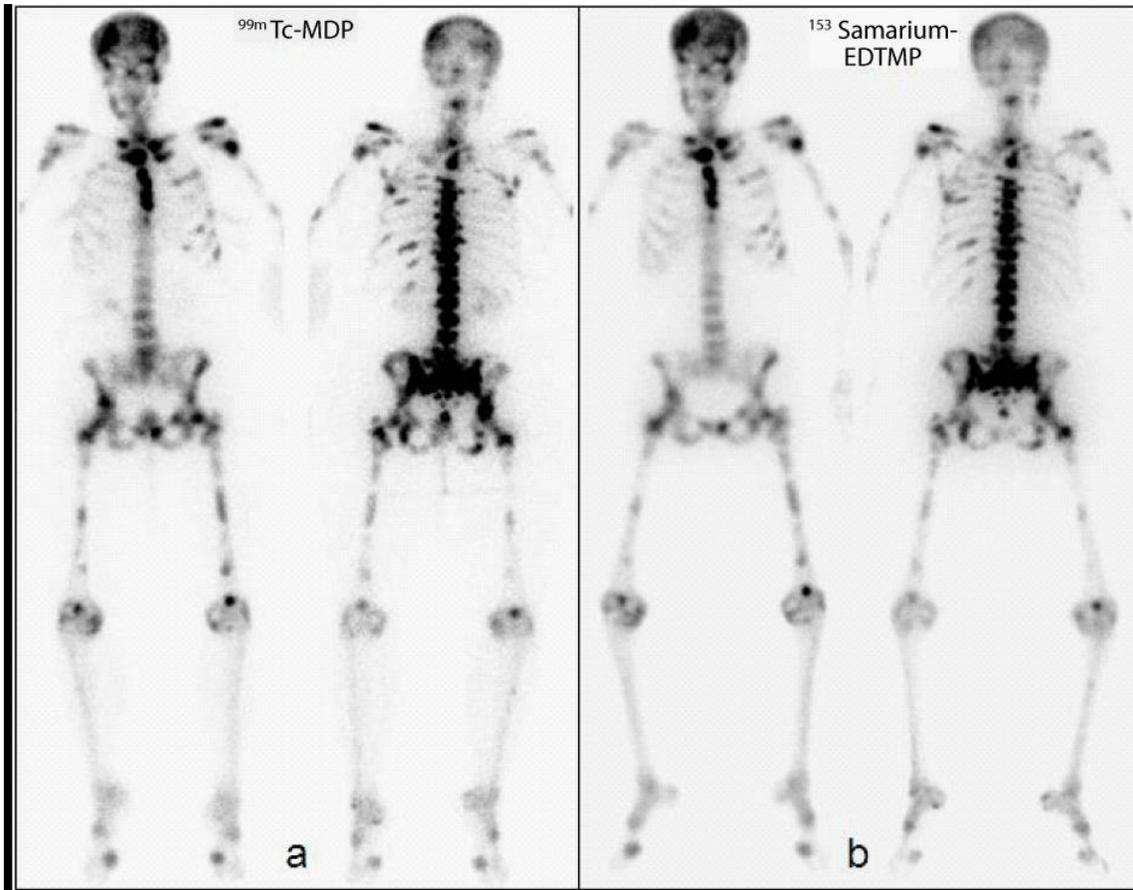


Comparison of Tc bone scan, FDG PET scan, and F-18 NaF PET scan



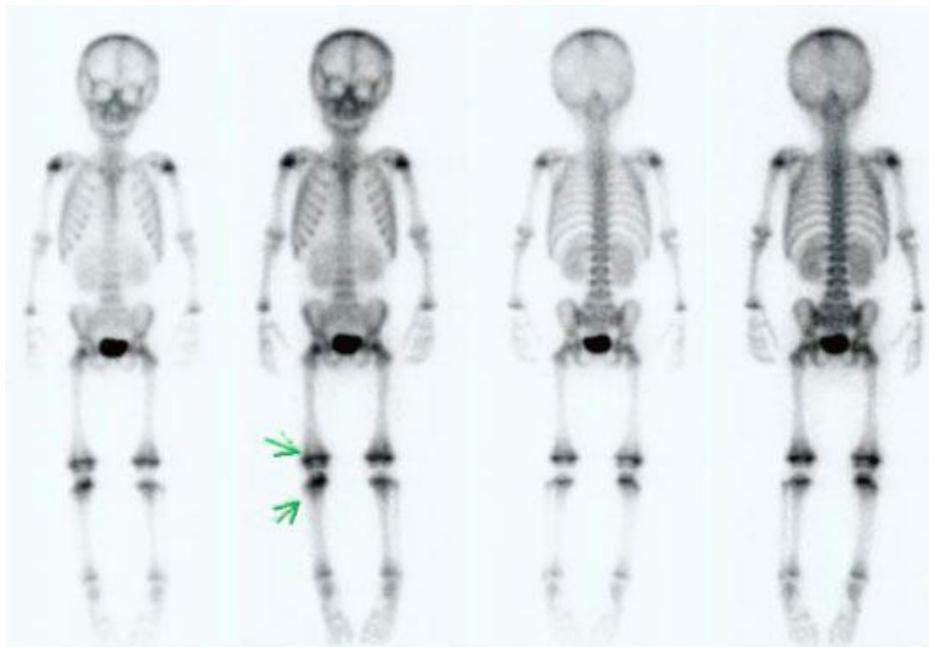
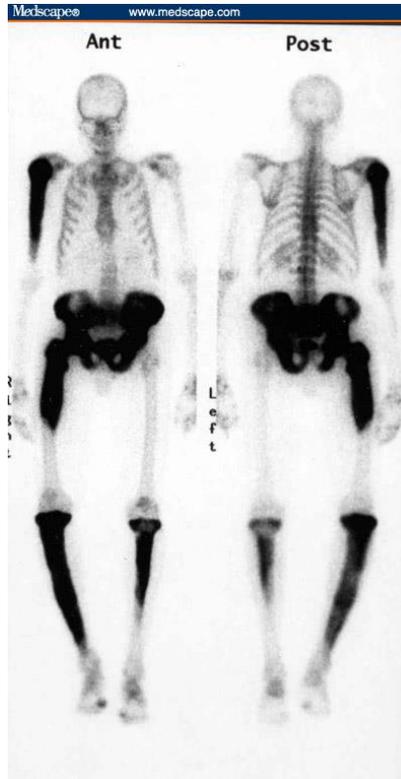
A. Conventional ^{99m}Tc -MDP planar scintigraphy shows several bone metastases in right scapula (black arrow), left lower anterior ribcage (red arrow), and right proximal femoral shaft (blue arrow) in patient with prostate cancer metastases. **B.** ^{18}F -NaF PET/CT bone scan obtained shortly afterward clearly shows greater burden of bone metastases than was seen on the ^{99m}Tc -MDP scan, especially in ribcage (black arrow), spine (red arrow), and pelvis (blue arrow).

J. Nucl. Med. Technol. December 1, 2016 vol. 44 no. 4 217-222



Superscan on both ^{99m}Tc -MDP and ^{153}Sm -EDTMP Bone Scans in a Patient with Breast Cancer

Paget's Disease



Whole body bone scan using Tc-99m MDP shows increased bone uptake in the lesions of a patient with juvenile idiopathic arthritis.

20. INTERNAL RADIATION DOSIMETRY

Radiation Dosimetry in Adults

Radiopharmaceuticals	Administered Activity MBq (mCi)	Organ Receiving the Largest Radiation Dose* mGy/MBq (rad/mCi)	Effective Dose mSv/MBq (rem/mCi)
^{99m} Tc-phosphates and phosphonates	740–1110 (20–30) Intravenously	Bone 0.063 (0.23)	0.0080 (0.030)

*International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals*. ICRP report 53. London, UK: ICRP; 1988:215. Values for normal bone uptake and normal renal function. See also Medical Internal Radiation Dose Committee dose estimate report No. 13: radiation absorbed dose for ^{99m}Tc-labeled bone imaging agents. *J Nucl Med*. 1989;30:1117–1122.

Radiation Dosimetry in Children (5 Years Old)

Radiopharmaceuticals	Administered Activity MBq/kg (mCi/kg)	Organ Receiving the Largest Radiation Dose* mGy/MBq (rad/mCi)	Effective Dose mSv/MBq (rem/mCi)
^{99m} Tc-phosphates and phosphonates	9–11 (0.20–0.30) Intravenously Min: 0.50 mCi Max: 30 mCi	Bone 0.22 (0.81)	0.025 (0.093)

*International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals*. ICRP report 53. London, UK: ICRP; 1988:215. Values for normal bone uptake and normal renal function. See also Medical Internal Radiation Dose Committee dose estimate report No. 13: radiation absorbed dose for ^{99m}Tc-labeled bone imaging agents. *J Nucl Med*. 1989;30:1117–1122.

Estimated Absorbed Radiation Dose² Technetium Tc 99m Medronate

Organ	mGy/740 MBq	rads/20 mCi
Total Body	1.3	0.13
Bone Total	7.0	0.70
Red Marrow	5.6	0.56
Kidneys	8.0	0.80
Liver	0.6	0.06
Bladder Wall	26	2.60
	4.8 hour void	62
Ovaries	2.4	0.24
	4.8 hour void	3.4
Testes	1.6	0.16
	4.8 hour void	2.2