BONE SCINTIGRAPHY
PROCEDURES GUIDELINES FOR TUMOUR IMAGING

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Aim

The purpose of this document is to provide general information about bone scintigraphy in oncology. This guideline describes procedures currently in routine clinical use but should not be interpreted as excluding alternative procedures also employed to obtain equivalent data. It must be remembered that the resources and facilities available to care for patients may vary from one country to another and from one medical institution to another. This document has been prepared primarily for nuclear medicine physicians and intends to offer assistance in optimising the diagnostic information that can currently be obtained from bone scintigraphy. The corresponding guidelines from the Society of Nuclear Medicine (SNM) have been taken into consideration, reviewed and partially integrated with this text. In addition the literature on this topic has been reviewed and discussed by an international group of distinguished experts.

Background

The radionuclide bone scan is the cornerstone of skeletal nuclear medicine imaging. Bone scintigraphy is an highly sensitive method for demonstrating disease in bone, often providing earlier diagnosis or demonstrating more lesions than are found by conventional radiological methods. Primary tumours of bone are relatively rare in adults whereas metastases to bone are very frequent (breast, prostate, lung, head and neck cancer, etc.). Phosphate analogues can be labelled with ^{99m}Tc and are used for bone imaging because of their good localisation in the skeleton and rapid clearence from soft tissues.

Bone scintigraphy images the distribution of a radioactive tracer in the skeletal system. It can be performed as:

a) limited bone scintigraphy or spot views (planar images of a selected portion of the skeleton);
b) whole-body bone scintigraphy (planar images of the entire skeleton in anterior and posterior views);
c) SPECT (tomographic image of a portion of the skeleton);
d) multiphase bone scintigraphy (immediate and delayed images to study blood flow).

In oncology the standard technique of bone scintigraphy is considered to be the whole-body scan. Limited bone scintigraphy or spot views are indicated only where a specific clinical problem detected on whole body imaging needs to be clarified. SPECT has a higher diagnostic specificity than planar imaging and may be preferable when there is diagnostic uncertainty. Multiphase bone scintigraphy is more useful when trauma or muscolo-skeletal inflammation/infection are suspected and is not usually indicated in oncology.

Over the last decades bone scintigraphy has been used extensively in the evaluation of oncological patients. It provides essential information about the sites of bone lesions (primary and metastatic tumours), their prognosis and the effectiveness of therapy by showing the sequential changes in tracer uptake. Bone scintigraphy offers the advantages of whole body examination and has the capability to discover some lesions earlier than other techniques. MR is potentially more sensitive for some regions but is impractical as a whole body screening technique.

Clinical Indications

1) The oncological indications are:

- Primary tumours (e.g. Ewing's sarcoma, osteosarcoma).
  Staging, evaluation of response to therapy and follow-up of primary bone tumors
- Secondary tumours (metastases)
  Staging and follow-up of neoplastic diseases.
  Distribution of osteoblastic activity prior to radiometabolic therapy (^{89}Sr, ^{153}Sm-EDTMP, ^{186}Re-HEDP).

2) Non neoplastic diseases:

Bone scan changes occur whenever there is an increase in blood flow to a lesion or there is an alteration of osteoblastic activity. For this reason bone scan images reveal abnormalities also in non neoplastic diseases such as:

- Osteomyelitis
- Perthe's Disease, Avascular necrosis
- Metabolic disorders (Paget, osteoporosis)
- Arthropathies
- Fibrous Dysplasia and other rare congenital conditions
- Stress fractures, Shin splints
- Loose or infected joint prosthesis
- Low back pain, sacroilitis
- Reflex sympatetic syndrome
- Any other bone injuries

Precautions

- Pregnancy (suspected or confirmed). In the case of a diagnostic procedure in a patient who is known or suspected to be pregnant, a clinical decision is necessary to consider the benefits against the possible harm of carrying out any procedure.
- Breast feeding should be discontinued and milk expressed and discarded when possible 24 hours (at least for 4 hours) post radiopharmaceutical administration).

Pre-examination procedures

1) Patient preparation

A thorough explanation of the test should be provided to the patient in advance by the technologist or physician (including hydration, time taken for scan, and details of the procedure itself).

2) Pre-injection

The nuclear medicine physician should take account of all information that is available for optimal interpretation of bone scintigraphy, especially:

- relevant history including type of suspected or known primary tumour(s) or/and metastases;
- relevant history of fractures, trauma, osteomyelitis, cellulitis, oedema, arthritis, neoplasms, metabolic bone disease or limitation of function;
- current symptoms, physical findings;
- results of previous bone scintigraphy or other recent nuclear medicine studies(^{131}I, ^{67}Ga, ^{111}In) (it is strongly recommended that every effort be made to obtain hard copy or computer files of previous examinations);
- results of other imaging studies such as conventional radiographs, CT, MRI (as with previous scintigraphic examinations it is recommended that every effort be made to obtain hard copy or computer files of previous examinations);
- history of therapy that could affect bone scintigraphy (e.g. antibiotics, steroids, chemotherapy, radiation therapy, diphosphonates, iron therapy);
- orthopaedic and non-orthopaedic surgery affecting the results of bone scintigraphy;
- relevant laboratory results (e.g. PSA for patients with prostate cancer);
- presence of urinary tract abnormalities;
- possible contraindications for hydration.

3) Radiopharmaceutical injection, dosage and administration

The radiopharmaceutical (MDP, HMDP, HDP, etc.) should be administered by the intravenous route, using an indwelling catheter or butterfly needle.

The activity of radiopharmaceutical to be administered should be determined after taking account of the European Atomic Energy Community Treaty, and in particular article 31, which has been adopted by the Council of the European Union (Directive 97/43/EURATOM). This Directive supplements Directive 96/29/EURATOM and guarantees health protection of individuals with respect to the dangers of ionising

radiation in the context of medical exposures. According to this Directive, Member States are required to bring into force such regulations as may be necessary to comply with the Directive. One of the criteria is the designation of Diagnostic Reference Levels (DRL) for radiopharmaceuticals; these are defined as *levels of activity for groups of standard-sized patients and for broadly defined types of equipment.* It is expected that these levels will not to be exceeded for standard procedures when good and normal practice regarding diagnostic and technical performance is applied. For the above mentioned reasons the following activity for ^{99m}Tc-diphosphonate should be considered only a general indication, based on the data of the literature and current experience. However it should be noted that in each Country nuclear medicine physicians should respect the DRLs and the rules set out by local Law.
The average activity administered for bone scintigraphy by a single i.v. injection should be 500 MBq (300-740 MBq) (8-20 mCi). The organ which receives the largest radiation is bone (see table of adsorbed Doses ICRP no. 80, 1998). The activity to be administered to children should be a fraction of the adult activity calculated from body weight according to the factors given by the EANM Paediatric Task Group. In children a minimum activity of 40 MBq is necessary in order to obtain images of sufficient quality. Practitioners could be required to justify administration of activities greater than local national DRLs.

2) Post injection

Unless contraindicated, patients should be well-hydrated and instructed to drink one or more litre of water (4-8 glasses) between the time of injection and the time imaging. All patients should be asked to void frequently during the interval between injection and delayed imaging as well as immediately prior to the scan.
The patients should drink a large amount of fluids during the 24 hours after radiopharmaceutical administration.

Physiological distribution of ^{99m}Tc-phosphonates

Phosphonates concentrate in the mineral phase of bone, nearly two thirds in hydroxyapatite crystals and one third in calcium phosphate. Two major factors control accumulation of phosphonates in bone, namely blood flow and extraction efficiency, which in turn depends on capillary permeability, acid-base balance, parathyroid hormone levels, etc. About 50% of the activity injected accumulates in the skeleton. Maximum bone accumulation is reached 1 hour after injection and remains practically constant up to 72 hours. The blood clearance of these radiopharmaceuticals is high. Three hours after injection only 3% of the administered activity remains in the blood stream. The peak of activity through the kidneys is reached after approximately 20 minutes. Within 1 hour, with normal renal function, more than 30% of the unbound complex has undergone glomerular filtration and within 6 hours 60%. The quantity of phosphonates eliminated via the intestines is insignificant. The biological half-life of phosphonates is 26 hours.
In a normal bone scan all but the smallest bones are recognizable. On the anterior view it is possible to distinguish the sternum. On the posterior view the bodies of individual vertebrae are seen, as well as pedicles, transverse and spinous processes in the lower dorsal and lumbar regions. In this projection the sacro-iliac joints usually have the highest uptake. In children the appearance of the bone scan is characterised by areas of uptake due to active growth in the epiphyseal regions. After fusion of the epiphyses these areas are no longer visible.

Radiation dosimetry

The estimated adsorbed radiation dose to various organs in healthy subjects following administration of ^{99m}Tc-labelled phosphates and phosphonates is given in the Table. The data are quoted from ICRP no. 80.

	Absorbed dose per unit activity administered (mGy/MBq)

Organ	Adult	15 years	5 years
Adrenals	0.0021	0.0027	0.0058
Bladder	0.048	0.060	0.073
Bone surfaces	0.063	0.082	0.22
Brain	0.0017	0.0021	0.0043
Breast	0.00071	0.00089	0.0022
Gall bladder	0.0014	0.0019	0.0042
Stomach	0.0012	0.0015	0.0035
Small intestine	0.0023	0.0029	0.0053
Colon	0.0027	0.0034	0.0061
Heart	0.0012	0.0016	0.0034
Kidneys	0.0073	0.0088	0.018
Liver	0.0012	0.0016	0.0036
Lungs	0.0013	0.0016	0.0036
Muscles	0.0019	0.0023	0.0044
Oesophagus	0.0010	0.0013	0.0030
Ovaries	0.0036	0.0046	0.0070
Pancreas	0.0016	0.0020	0.0045
Red marrow	0.0092	0.010	0.033
Skin	0.0010	0.0013	0.0029
Spleen	0.0014	0.0018	0.0045
Testes	0.0024	0.0033	0.0058
Thymus	0.0010	0.0013	0.0030
Thyroid	0.0013	0.0016	0.0035
Uterus	0.0063	0.0076	0.011
Remaining organ	0.0019	0.0023	0.0045
Effective dose (mSv/MBq)	**0.0057**	**0.0070**	**0.014**

Radiopharmaceutical Technetium [^{99m}Tc] diphosphonates.

Definition

The most commonly used diphosphonates are methylene diphosphonate (MDP), hydroxymethylene diphosphonate (HMDP) and hydroxyethylene diphosphonate (HDP/HMDP). All are commercially available and supplied as a vial containing the relevant diphosphonate, a stannous reducing agent and other excipients in a lyophilised form.

Preparation

^{99m}Tc-labelled diphosphonates are prepared by addition of the required amount of sodium [^{99m}Tc] pertechnetate diluted in sterile physiological saline to the vial according to the manufacturers instructions.

Quality control

The radioactive concentration should be determined by measuring the activity of the vial in a calibrated ionisation chamber. Radiochemical purity may be confirmed using a TLC method. (Solid-phase ITLC, mobile-phase I methylethylketone; Rf ^{99m}Tc-MDP 0.0, reduced hydrolysed ^{99m}Tc 0.0, ^{99m}Tc-pertechnetate 1.0; mobile phase II 0.9% sodium chloride solution; Rf ^{99m}Tc-MDP 1.0, reduced hydrolysed ^{99m}Tc 0.0, ^{99m}Tc-pertechnetate 1.0. Labelling efficiency should be >95%.

Special precautions

The preparation may be diluted with sterile physiological saline if required. These radiopharmaceuticals are subject to oxidation, care should be taken to avoid introducing air into the multidose vial during preparation or removal of doses. The radiopharmaceutical should be used within 6 hours of preparation.

Gamma-camera quality control

A strict quality control programme should be routinely performed, according to the rules of each country, as stated in the Council Directives 97/43/EURATOM.

Image acquisition

1) Instrumentation

Single or double head gamma-camera equipped with a low-energy, high-resolution collimator.

Energy window: 10% energy window (±5%) centred over the 140 keV photopeak of ^{99m}Tc.

2) Acquisition modality

Routine images are usually obtained between 2 and 5 hours after injection.

Later (6-24 hour) delayed images result in a higher target-to-background ratio and may permit better evaluation of the pelvis if this was obscured by bladder activity on the routine (2-5 hour) images. Six- to 24-hr delayed imaging may be particularly helpful in patients with renal insufficiency or peripheral circulatory disorders and those with urinary retention.

Whole-body bone scintigraphy can be accomplished with multiple overlapping (spot) images or with continuous imaging (i.e. whole-body scan) obtained in both anterior and posterior projections. In adults, whole-body studies are currently preferred. For paediatrics, spot views are commonly used.

When spot views are used as the primary method of acquisition, the regions of skeleton covered by each spot view must overlap, to avoid missing any area. The first spot view of the axial skeleton, usually the posterior projection of the chest, is acquired for approximately 500,000 to 1 million counts depending on the FOV of the gamma-camera. The larger the FOV, the larger the number of total counts required to give similar count densities over equivalent regions of the skeleton. Moreover, the presence of physiologically high counts density organs (typically the kidneys) may hamper visualisation of contiguous structures (typically the spine). Each of the remaining spot views is then acquired for the same time as the first view. Spot images may be obtained using a 128x128 or a 256x256 matrix (>200,000 counts). Whole-body views are usually obtained in 256x1024 or greater matrix.

Computer acquisition, processing and display of images may be particularly helpful in paediatric populations because of the extreme range of normal uptake. Films of scintigrams photographed with different intensities may also be helpful if digital processing and review are not available.

When whole-body scanning is used, the count rate (usually the posterior thorax) should be determined before starting the definitive acquisition. The scanning speed should be adjusted so that routine anterior and posterior whole-body images obtained 2-5 hours after injection each contain > 1.5 million counts.

3) Optional Images

In some patients, SPECT imaging is helpful to better characterise the presence, location and extent of disease. SPECT imaging should be performed as recommended by the gamma-camera manufacturer. Typical acquisition and processing parameters with a single-headed gamma camera are 360° circular orbit, 60 – 120 steps, 64x64 or greater matrix, and 10 – 40 sec/stop. An equivalent total number of counts should be acquired if continuous acquisition is used.

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 may also be used to improve resolution, particularly when small structures or paediatric patients are being imaged. The physician interpreting the image should be notified when collimators such as a pinhole, which introduce distortions, are used.

Additional projections, such as lateral, oblique, tangential and special views may be obtained if necessary.

The pelvis can be difficult to evaluate when there is overlying bladder activity. In patients with pelvic symptoms, one or more of the following may better visualise the bony pelvis:

- Repeat images immediately after voiding
- Sitting-on-detector (caudal) or oblique views
- Lateral views
- 24-hours delayed images
- SPECT acquisition. Single or multiple rapid (5 – 10 min per acquisition) SPECT acquisition(s) are preferred to avoid artefacts caused by changing activity in the bladder. Bladder artefacts are exaggerated in the plane where the SPECT acquisition begins and ends.
- Image immediately following catheterization of the bladder. (Note: Bladder catheterization should be reserved as a last resort for patients in whom visualisation of the pelvis is essential).

Image Processing

No particular processing procedure is needed for planar images.

In case of SPECT one should take into account the different types of gamma camera and software available: careful choice of imaging processing parameters should be adopted in order to optimize the imaging quality.

Interpretation criteria

When evaluating bone scan images, the following points should be taken into consideration:

- The bone scan is very sensitive for localization of skeletal metastases or tumours, but the specificity is low. It must be interpreted in the light of all available information, especially patient history, physical examination, other test results and comparison with previous studies.
- Symmetry in the representation of right and left sides of the skeleton and homogeneity of tracer uptake within bone structures are important normal features. Particular attention should be paid to left-right asymmetries and/or heterogeneity of tracer uptake.

<u>Bone abnormalities</u>

- Both increases and decreases of tracer uptake have to be assessed; abnormalities can be either focal or diffuse.
- Increased (decreased) tracer activity in the bone compared to normal bone, indicates increased (decreased) osteoblastic activity.
- Differential diagnosis can sometimes be based on the configuration of the abnormality or abnormalities and the location and number of abnormalities. Most patterns are non-specific.
- Focal decrease without adjacent increase in tracer uptake is less common than focally-increased activity and is often caused by benign conditions (attenuation, artefact or absence of bone e.g. surgical resection).
- Decrease in intensity of tracer uptake and in number of abnormalities compared to a previous study often indicates improvement or may be secondary to focal therapy (e.g. radiation therapy).
- Increase in intensity of tracer uptake and in the number of abnormalities compared to a previous study often indicates progression of disease but may be a flare response to therapy.

<u>Soft tissues findings</u>

- Normal structures should be noted: kidneys and bladder. Tracer uptake in the kidney can be focal or diffuse.
- Generalised increased soft tissue uptake compared to normal bone can be due to renal failure, dehydration or shortened interval between injection and imaging.
- A generalized decreased soft tissue uptake compared to normal bone can be due to superscan or a prolonged interval between injection and imaging.

Reporting

The nuclear medicine physician should record appropriate information regarding the patient, especially type of examination, date, radiopharmaceutical (administered activity and route), a summary of patient history, all correlated data from previous diagnostic studies and the clinical problem.

The report to the referring physician has to describe:

1) The procedure (whole body, SPECT if applicable, radiopharmaceutical, injected activity, delayed images, blood pool images etc.).
2) Findings. Abnormal tracer uptake (increased, decreased, pattern of abnormal uptake, bone findings, soft tissue findings).
3) Comparative data (correlation with other diagnostic results and comparison with previous studies).
4) Interpretation. A clear diagnosis should be given if possible, accompanied when appropriate with a description of the study limitations. Recommend further, more definitive study or studies and evaluations if differential diagnosis is broad.

Sources of error

- Patient movement.
- Greater than necessary collimator-to-patient distance.
- Imaging too soon after injection, before the radiopharmaceutical has been optimally cleared from soft tissues.
- Injection artefacts.
- Radiopharmaceutical degradation.
- Urine contamination or a urinary diversion reservoir.
- Prosthetic implants, radiographic contrast materials or other attenuating artefacts which may obscure normal structures.
- Homogeneously increased bony activity (e.g. ‘superscan’).
- Restraints artefacts caused by soft-tissue compression.
- Prior administration of a higher energy radionuclide (^{131}I, ^{67}Ga, ^{111}In), or of a ^{99m}Tc radiopharmaceutical which accumulates in an organ that could obscure or confound skeletal activity.
- Significant findings outside the area of interest may be missed if a limited study is performed.
- Changing bladder activity during SPECT of pelvic region.
- Purely lytic lesions.
- Pubic lesions obscured by underlying bladder activity.
- Renal failure.

Issues requiring further clarification

- The role of ^{99}Tc-phosphonate bone scintigraphy in follow-up of treated cancer patients is still a matter of discussion. There is general agreement that bone scintigraphy is indicated in symptomatic patients. However it is unproven whether bone scintigraphy is cost-effective in all asymptomatic patients at risk of metastases (with worse prognostic factors). There are discussions in order to establish which subgroups of patients at high risk of metastases can benefit from periodic bone scan examinations.
- Although the clinical role of PET (^{18}F-fluoride and ^{18}F-fluorodeoxyglucose) in the diagnosis and management of bone tumours is not yet fully defined, the available reports suggest that it should have great potential to provide further clinically relevant information in these patients. The position of ^{99}Tc-phosphonate bone scintigraphy in comparison with PET should be better investigated (according to tumour type and clinical indications) in order to know if bone scintigraphy can keep its current role, in spite of the emerging high diagnostic accuracy of PET.

Disclaimer

The European Association has written and approved guidelines to promote the use of nuclear medicine procedures with high quality. These general recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures and exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialised practice setting may be different than the spectrum usually seen in a more general setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, resource available for patient care may vary greatly from one European country or one medical facilty to another. For these reasons, guidelines cannot be rigidly applied.

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