

REVIEW ARTICLE

A review of the current status of radionuclide bone scanning

Ali Nawaz Khan

Department of Radiology, North Manchester General Hospital, Pennine Acute Hospital Trust, Manchester

Abstract

Radionuclide bone scanning (RNBS) using technetium-99m–labelled diphosphonates (MDP) is a frequently performed technique in nuclear medicine. It is widely regarded as the most cost-effective and widely available whole-body screening test for the assessment of bone metastases and other focal bone lesions. The technique is often combined with conventional radiography to improve the diagnostic accuracy.

Recently, this role has been challenged by newer imaging modalities such as CT, MRI and PET-CT. These techniques have limited worldwide availability, are expensive and have their own limitations but can complement RNBS. For example, CT scanning is useful in guiding needle biopsy, particularly in vertebral lesions. MRI is helpful in determining the extent of local disease in planning surgery or radiation therapy.

RNBS, although non-specific, has an excellent sensitivity, which makes it a useful tool for characterizing some conditions that are not clearly depicted on anatomic images. Bone metastases generally appear as multiple 'hot' lesions, although occasionally they may be 'cold'.

Fractures can be detected, even when radiographic findings are negative. In athletes who have sustained musculoskeletal trauma, RNBS is an excellent screening tool and can identify many conditions where conventional radiographic techniques are often negative including, for example, plantar fasciitis, shin splints, spondylolysis, etc. Osteomyelitis can be diagnosed with great confidence in a non-traumatized bone when focal hyperperfusion, focal hyperaemia, and focally increased bone uptake is seen within a bone. RNBS is often useful in metabolic bone disease.

The selection will become less of an issue when more MRI units are established and when its cost decreases. Factors such as cost and relatively long imaging times, as well as considerations of patient throughput, are important. MRI is estimated to cost approximately three times the cost of RNBS and fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning, costs considerably more.

In view of the current worldwide increase in the cost of healthcare, RNBS remains the first-line screening test for detection of bone metastases and other non-malignant bone lesions, and it is predicted that RNBS is likely to remain a major tool in the diagnosis of bone disease for years to come.

Key words: *radionuclide bone scan, bone metastases, osteomyelitis, trauma, reflex sympathetic dystrophy, spondylolysis, metabolic bone disease*

Correspondence

Prof Ali Nawaz Khan
North Manchester General Hospital
Pennine Acute Hospital Trust
Manchester M8 5RB
Email: drkhan1966@msn.com

 2221-0288(201106/01)1:1<3:RCSRBS>2.0.TX;2-M

Introduction

Radionuclide bone scanning (RNBS) with ^{99m}Tc-MDP is one of the most frequently performed techniques in nuclear medicine. RNBS is widely available, relatively inexpensive and an extremely sensitive technique that remains the backbone of detecting bone metastases and other lesions such as traumatic, inflammatory and metabolic bone diseases.

Chiewvit et al. found MRI more efficient than the RNBS in detecting vertebral metastases, especially in cases where RNBS results were equivocal or negative for vertebral metastases in the face of a high index of clinical suspicion [1]. They also found that MRI was important for further treatment planning such as radiation therapy or systemic chemotherapy. The authors concluded that although MRI was useful in the detection of early metastases that are localised completely in the bone marrow cavity, routinely RNBS remains the most cost-effective method for examination of the entire skeleton. Tausig et al. found the detection rate of bone metastases within the thorax and the skull using conventional Turbo-STIR-MRI whole-body scans even less accurate than conventional planar RNBS in these regions [2].

Conventional radiography is the best modality for characterizing lesions that are depicted on RNBS. Combined analysis and reporting of findings on radiographs and RNBS improve the diagnostic accuracy in detecting bone metastases and assessing the response to therapy [3-6].

CT and MRI are both useful in evaluating suspicious lesions seen on RNBS that appears equivocal on radiographs. MRI can also help in detecting metastatic lesions before changes in bone metabolism make the lesions detectable on RNBS [6-12]. CT scanning is useful in guiding needle biopsy, particularly in vertebral lesions. MRI is helpful in determining the extent of local disease in planning surgery or radiation therapy.

The major limitation of RNBS is a lack of specificity and radiation exposure. Whilst the study is more sensitive in the detection of stress fractures, the radiation dose delivered to the patient, typically four millisieverts, is much greater than the dose in routine radiographs. The spatial resolution of RNBS is also limited. Increased isotope activity in the sacral region, may be interpreted as arising in the sacroiliac joints when caused by either sacroiliac joint dysfunction or sacroiliitis. This is a major clinical limitation [13].

In this pictorial review we discuss RNBS findings in a variety of bone disorders.

Technique

RNBS is performed using ^{99m}Tc-labelled diphosphonates, most commonly, ^{99m}Tc-methy lene diphosphonate (^{99m}Tc-MDP). Fifty percent of ^{99m}Tc-MDP accumulates in skeletal tissue by 2–6 hours following intravenous injection. The exact mechanism of the isotope uptake in the bone is not known, but it is postulated that the MDP is adsorbed to the inorganic crystalline mineral matrix (calcium hydroxyapatite) of the bone. The amount of the isotope uptake depends on blood flow and the rate of bone turnover [14-16].

Protocols vary, but typically imaging follow 2-6 hours after intravenous delivery of 740–925 MBq (20–25 mCi) of ^{99m}Tc-MDP. A 2-6 hour delay allows clearance of the isotope from the soft tissues, allowing a higher target-to-background ratio with a clearer depiction of bone. Bone detail can be improved by oral intake of copious amounts of fluid following MDP injection. A gamma camera equipped with a low-energy high-resolution collimator is used to obtain high-resolution images. Spot films and additional views are obtained when needed.

Normal Bone Scan

Normally, radionuclide activity in the bones has a symmetrical distribution. There is some

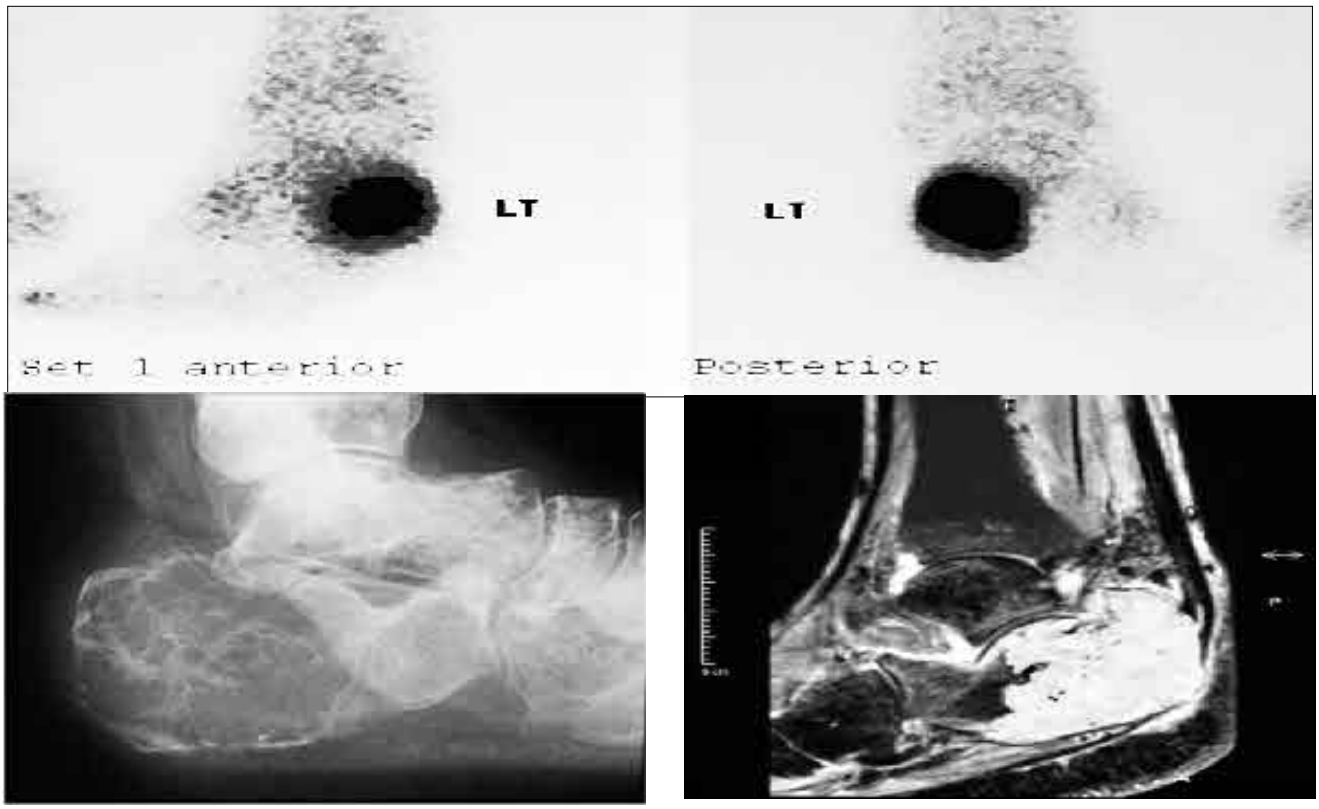

Figure 1 *This 42-year-old painter and decorator was up on a ladder whilst his assistant was messing around and pretended to hit his boss's heel with a hammer. At the time the patient did not feel pain but a few days later his heel became painful. An x-ray of the heel at the time showed no abnormality (not shown). Over the next few weeks his heel pain got progressively worse. An MDP scan was performed after three weeks, which showed intense activity over the calcaneum. The subsequent x-ray and MRI showed grossly abnormal calcaneum. A needle biopsy showed a clear cell metastasis from a renal cell carcinoma subsequently proved on an ultrasound scan*

associated soft-tissue activity and faint renal and bladder activity due to renal excretion [16]. Intense symmetric activity in the epiphysis of the long bones and the facial flat bones is seen in children [16]. In aging population radionuclide skeletal uptake decreases. However, in some parts of the skeleton such as the acromial and coracoid processes of the scapulae, the sternal ends of the clavicles, the junction of the body and manubrium of the sternum, and the sacral alae, isotope uptake is increased. There is the often asymmetrical activity in the neck in the mature population due to activity in a calcified thyroid cartilage and in the apophyseal joints of the cervical vertebrae due to asymptomatic degenerative disease in the cervical spine [16].

Metastatic Disease

Three mechanisms are primarily involved in the spread of malignant disease to bones: (1) direct extension, (2) retrograde venous flow, and (3) seeding of tumour emboli via the blood circulation. Seeding is by far is the most common mechanism where the initial deposition of tumour cells occurs in the red marrow containing areas within the bones in adults. In children where the bone marrow is more extensive, bone metastases are more widespread. Bone metastases from intra-abdominal lesions, initially preferentially involve the vertebral column. Here retrograde venous embolism to the spine seems to be the mechanism of spread from the abdominal malignancy. Increased abdominal pressure

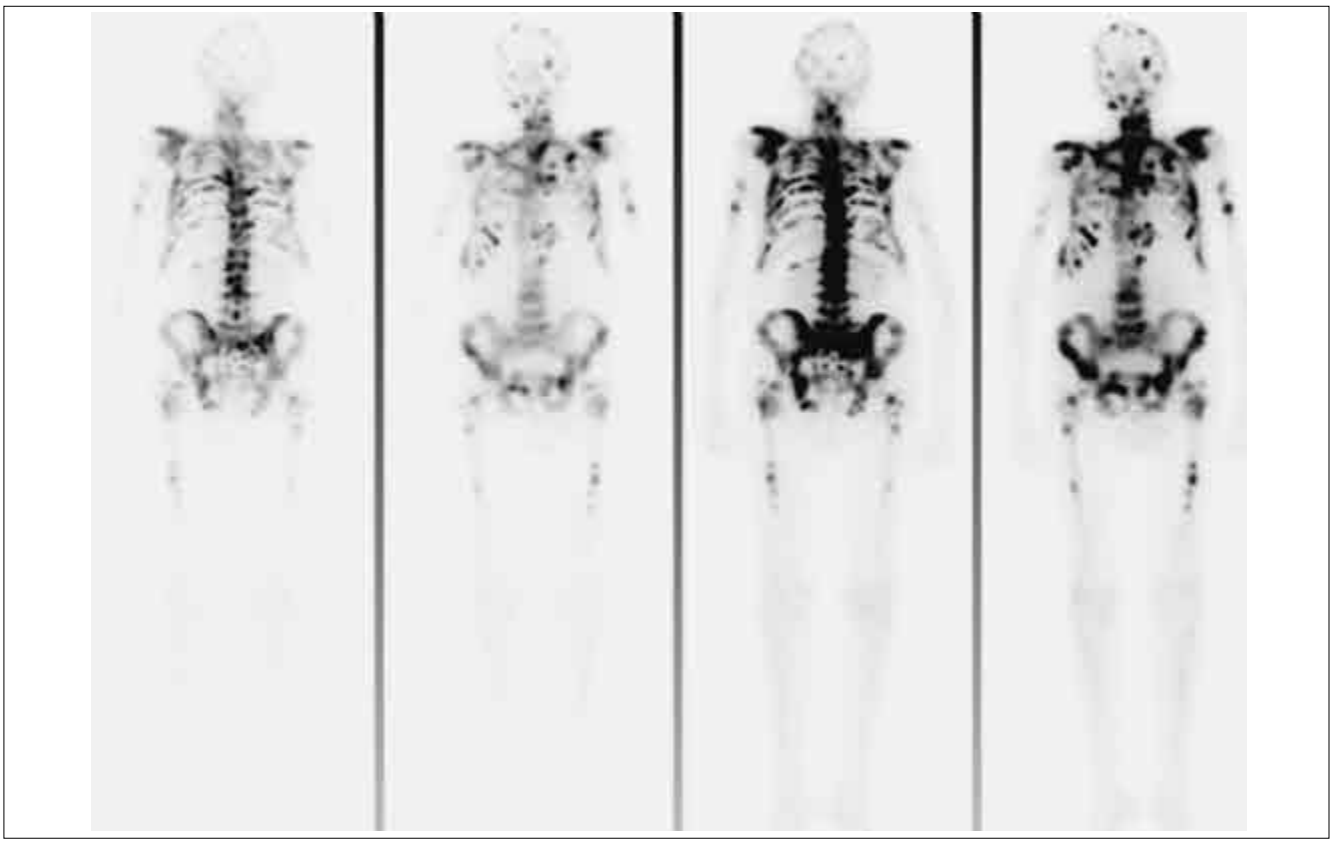

Figure 2 *An MDP scan shows multiple metastases from a prostatic cancer as "hot-spots"*

facilitates this process by diverting blood from the inferior vena cava to the valve-less vertebral venous plexus. Initially, tumour seedlings grow within the bone medullary cavity whilst the surrounding bone is re-modelled either by osteoclastic or osteoblastic process. The relationship of the degree osteoclastic and osteoblastic activity depends on the type of tumour and location of the metastatic deposit within the bone. The relationship between osteoblastic and osteoclastic activity determines whether a predominant lytic, sclerotic, or mixed pattern is seen on radiographs and CT [17, 18]. RNBS is an integral part of cancer staging, especially carcinoma of the lung, breast and prostate. It is an extremely sensitive technique as has been shown by several reports [19-22].

Although the majority of patients with bone pain and primary malignancy have bone metastases, only 25%-45% show asymptomatic metastatic bone disease. Generally, bone metastases show increased radioisotope uptake in areas of osteoblastic reparative activity in response to tumour osteolysis. The increased focal activity in the bones is random with varying sizes and shapes [19-21]. See Figures 1, 2, 3 & 4.

Foci of enhanced isotope uptake may occur in several non-metastatic bone diseases, but it is often possible to distinguish these from bone metastases by their distribution, location and the extent of isotope uptake (Figures 5 & 6). For example, with a rib fracture, the isotope activity has a linear distribution. In osteoporosis, an H-shaped sacral uptake pattern, the so-called Honda sign, suggests an sacral insufficiency fracture (Figure 7). In arthritic patients, increased activity is noted in the distribution of joints (such as the facet joints, hips, knees, hands and wrists). In arthritic joints, increased activity is generally present on both sides of the joint, which is unusual in metastatic bone disease [20].

In diffuse metastatic bone disease, the whole of the delivered dose of the radionuclide may

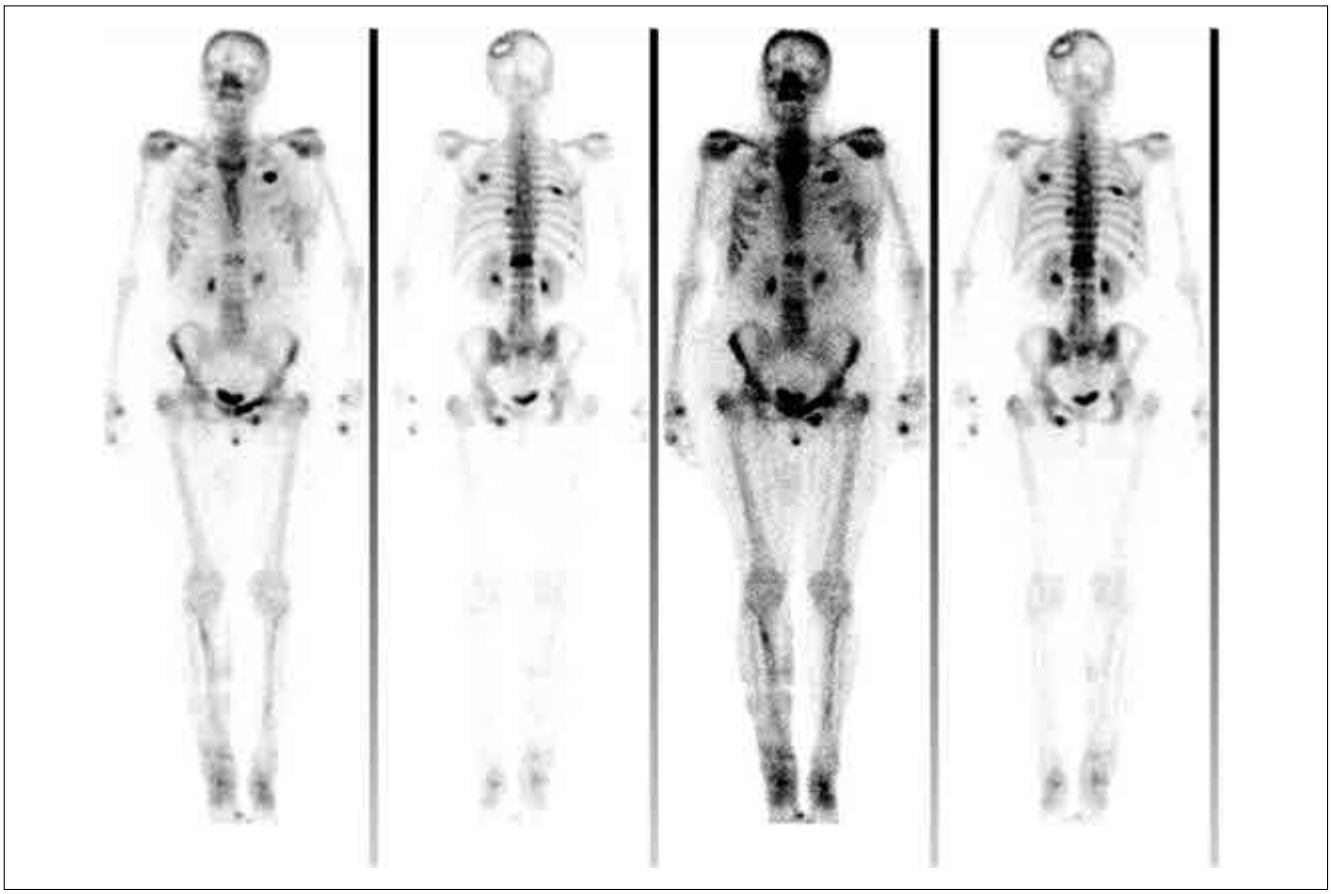

Figure 3 *An MDP scan shows both photon-deficient and "hot" multiple metastases from a prostatic cancer*

accumulate in the skeleton leaving little activity if any in the soft-tissue and the renal tracts. This results in intense isotope activity in the axial skeleton giving rise to a 'punched out' appearance of the bones referred to a 'superscan' [19-21] as shown in Figure 8.

The differential diagnosis of a 'Superscan'' includes metabolic bone disease where the enhanced isotope uptake is much more uniform with involvement of the appendicular skeleton and the intense calvarial activity is out of proportion to the activity in the rest of the skeleton [20].

Whilst the majority of bony metastases tend to be generally multiple solitary bone metastases may occur particularly in the spine where confusion with degenerative change may occur. In this scenario, Single photon emission computed tomography (SPECT), is useful in arriving at a correct diagnosis. SPECT imaging is invaluable when looking at complex structures such as the spine [23-24]. SPECT is useful as it allows multiplanar reconstruction and 3D images facilitating the location and characterization of bone lesions [25].

Benign activity is often present in osteophytes and the facet joints in the older population. Unlike spinal metastases osteophytes often extend beyond the vertebral body. Any confusion caused can frequently be clarified by SPECT images. Spinal bone metastases often occur within the vertebral body or spinal pedicles. Activity within the vertebral body has a wider differential and may be due to neoplasm, trauma or infection [23-26].

Whilst most metastatic bone deposits show enhanced bone activity, some metastases

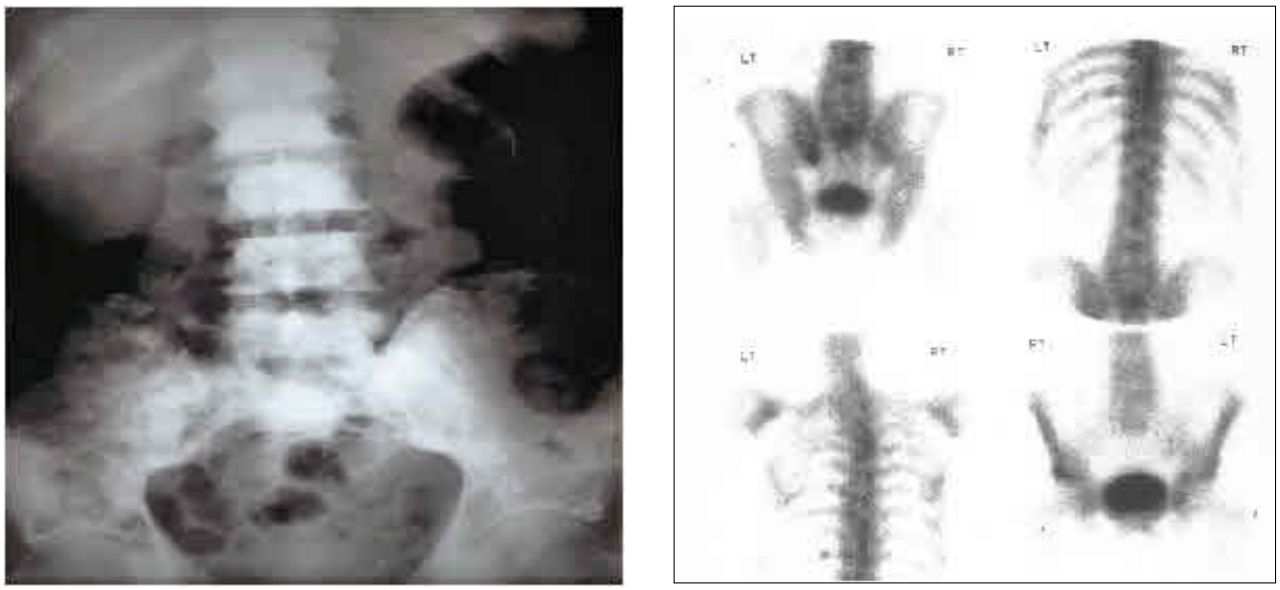

Figure 4 *A conventional radiograph (left) shows features of osteoblastic metastases from a prostatic adenocarcinoma. The MDP scan (right) shows patchy non-uniform activity*

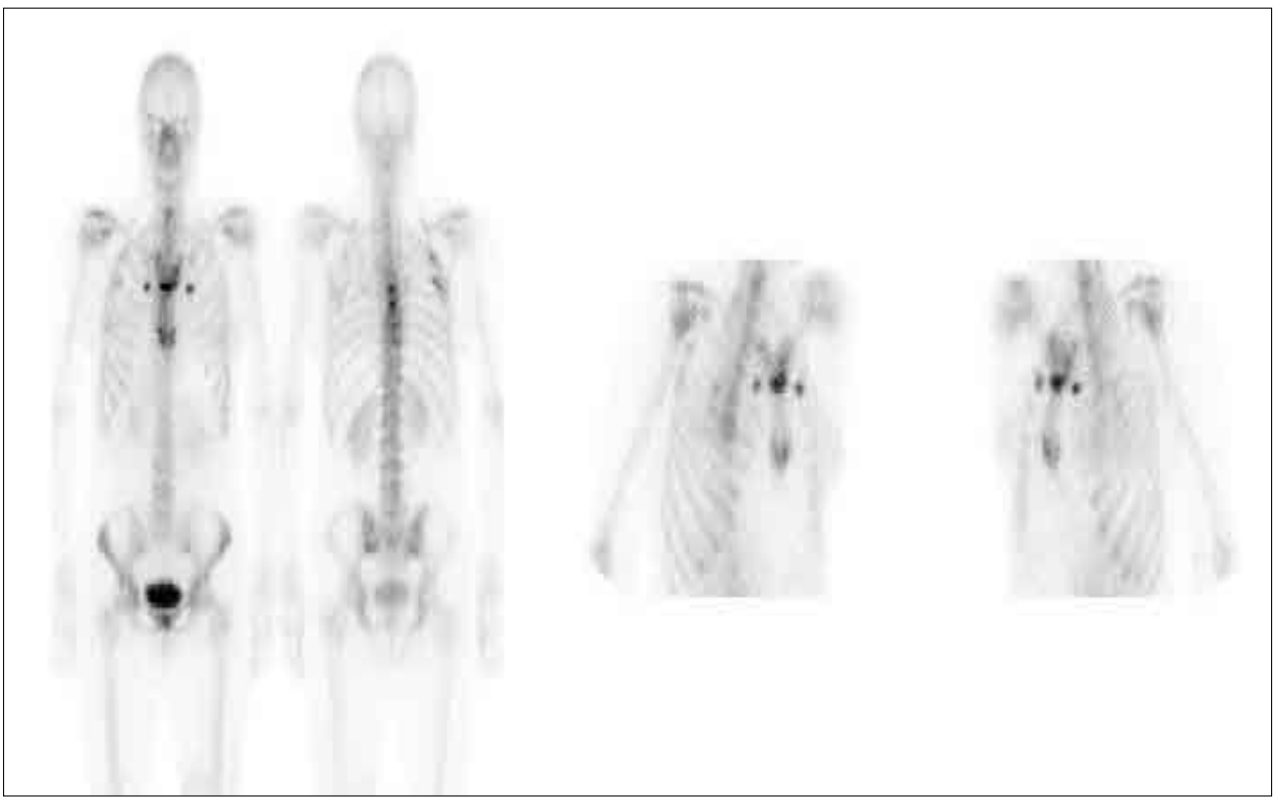

Figure 5 *This patient was involved in a road traffic accident and an MDP scan followed complaints of pain over the thoracic wall. The chest x-ray was normal. The MDP scan shows activity over the angle of Louis and several ribs due to fractures. These hot spots need to be differentiated from metastases; however, neither the distribution pattern of activity nor the clinical context are not suggestive of metastases in this case*

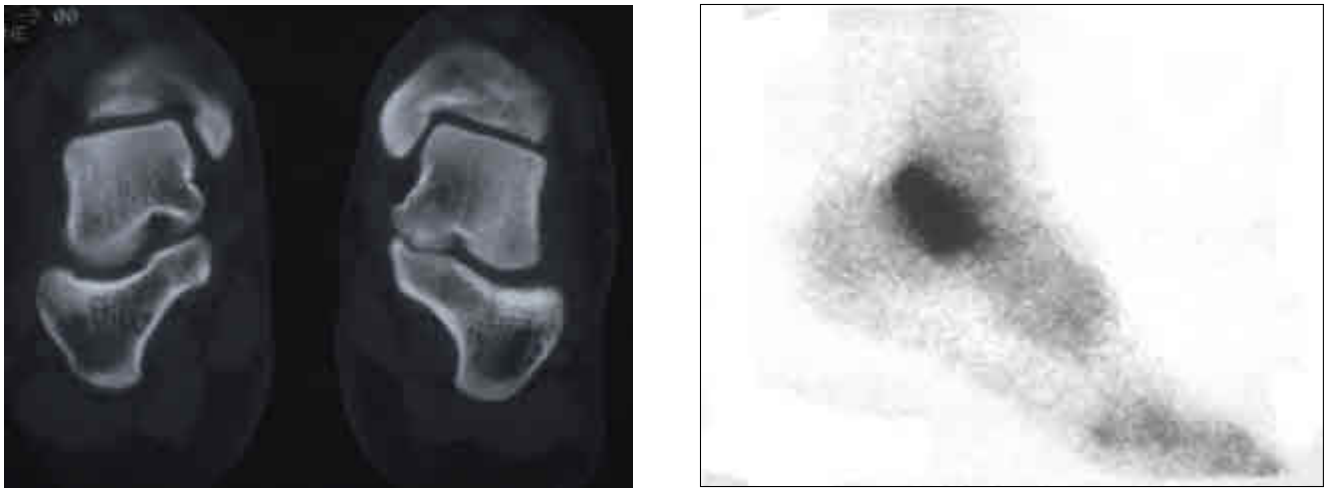

Figure 6 *Tarsal coalition is an elusive cause of heel and tarsal pain. The coalition may be bony, cartilaginous or fibrous. Because of the abnormal stresse and strain over the involved bones there is usually intense activity of MDP in the area as in this case of a cartilaginous union of the talus and calcaneum. CT or MRI usually differentiates between the various types of union*

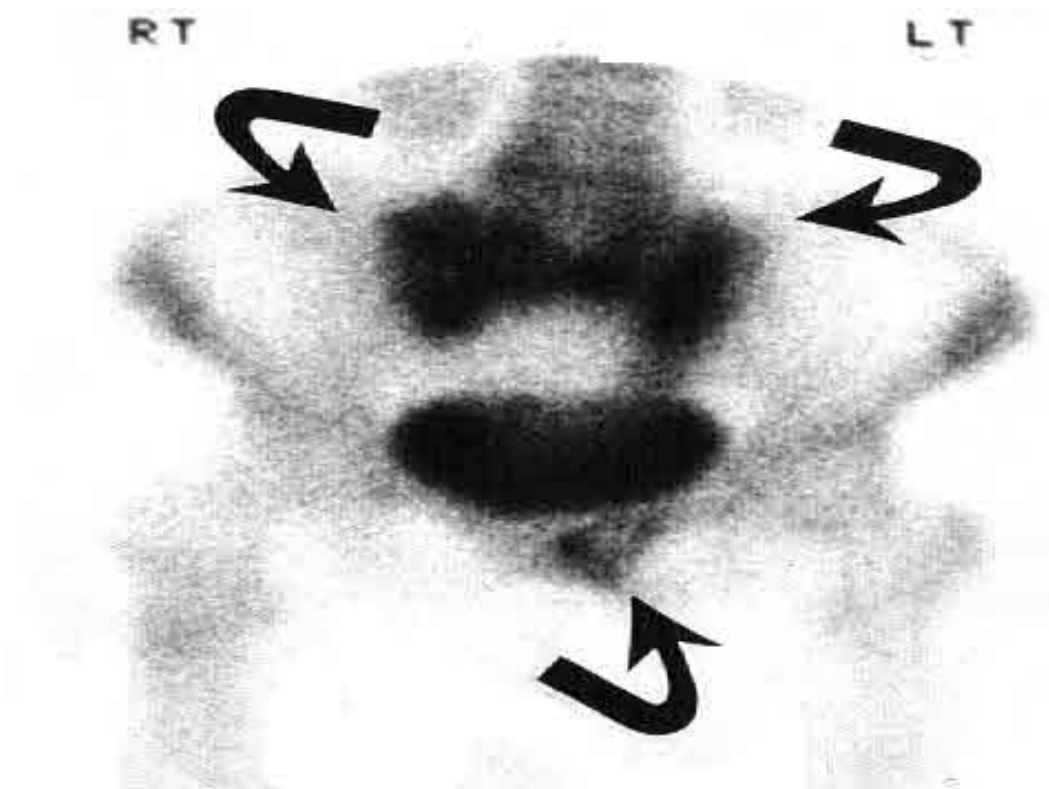

Figure 7 *Sacral insufficiency fractures in the elderly can be an illusive cause of pain over the lower back. Because of the osteoporotic bones these fractures may not be seen on conventional radiographs. RNBS or MRI is the imaging of choice. This MDP scan show intense activity over the sacrum in the form of an H, the so-called Honda sign. Also note the activity over the pubic rami due to fractures*

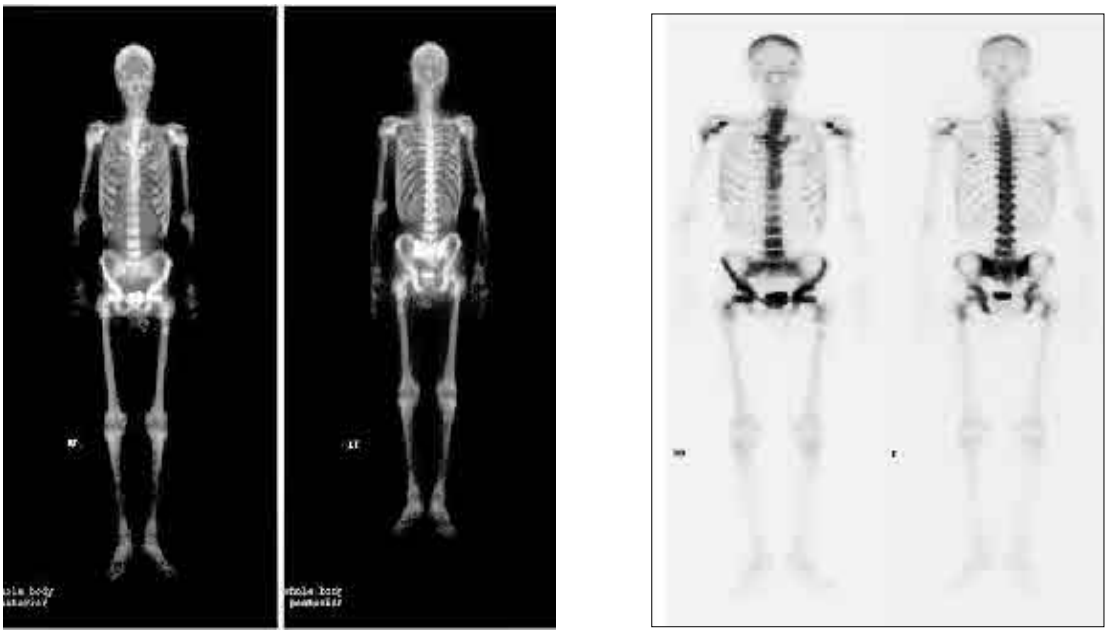

Figure 8 *In diffuse metastatic bone disease the whole of the delivered dose of the radionuclide may accumulate in the skeleton leaving little activity if any in the soft tissue and the renal tracts. This results in intense isotope activity in the in the axial skeleton giving rise to a 'punched out' appearance of the bones referred to a 'superscan'*

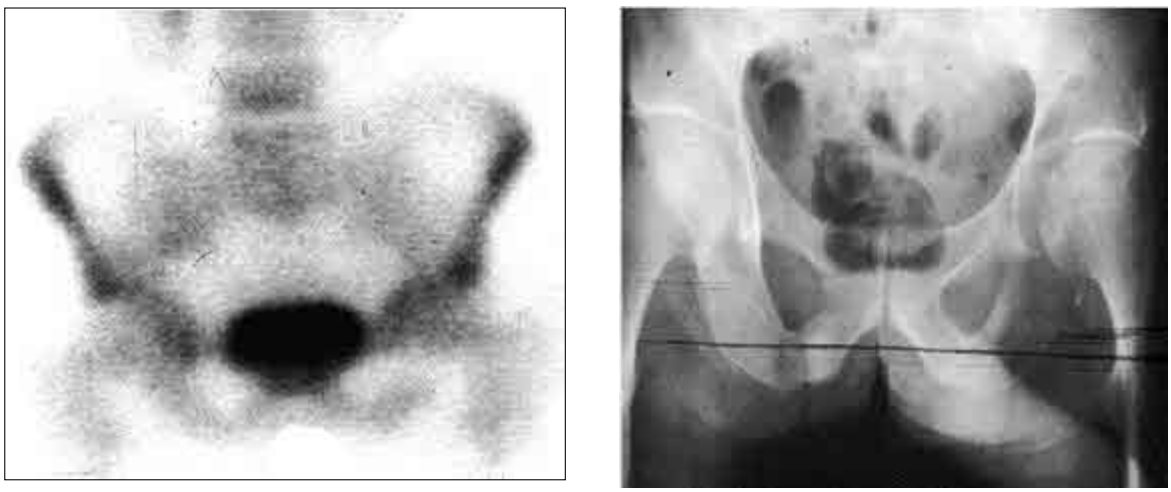

Figure 9 *Whilst most bone metastatic deposits show enhanced bone activity some metastases may be photon-deficient. These are usually aggressive secondary bone tumours*

may be photoeficient (Figure 9). Photodeficient bone lesions have a wider differential such as plasmacytoma, lymphoma, acute phase of avascular necrosis, eosinophilic granuloma and rarely, osteomyelitis [26] (Figures 10 & 11). Not all skeletal eosinophilic granuloma foci are photon deficient (Figure 12). Late phase of radiation osteitis may also present as a photon deficient lesion. Radiation osteitis may follow radiation therapy for tumours such as lung and breast. Initially there is enhanced isotope uptake in the irradiated field due to hyperaemia; the

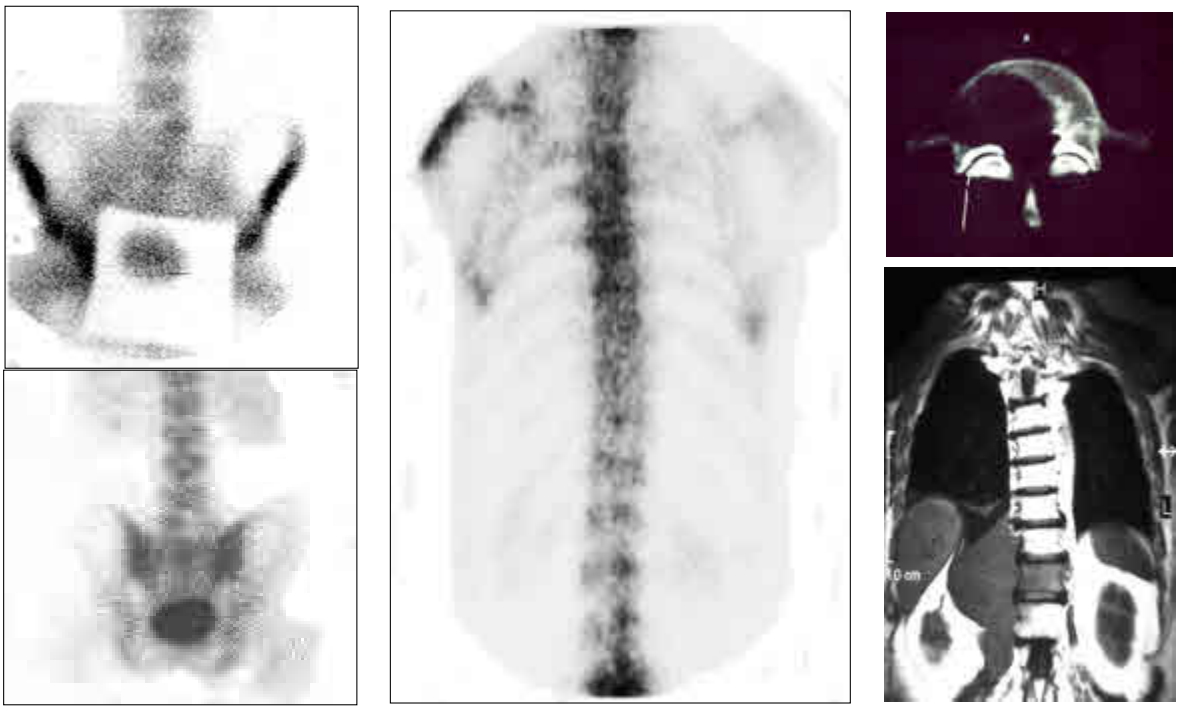

Figure 10 *Photodeficient bone lesions have a wider differential such as plasmacytoma, lymphoma, acute phase of AVN and rarely osteomyelitis. Here we show a plasmacytoma (top row) and a lymphoma (bottom row). Examples show superiority of CT and MRI in depicting photon deficient lesions*

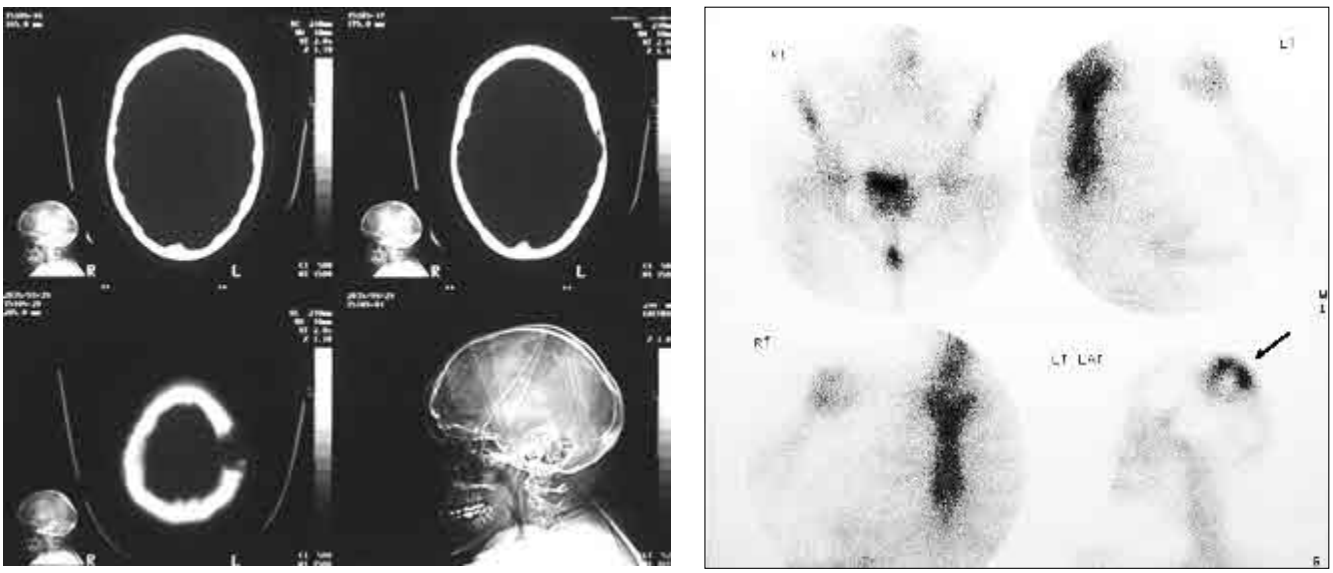

Figure 11 *Eosinophilic granuloma is yet another cause of skeletal photon deficient lesion. Here in this patient an axial CT scans shows a geographic lytic lesion in the parieto-occipital region of the skull within the diploic space. An MDP scan (bottom) show a solitary lesion within the skull as photon-deficient mass surrounded by a rim of intense activity. Biopsy results confirmed the diagnosis of eosinophilic granuloma*

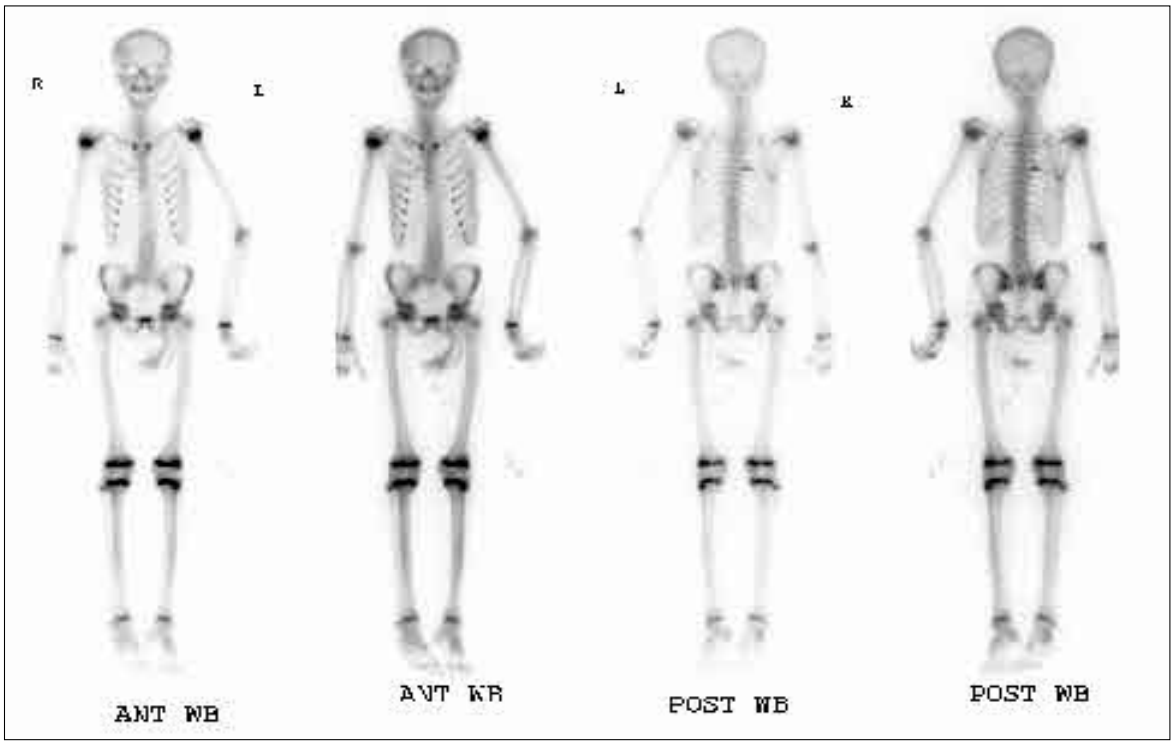

Figure 12 *Not all eosinophilic granulomas are photon-deficient as this young patient with histiocytosis x shows intense activity in one of the posterior ribs on the right*

activity generally peaks at 2-3 months following treatment. Decreased activity in the irradiated field can be identified approximately six months following treatment; Furthermore, chemotherapeutic agents and hormonal treatment of cancers affect the degree of isotope uptake [26].

An increased activity may be observed in patients with known metastatic bone disease as a response to hormonal treatment, which indicates a healing process rather than disease progression. This enhanced activity in pre-existing bone metastases indicates a healing process generally seen within three months following initiating treatment and is termed the 'flare' phenomenon. However, progressive increase in activity in existing lesions and appearance of a new crop of lesions beyond six months is indicative of cancer progression [27, 28].

Trauma

RNBS is a highly sensitive technique in the detection of bone turnover and bone injury and is an excellent tool in the detection of stress fractures where conventional radiographs may be falsely negative. (Figures 13 &14)Cortical stress fractures show focal enhanced isotope uptake at the site of injury and can be easily distinguished from the more diffuse uptake as seen in the re-modelling stage and micro-damage repair seen in conditions such as in medial tibial stress syndrome [29] (Figure 15).

Stress fractures are a special case where RNBS outperforms conventional radiography. However, the imaging of choice in bone trauma remains conventional radiography occasionally aided by CT where joints are involved and 3D reconstructions are important for clinical management. RNBS comes into its own, when the history of trauma is equivocal or the radiographs are negative in a symptomatic patient with a clear history of trauma. RNBS show enhanced activity at the fracture site within 24 hours following trauma. However, in elderly patients with osteoporosis, it may take up to 72 hours for increased activity to appear at the fracture site. Therefore, in the elderly patients with a clear

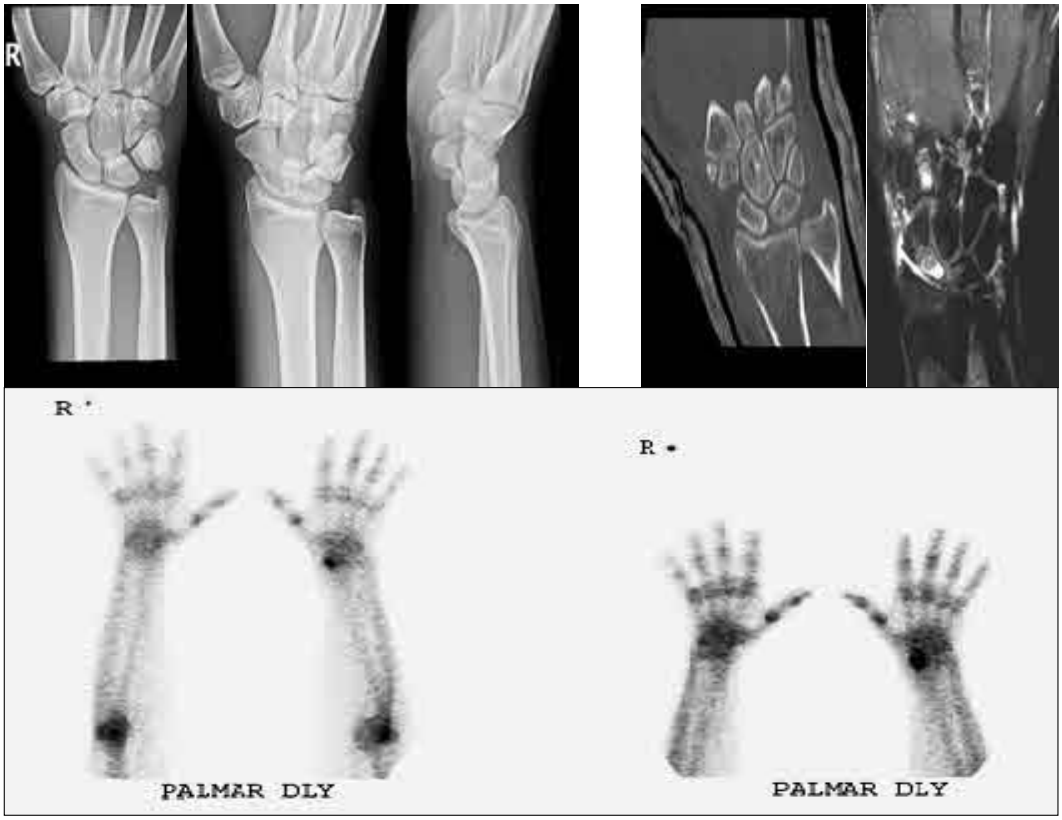

Figure 13 *This 28-year-old man had a fall on the outstretched hand. Conventional radiographs and CT scans were normal. An MDP scan performed 48 hours later showed no features of a fracture However, an MRI scan performed after about 10 days due to persistent pain shows a fracture of the waist of the scaphoid with oedema of the proximal pole of the scaphoid. This series of investigations shows the limitations and advantages of the various modalities when used appropriately*

Figure 14 *This young female athlete had persistent right patellar pain following a knock on the knee. Conventional radiographs were normal. In view of continuing symptoms and as the patient was keen to go back to training, an MDP scan was performed, which shows intense activity both sides of the right knee joint and the patella. An MRI scan (not shown) a day later confirmed a right patellar stress fracture*

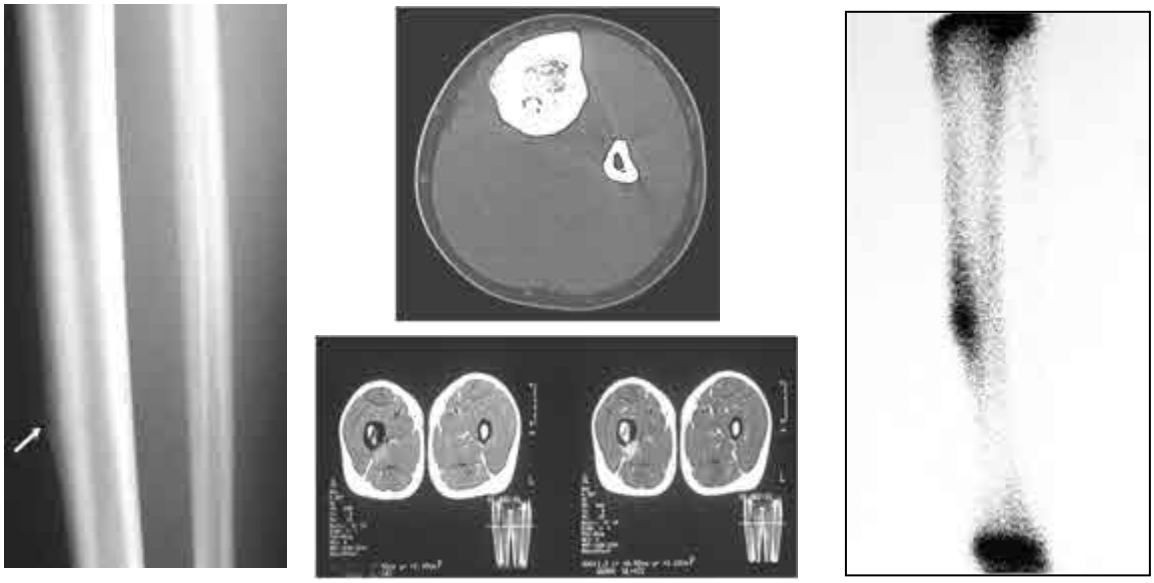

Figure 15 *MDP scans can differentiate tibial stress fractures from shin splints. Hyperperfusion is usually present in acute stress fractures whilst delayed images show fusiform enhanced activity within the tibia at the junction of the middle lower diaphysis of the tibia as in this case. Conventional radiograph of one tibia shows a break in the anterior cortex (top right). Coronal reconstructions of CT scans show bone marrow oedema at the fracture site*

history of injury with an initial negative RNBS who remain symptomatic, it is justified to repeat the scan at 72 hours or preferably schedule bone scanning not before three days. It may take 6-24 months for isotope activity to return to normal following a fracture, but some fractures sites may never return to normal activity [30].

Athletes are particularly pre-disposed to stress fractures and lower limb trauma. Conditions that may incapacitate athletes include enthesopathies, stress fractures, "shin splints" and plantar fasciitis. All these entities are MDP-avid. The differentiation of stress fracture from shin splints is important because their treatments are very different [31-33] (Figures 15, 16, 17).

RNBS can differentiate tibial stress fractures from shin splints. Hyperperfusion is usually present in acute stress fractures whilst delayed images show fusiform enhanced activity within the tibia at the junction of the middle lower diaphysis of the tibia [34]. Shin splints are the result of excessive strain of the tibialis and soleus muscles giving rise to periostitis at the muscle insertions. Hyperperfusion does not occur and the blood pool images are usually normal with shin splints. However, delayed bone images show longitudinally oriented linear activity in the region of the posterior cortex of the tibia [35].

Avascular necrosis is the term applied to osteonecrosis of the epiphysis. Ischaemic cell death and necrosis are the result of a reduced blood supply to the bone, which in turn can result from an intrinsic abnormality in the blood vessel supplying part of the bone, an extrinsic abnormality, or a combination of both. The primary cause of ischaemic compromise is either interruption of the arterial blood supply or obstruction of venous outflow from an enclosed joint such as the hip resulting in oxygen deprivation, which leads to the death of osteocytes. Vascular insufficiency for as little as 12 hours can cause osteonecrosis. The death of bone does not alter its radiographic opacity. Living bone becomes osteoporotic as a result of osteoclastic bone resorption secondary to reactive hyperaemia. Dead bone cannot undergo

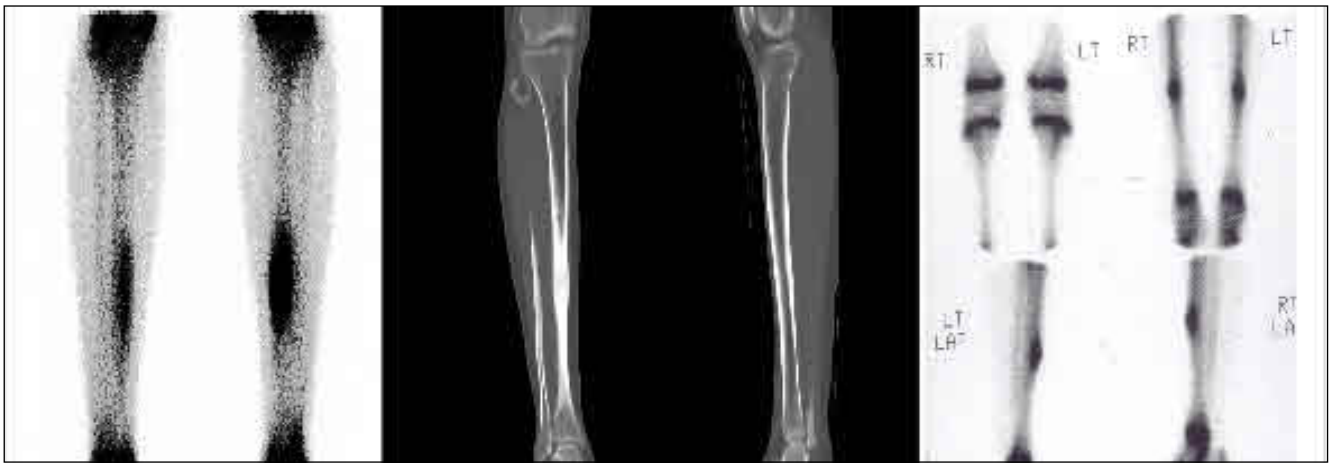

Figure 16 *Athletes are particularly predisposed to stress fractures and lower limb trauma, shin splints and pars fractures. Here is an example of shin splints (left). An MDP scan did not show hyperperfusion and the blood pool images were normal. However delayed bone images showed longitudinally oriented linear activity in the region of the posterior cortex of the tibia. The right image is that of a 14-year-old boy who presented with bilateral shin pain following strenuous athletic activity. Conventional radiographs were normal (middle). Because of persistent pain a RNBS was initiated which shows fairly intense fusiform foci of increased activity in the mid shafts of both tibia due to bilateral stress fractures*

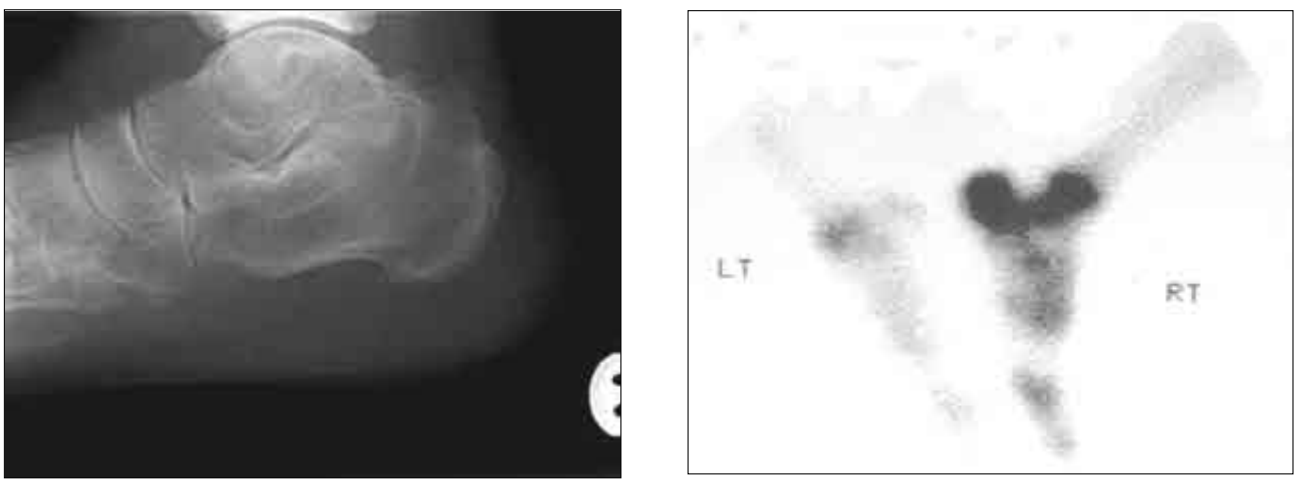

Figure 17 *MDP bone scan shows a stress fracture of the calcaneum in a patient with a normal x-ray of the foot*

resorption; therefore, it appears relatively more opaque.

Repair of ischaemic bone occurs in two phases. First, when dead bone abuts live marrow, capillaries and undifferentiated mesenchymal cells grow into the dead marrow spaces, while macrophages degrade dead cellular and fat debris. Second, mesenchymal cells differentiate into osteoblasts or fibroblasts. Under favourable conditions, layers of new bone form on the surface of dead spongy trabeculae. If sufficiently thickened, these layers may increase the radiopacity of the bone; therefore, the first radiographic evidence of previous necrosis may be patchy sclerosis resulting from repair. In the acute phase of vascular compromise, no radionuclide can be delivered to the compromised bone. RNBS at this stage may show a photo-

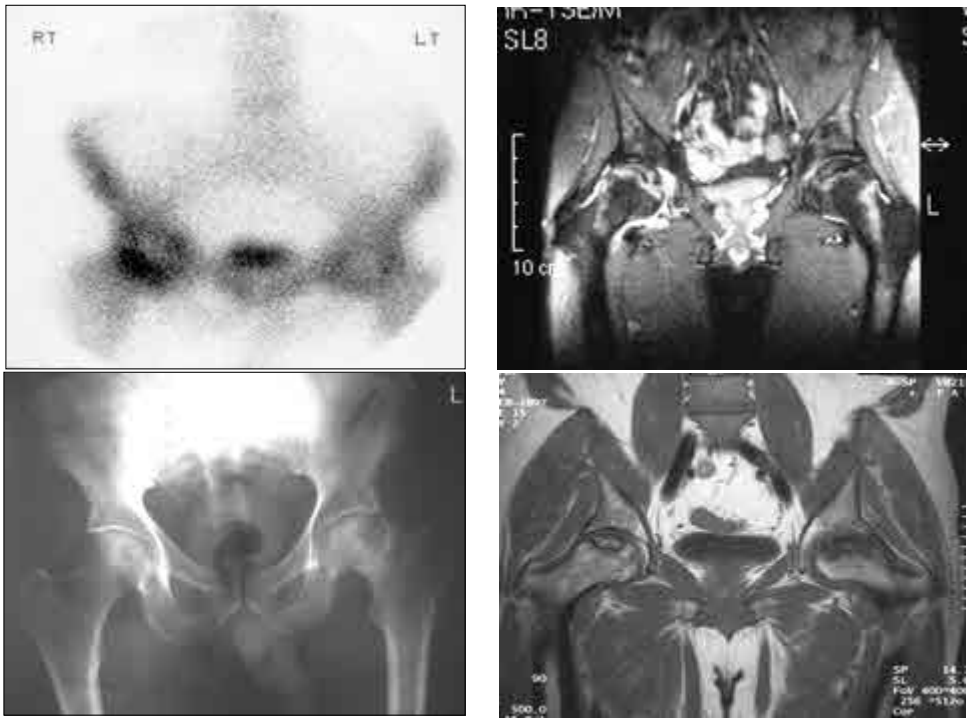

Figure 18 *Bilateral AVN of femoral heads shown on different modalities: all complimentary and important for clinical management*

-paenic defect in the involved bone. Following revascularization, there is intense osteoblastic activity depicted by intense isotope uptake. Finally, when bone repair is complete, the isotope activity returns to back to normal [31] (Figure 18).

Spontaneous osteonecrosis may occur in the elderly characterized by a sudden onset of knee pain with normal radiographic findings. RNBS finding in spontaneous osteonecrosis is focally increased isotope uptake, usually in the medial femoral condyle, although the lateral femoral condyle and tibia may also be involved [36]. Radionuclide imaging is superior to conventional radiography in the detection of AVN but is less sensitive than MRI, which is currently the examination of choice if available [37] (Figure 19).

Spondylolysis represents a stress fracture, which is the most common overuse back injury in sports and, is a common cause of back pain in adolescents, being particularly common in young cricket fast bowlers. The fracture occurs in the pars interarticularis of a vertebra. Conventional radiographs, CT, MRI and RNBS may be used to achieve a diagnosis. However, controversy surrounds the designation of which one of these tests is the most useful in the evaluation of spondylolysis. When initial radiographs are negative, a positive planar RNBS may serve to initiate other imaging such as SPECT. Using RNBS, false-positive diagnoses of spondylolysis include infection and osteoid osteoma. Healing stress reactions also may show increased activity in the pars interarticularis. On planar imaging, increased activity in the pars interarticularis may be mistaken for osteoarthritis in the facet joints. False-negative diagnoses can occur in the setting of chronic spondylolysis. The sensitivity and specificity of MRI in the diagnosis of spondylolysis is high, so when oedema in the region of the pars is identified, no further imaging is required. This applies to stress reaction in the pars, as well as to fractures. However, false-positive MRI findings may occur due to active facet joint arthropathy. A false-negative MRI of the lumbar spine may

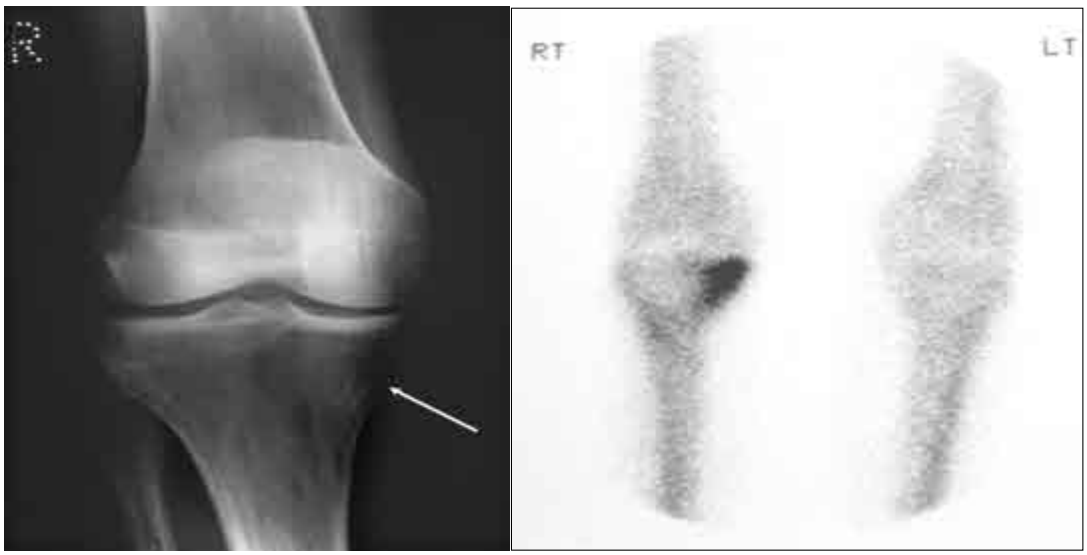

Figure 19 *This is an example of spontaneous osteonecrosis of the tibia, which occur in the elderly characterized by a sudden onset of knee pain with normal radiographic findings. Spontaneous osteonecrosis is characterized by focally increased isotope uptake, usually in the medial femoral condyle, although the lateral femoral condyle and tibia may also be involved. MDP is superior to conventional radiography in the detection of AVN but is less sensitive than MRI, which is currently the examination of choice if available*

be seen in the setting of facet joint arthropathy with facet osteophytes that obscure the pars defect [38-42] (Figure 20).

Infection

Imaging plays an important role in the diagnosis of osteomyelitis (Figures 20-22). Imaging is initiated with plain radiographs of the affected area. Current imaging recommendations include plain radiography followed by 3-phase bone scanning and/or MRI, if available. Although osseous changes become apparent on conventional radiographs 5-7 days into the disease process, plain radiographs are useful in ruling out other causes of bone pain such as stress fractures. Plain radiography and radionuclide bone scanning greatly aid early diagnosis in cases of acute osteomyelitis. Plain radiography is useful for excluding other conditions, whereas RNBS reveals evidence of inflammation at the site of bone pain. RNBS is a highly sensitive (>90%) modality in the diagnosis of osteomyelitis. RNBS is performed as 3-phase study to determine areas of infection and bone remodelling dependent on local blood flow. The sensitivity of RNBS is often helpful when the exact site and extent of the infection is not known [43]. The three phases of RNBS reflect the following processes: the first phase determines the relative amount of blood flow to the area of interest, the second or blood pool phase depicts local hyperaemia, and the third phase or delayed phase reflects the rate of bone turnover in the focus of interest. Classically, the three phases of RNBS show focal hyperperfusion, focal hyperaemia and focal increase in isotope uptake. Other conditions that are associated with an increased bone turnover such as bone tumours, fractures and joint neuropathy can mimic osteomyelitis on 3-phase RNBS. To improve specificity, other types of radionuclide imaging may therefore be required, including gallium-67 citrate imaging for suspected spinal osteomyelitis or indium-111–labelled autologous leukocytes for suspected appendicular osteomyelitis [43] (Figures 21 & 22).

RNBS is often used to evaluate painful prosthetic joints. RNBS is not affected by the presence of metallic hardware and is therefore useful for evaluating the painful prosthesis.

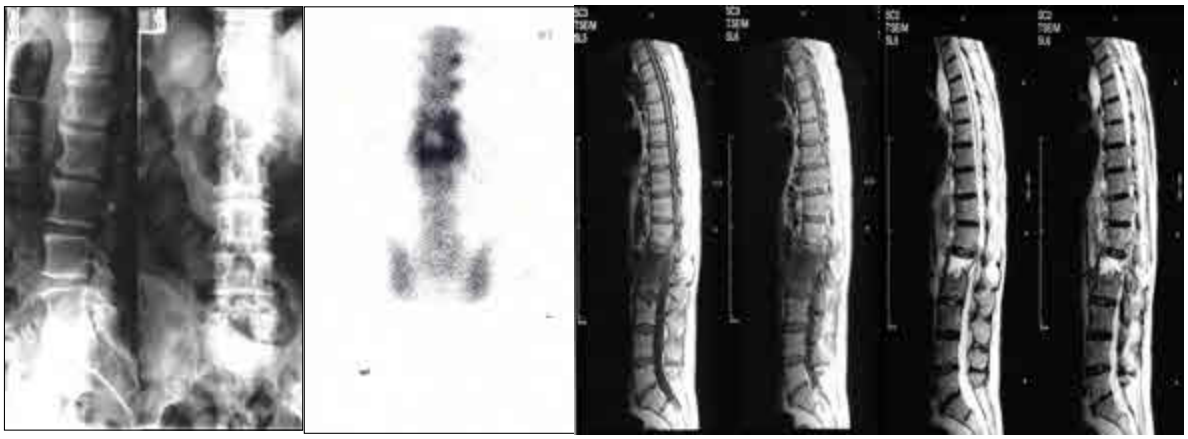

Figure 20 *Differentiation between degenerative diseases can be difficult with osteoarthritis and osteomyelitis in the elderly on conventional radiographs. This 81-year-old had persistent upper back ache with raised inflammatory markers. The conventional radiograph (left) shows bridging osteophytes at LI/2 level interpreted as osteoarthrosis. With continuing complaint from the patient, an MDP scan (middle) was performed, which shows an active bone lesion in the spine with the CT scan (not shown) and MRI (right) showing fragmentation of the vertebral body and oedema of the disc. The findings are highly suggestive of infective discitis*

useful for evaluating the painful prosthesis. Despite an accuracy of only 50%–70%, RNBS is used as a screening test since a negative scan essentially excludes prosthetic complications such as loosening or infection (Figure 23). However, the significance of increased isotope uptake at the site of the prosthesis remains uncertain. The addition gallium-67, improves the accuracy of radionuclide imaging to 70%–80%. The accuracy of combined leukocyte-marrow imaging, of 90%, is the highest among available radionuclide studies. Leukocyte-marrow imaging is not without limitations as problems may arise with *in-vitro* labelling [44].

Metabolic bone disease & allied pathologies

RNBS is not an effective method for detecting or ruling out most osteoporotic diseases, unless complicated by fractures. However, RNBS is either better or supplements conventional radiographic findings in evaluating the focal complications of metabolic bone disease, including fractures, microfractures, stress fractures, vertebral wedge fractures, Looser zones, AVN and acute infarction. RNBS provides a valuable imaging modality in investigating hypercalcaemia, because the major cause of this abnormality is skeletal metastatic malignancy. In defective bone mineralization due to hyperparathyroidism or osteomalacia, there is general increase in skeletal isotope uptake, which occurs more frequently than abnormalities detected on conventional radiography. It is important to note that a normal RNBS does not rule out metabolic bone disease. Blood biochemistry is more reliable in detecting primary hyperparathyroidism but biochemical levels are not as reliable in renal osteodystrophy where RNBS is more helpful in assessing the severity of skeletal involvement (Figure 24). Several quantitative radionuclide methods have been explored for the assessment of metabolic bone disease, which have not been widely accepted. RNBS is valuable in other systemic diseases such as hypertrophic pulmonary osteoarthropathy (Figures 25 & 26), hyperostosis frontalis interna (Figure 27), Paget's disease (Figures 28 & 29), fibrous dysplasia, sympathetic dystrophy and sickle cell disease [45] (Figure 30).

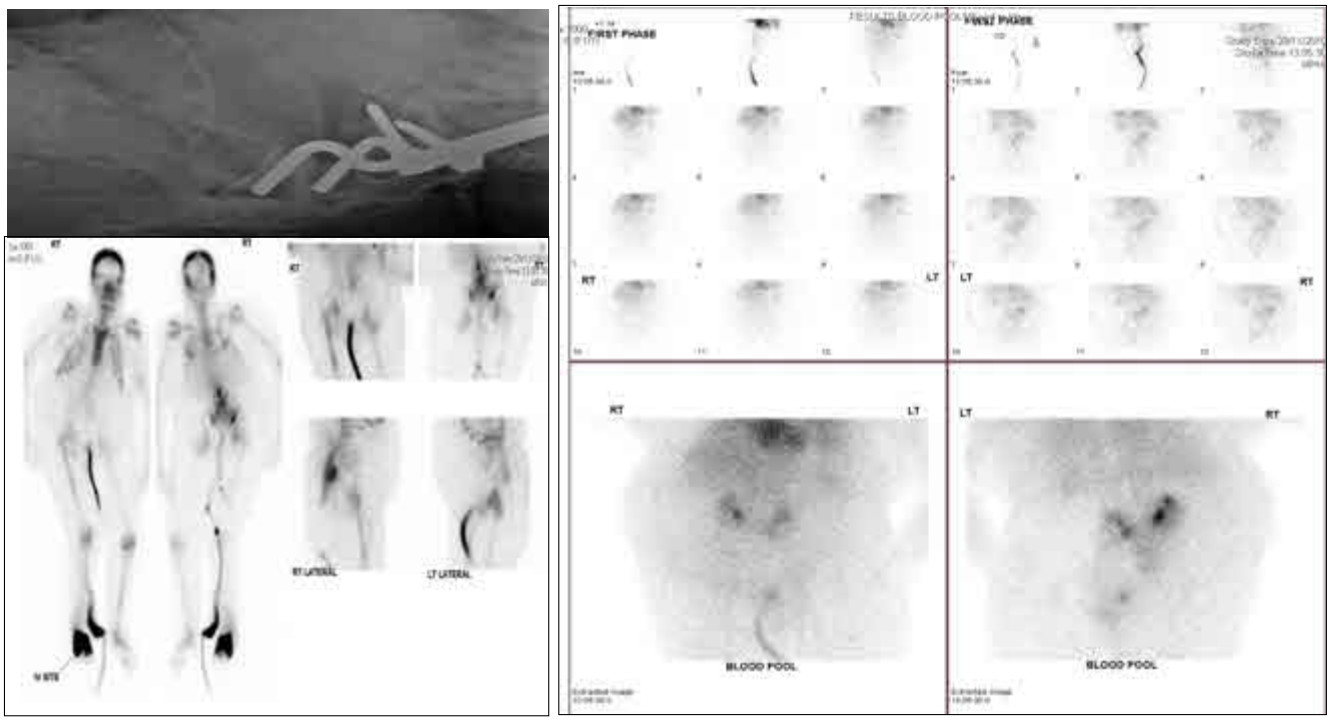

Figure 21 *Diagnosis of vertebral osteomyelitis can be difficult in the presence of metal works. A normal RNBS excludes the presence of infection whilst a "hot scan" may not indicate an infection. Usually other radionuclide agents such as Gallium-67 and labelled white cells may be more informative*

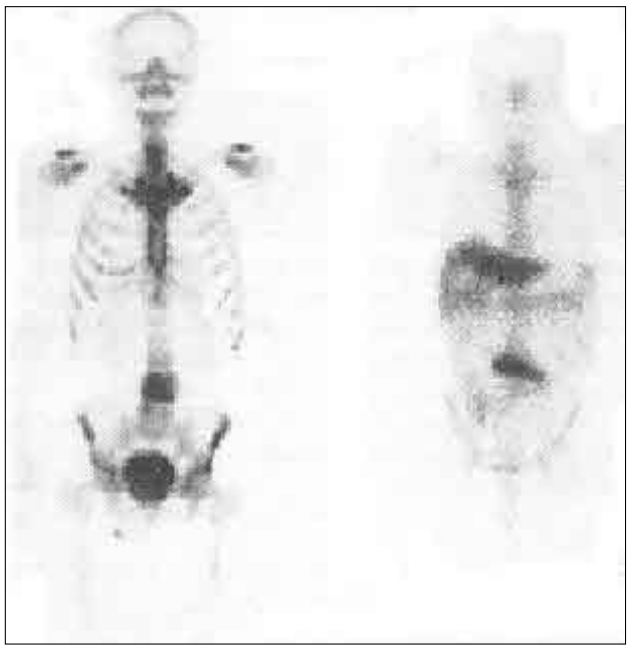

Figure 22 *An example of vertebral osteomyelitis shown on MDP (left) and a labelled white cell scan (right). The labelled white cell scan shows spread of the disease to the right psoas*

Paget's disease is a focal or multifocal metabolic skeletal disorder of unknown aetiology. The disease occurs with variable severity from very focal to more diffuse skeletal disease often asymptomatic but severe complications may occur such as bone pain, hypercalcaemia, high out cardiac failure and sarcomatous change. It is characterized by increased resorption, disordered remodelling and non-uniform mineralization of bone. The involved bones undergo hypertrophy, become irregular and deformed. RNBS shows intense isotope uptake in the affected bones except for osteoporosis circumscripta where there is intense activity confined to the margins of the lesion [46-48].

Hypertrophic osteoarthropathy represents a symmetrical cortical periostitis of the four limbs, mainly localized to the phalanges and the terminal epiphyses of the long bones of the forearm and leg, sometimes extending to the proximal ends of the limbs and the flat bones. The condition may be primary, usually congenital, but most cases are secondary to

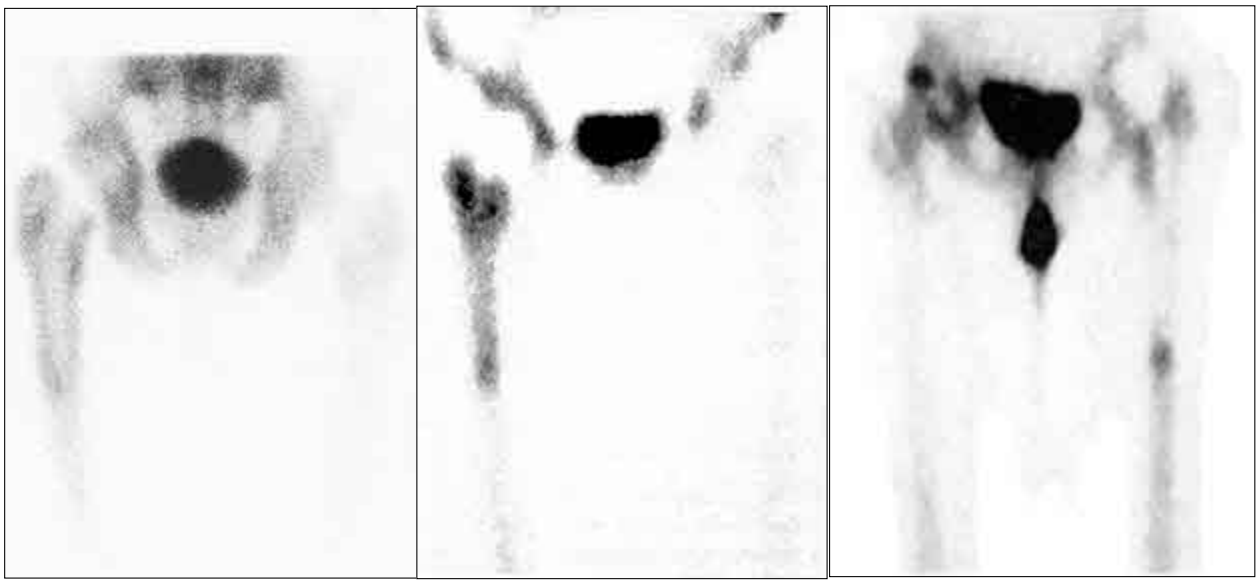

Figure 23 *MDP scans are often used to evaluate painful prosthetic joints. RNBS is not affected by the presence of metallic hardware and is therefore useful for evaluating the painful prosthesis. RNBS is used as a screening test, despite an accuracy of only 50%–70%, because a negative scan essentially excludes prosthetic complications such as loosening or infection. However, the significance of increased isotope uptake at the site of prosthesis remains uncertain. Above we show examples of a normal (left), infected (middle) and loose (right) hip prosthesis*

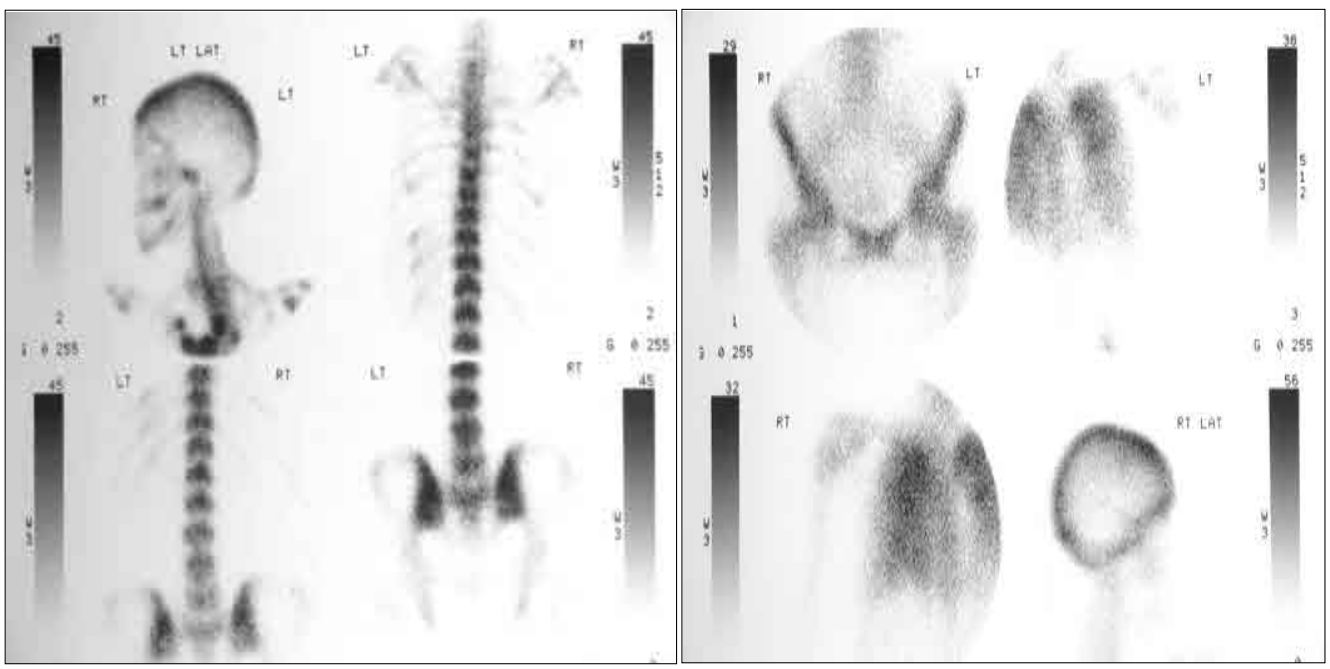

Figure 24 *Examples of primary hyperparathyroidism (left) and renal osteodystrophy (right)*

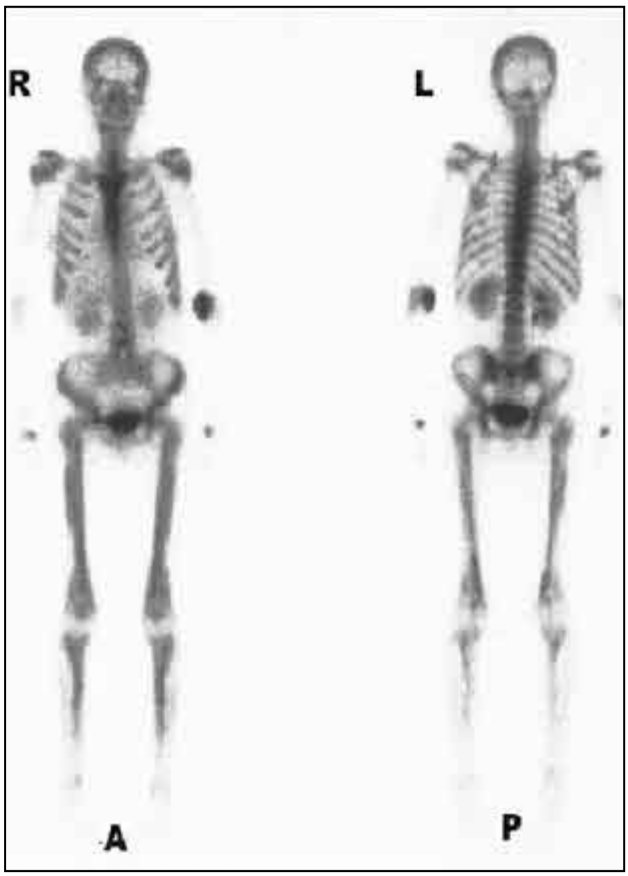

Figure 25 *Hypertrophic osteoarthropathy represent a symmetrical cortical periosteitis of the four limbs, mainly localized to the phalanges and the terminal epiphyses of the long bones of the forearm and leg, sometimes extending to the proximal ends of the limbs and the flat bones. The most common isotope uptake pattern is nonuniform, irregular cortical activity involving the long bones and giving rise to the "tramline sign"*

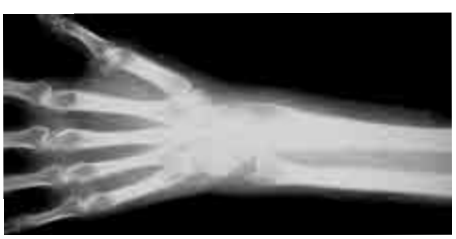

Figure 26 *The radiograph of the hand in the patient in Figure 25 showing extensive periosteal reaction*

intrathoracic tumours, pulmonary diseases, cardiac conditions, and chronic intraabdominal disease. The most common isotope uptake pattern is inhomogeneous and irregular cortical activity involving the long bones known as the so-called "tramline sign" [26, 49].

Reflex sympathetic dystrophy also known as complex regional pain syndrome (CRPS) is a chronic condition characterized by continuous intense pain out of proportion to the severity of the injury getting worse over time. Limbs are the most common effected parts of the body.

Clinical features include dramatic changes in the colour and temperature of the skin over the affected limb or body part, accompanied by intense burning pain, skin sensitivity, sweating, and swelling. RNBS is the imaging modality of choice and provides objective and relatively specific evidence of reflex sympathetic dystrophy in the limbs.

CRPS usually manifests as diffuse, uniformly increased uptake throughout the affected region. Occasionally, CRPS may manifest as a focal abnormality limited to, for example, the hand or knee. Decreased radiotracer accumulation has also been described, especially in children. In some patients who present with acute or subacute pain and vasomotor or neuroregulatory signs or with symptoms, do not demonstrate the classic diffuse increased uptake on delayed RNBS.

The cause of this phenomenon and the relationship of these patients to those with abnormal RNBS remain unexplained. Plain radiography is only 60% sensitive and not specific; when positive, radiographs often show only osteoporosis, occasionally in combination with soft-tissue swelling or diffuse soft-tissue atrophy. No consistent findings have been found in the occasional study done with other imaging modalities, and none of these are suggested in the diagnostic workup [31, 38, 50, 51].

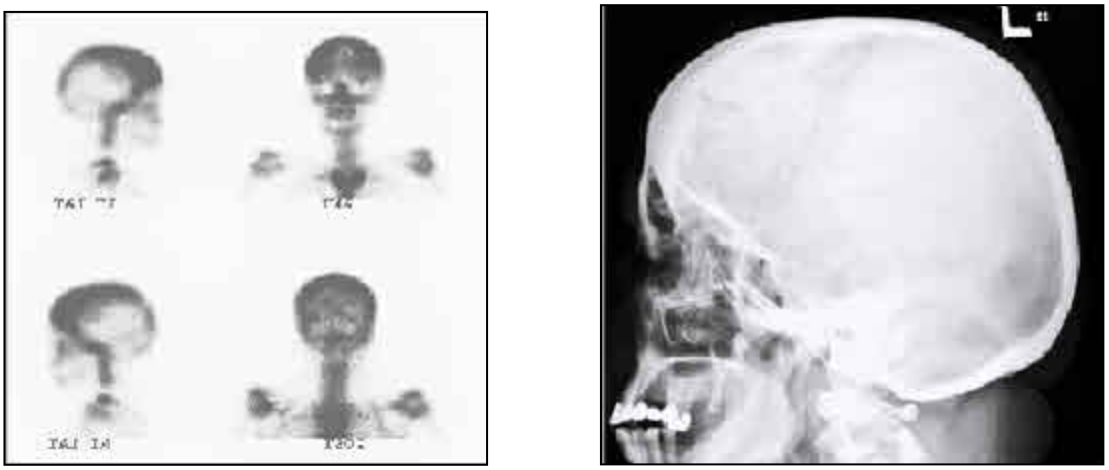

Figure 27 *This 32-year-old lady had an aggressive breast cancer had an MDP scan as a part of staging. The MDP scan (left) shows localised intense activity in the frontal bone. A conventional radiograph (right) shows sclerosis of the frontal bone typical of hyperostosis frontalis interna*

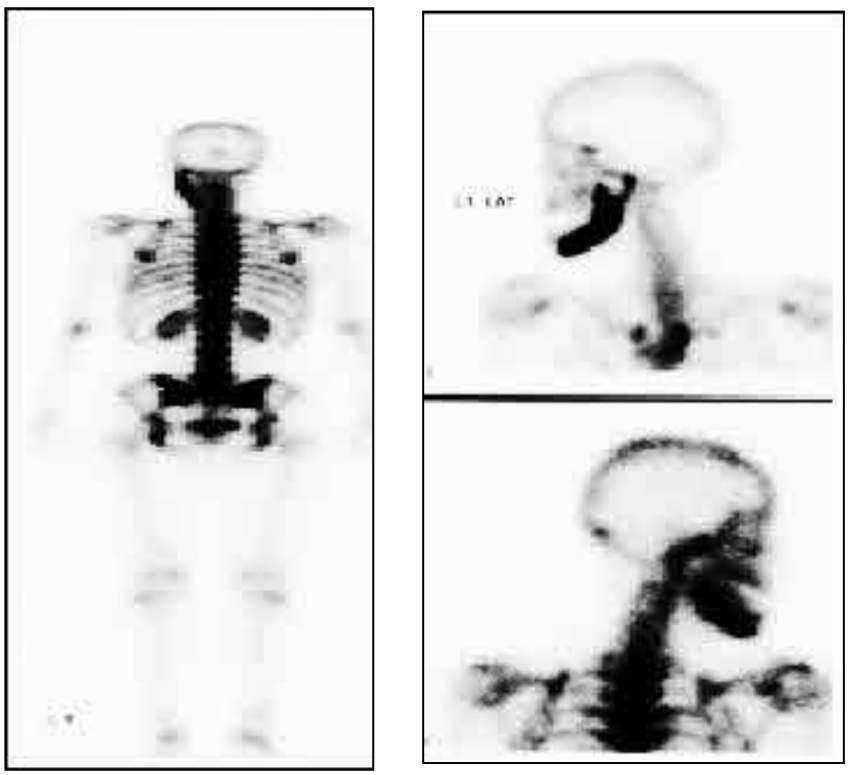

Figure 28 *This patient being staged for prostatic cancer had a conventional radiograph of the mandible because of pain in the mandible, with the radiograph showing sclerosis of the whole of the left mandible associated with bone hypertrophy. An MDP bone scan was therefore performed to look for other bone lesions. The scan shows hypertrophy of the left mandible together with involvement of the mandibular condyle (unusual for a metastatic deposit). The appearances are typically those of Paget's disease. The activity in the occipital protuberance is a normal variant*

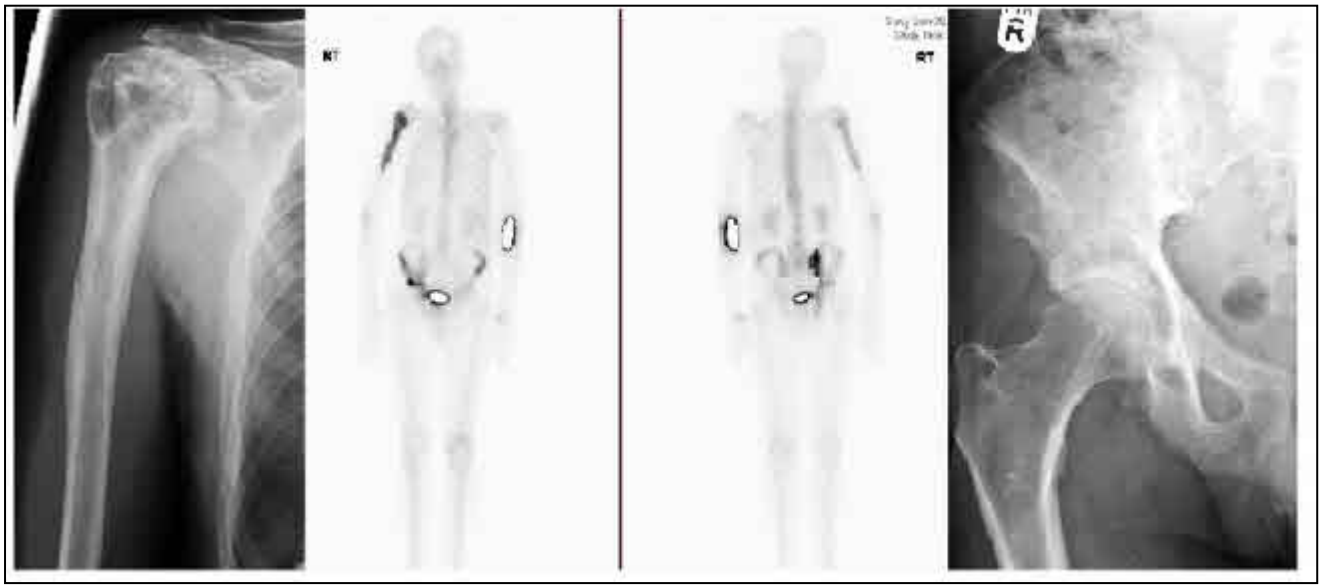

Figure 29 *Another patient with prostate cancer was x-rayed because of pain in the right shoulder. The radiograph showed coarsened bone trabecular pattern with differential diagnosis of fibrous dysplasia and Paget's disease. An MDP scan shows intense activity in the right upper humerus, the humeral head and the right hemi-pelvis highly suggestive of Paget's disease*

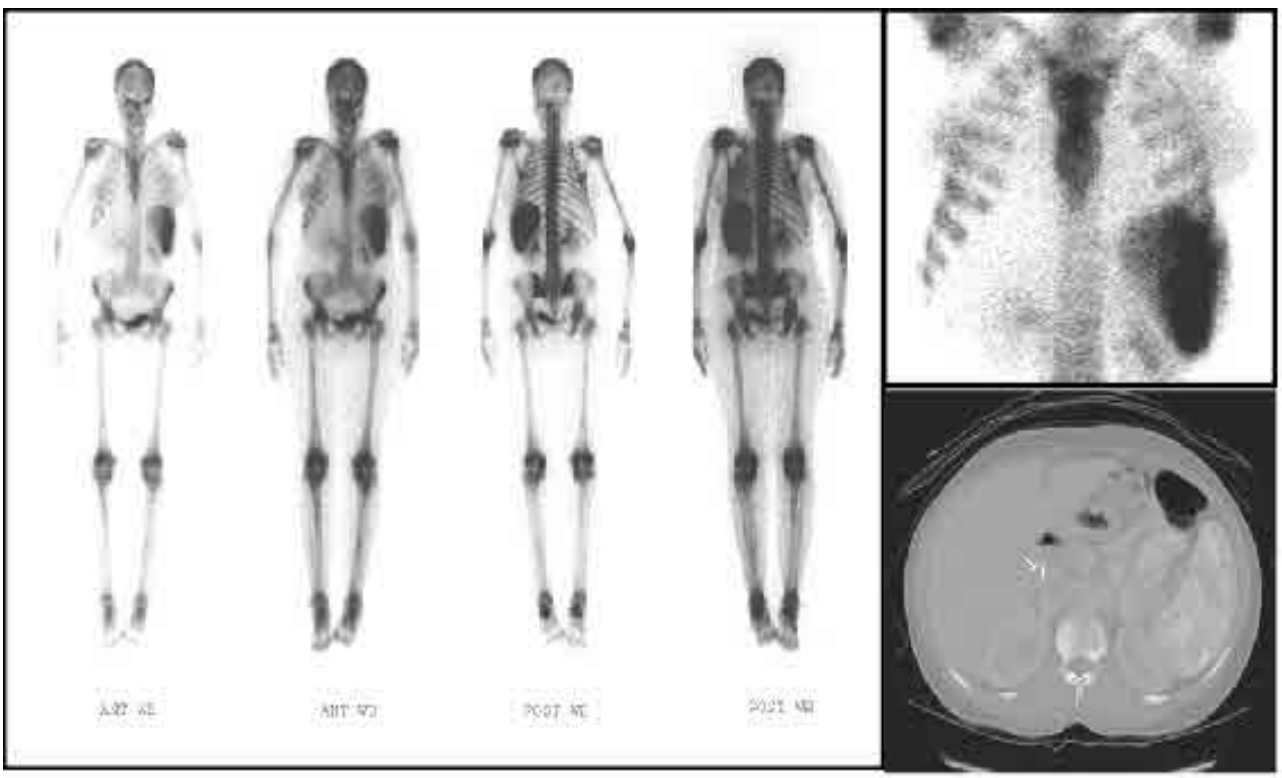

Figure 30 *MDP bone scan was performed as a part of cancer staging in this 28-year-old with breast cancer and Sickle cell disease. The RNBS shows intense activity in a calcified spleen, not to be confused with metastases*

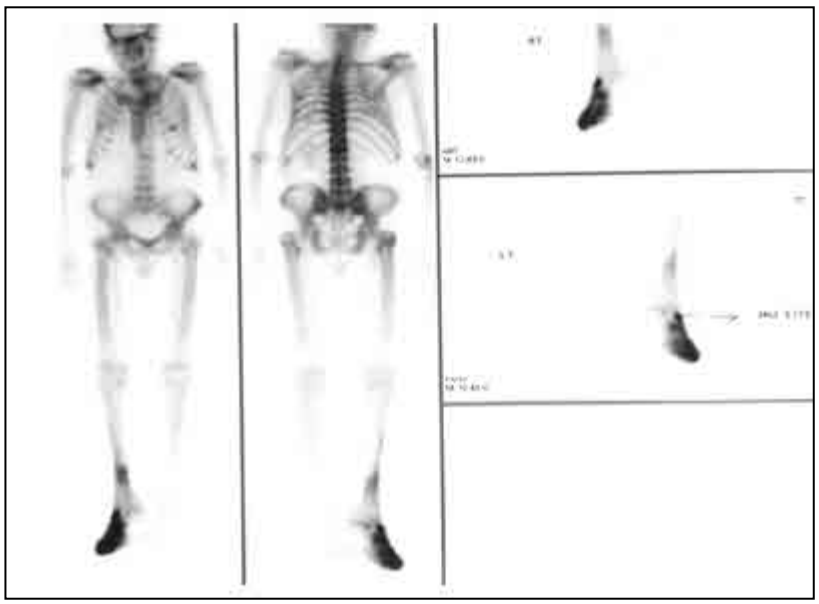

Figure 31 *Distal activity in a patient with difficult venous access where the foot was used to inject the radionuclide and part of the injection was given intra-arterially by error*

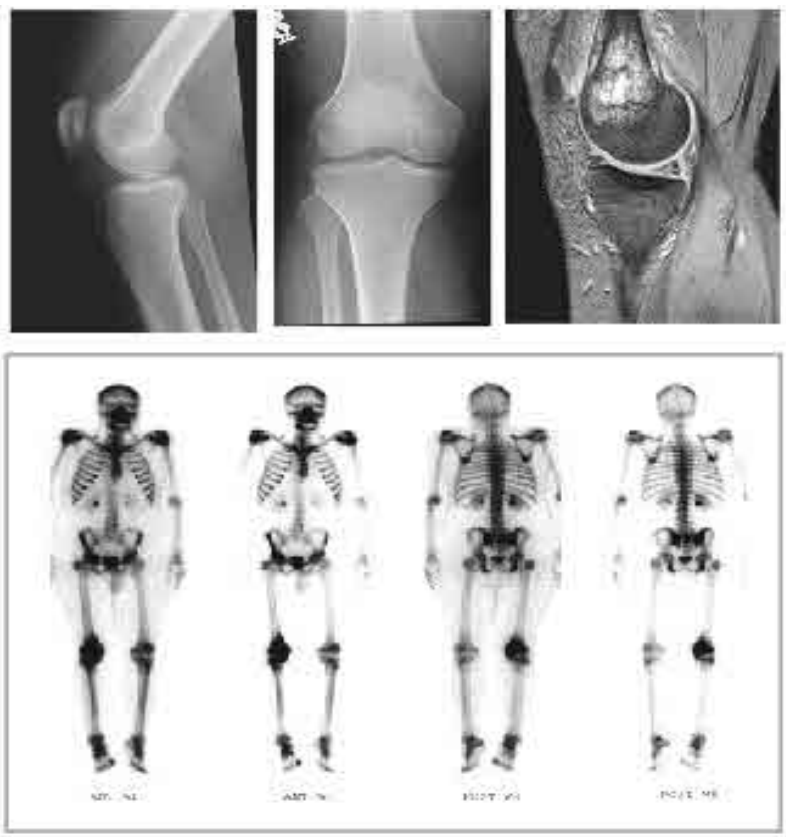

Figure 32 *Series of images on 14-year-old boy with an osteogenic sarcoma of the distal left femur. From the images, it is evident that the MDP scan is much more superior to conventional radiographs and that the MRI provides superb local staging for therapy. MDP scan excludes skip lesions and bony and calcified/ossified metastases*

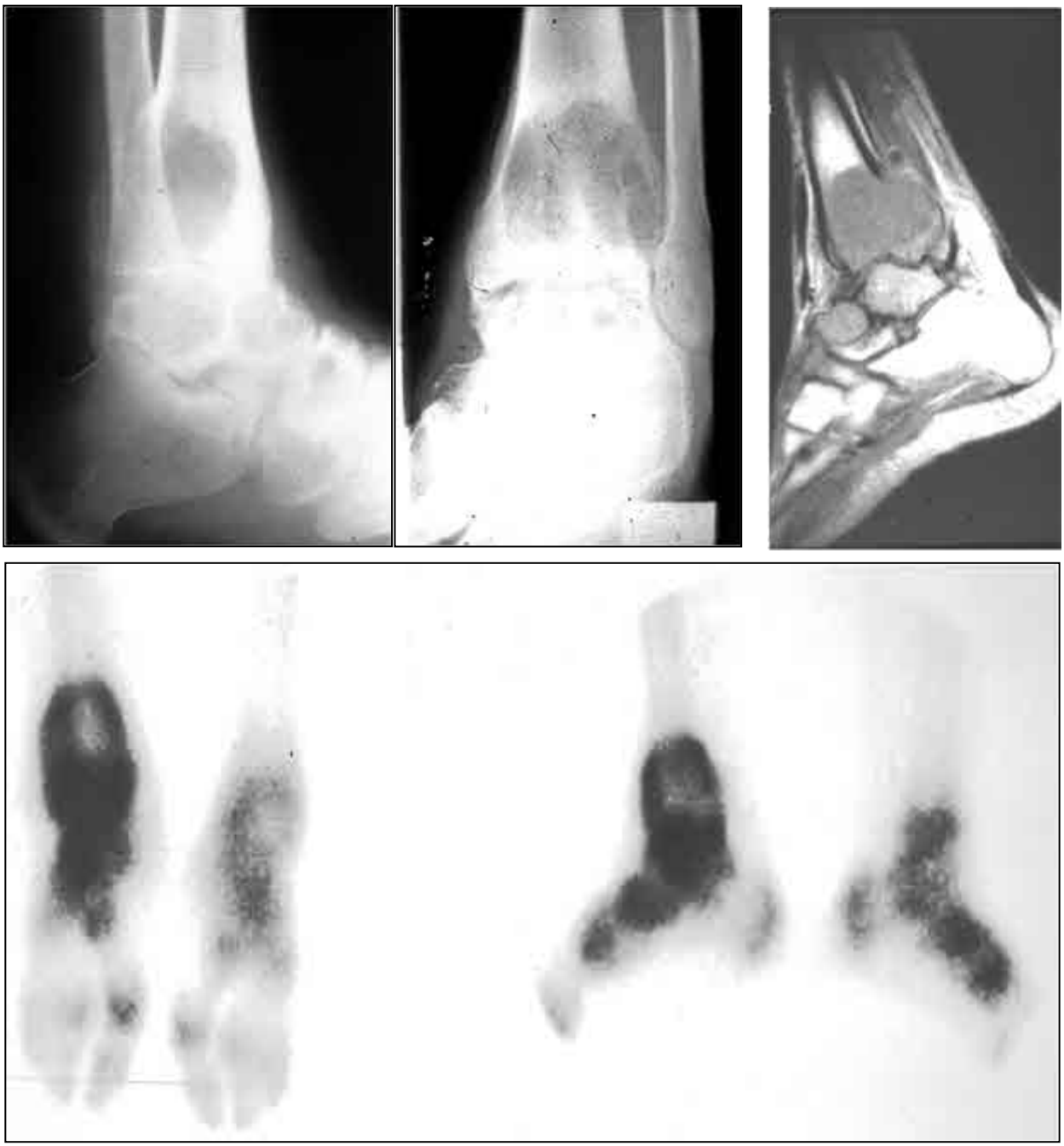

Figure 33 *Various modalities used in the diagnosis of a Giant cell tumour of the lower tibial epiphysis showing a much superior depiction by MRI for local staging purposes.*

Artifactual increased focal activity may be related to urine contamination and inadvertent arterial injections among other things (Figure 31).

Extraosseous Activity

There are a variety of pathological, physiological and artifactual states where MDP accumulates in

the soft-tissues. The pathogenesis of this phen- omenon is not clear but one important factor is the formation of calcium phosphate salts from calcium and phosphate that leak into the extracellular fluid from hypoxic injury or dead cells binding to the diphosphonates.

Examples of non-skeletal MDP distribution include: calcinosis cutis and pulmonary mineralization in hyperadrenocorticism, renal infarct, acute rhabdomyolysis, urine contamination, lymph node uptake following extravasations of the radio-pharmaceutical, thyroid, salivary gland and stomach uptake due to free pertechnetate in the injected radiopharmaceutical, and intramuscular uptake following injection of butorphanol. MDP accumulation may occur in heterotopic ossification, which is known to occur in patients following fractures, arthroplasty, paraplegia and hemiplegia. MDP often accumulates in calcified splenic infarction in sickle cell disease.

Other Primary Tumors

These are focal bone lesions, usually solitary, which shows increased or decreased activity, which have not been covered in this review due to space limitations.

Most primary bone tumours such as osteogenic sarcomas, osteoid osteoma and giant cell tumours are better characterized by MRI, which provides superb surgical and radiation therapy planning (Figures 32-33). However, RNBS is still a useful adjunct and helps to define skip lesions in malignant tumours.

Osteoid osteoma is a benign but disabling tumour that shows intense MDP activity at the site of the tumour. Occasionally, a double-density sign is seen in which a small focus of radioactivity in the nidus is superimposed on a larger area of radioactivity. RNBS is considered mandatory in patients with painful scoliosis. A radionuclide bone scan can demonstrate the tumour before abnormal radiographic findings are apparent [59].

Osteogenic sarcomas are extremely aggressive tumours, which are the most frequent primary bone tumours of children and adolescents. Imaging plays a vital role. Conventional radiography is the prime imaging modality for diagnosis of bony tumours.

CT may be used as an adjunct to conventional radiography. MRI is the imaging modality of choice for local staging and monitoring response to chemotherapy and distinguishing postsurgical changes from residual tumour. Dynamic contrast-enhanced MRI has been introduced to quantify the percentage of tumour necrosis, identify early responders, and thus predict survival. The role of ^{18}FDG-PET in the staging and management of osteogenic sarcoma is evolving [60].

Conclusions

One of the major successes of nuclear medicine in recent years has been the clinical uses of the ^{99m}Tc-labelled bone-imaging agents. With worldwide increasing costs of healthcare, RNBS remains a cost-effective screening test for the detection of bone metastases and other metabolically active osseous lesions.

Factors such as cost, the relatively long imaging times and considerations of patient throughput are presently important limitations of MRI. The estimated to cost of an MRI is approximately three times the cost of a RNBS. Further, MRI has limited availability, carries a risk from gadolinium-based contrast agents and claustrophobia may be an issue in some patients. Although RNBS lacks specificity, its high sensitivity makes it a valuable screening procedure for many osseous pathologic conditions. A positive scan generally indicates a pathological state, which can be subjected to further imaging/tests. RNBS detects physiological dysfunction before abnormalities become evident on anatomical imaging. Even so, what is clear from this review is that no one modality is perfect and all are complimentary. Some pearls are presented in Table1.

Table 1 Some important imaging pearls in RNBS

Pearls

- Do not exclude a fracture on MDP scan in any age group before 72 hours after trauma. RNBS scans should be performed as 3-phase study to improve sensitivity
- Extra care should be taken in the diagnosis of fractures in the elderly patients on steroids and in stable fractures. alternatives such as MRI should be considered
- Remember, early fracture may mimic focal cellulitis or septic arthritis
- An old fracture may mimic metastasis or osteomyelitis
- Presently no imaging can predict post traumatic AVN. MDP bone scan 6 weeks following surgery is a good predictor of AVN. If the femoral head is potentially viable pinning should be undertaken rather the hip replacement.
- A non-vascularized femoral head makes a perfect prosthesis as it may take several years to develop AVN
- If a bone scan is abnormal & radiograph is normal, repeat the scan in 3 months, but if would change the management immediate MRI or CT should be undertaken
- Osteomyelitis: focally hot on blood flow/pool, focally hot on delayed scan
- Cellulitis: diffusely hot on blood flow/pool but delayed images normal or mild increase in uptake due to hyperaemia
- Septic arthritis: diffuse uptake around joint capsule on blood flow/pool, normal or diffuse uptake around joint, both sides on delayed scans
- Be ware of the full bladder!

References

1. Chiewvit P, Danchaivijitr N, Sirivitmaitrie K, Chiewvit S, Thephamongkhol K. Does magnetic resonance imaging give value-added than bone scintigraphy in the detection of vertebral metastasis? J Med Assoc Thai. 2009 Jun;92(6):818-29.
2. Tausig A, Manthey N, Berger F, Sommer H, Pfluger T, Hahn K. Advantages andlimitations of whole-body bone marrow MRI using Turbo-STIR sequences in comparison to planar bone scans. Nuklearmedizin. 2000 Sep;39(6):174-9. [Article in German].
3. Bellamy EA, Nicholas D, Ward M, et al. Comparison of computed tomography and conventional radiology in the assessment of treatment response of lytic bony metastases in patients with carcinoma of the breast. Clin Radiol. Jul 1987;38(4):351-5.
4. Libshitz HI, Hortobagyi GN. Radiographic evaluation of therapeutic response in bony metastases of breast cancer. Skeletal Radiol. 1981;7(3):159-65.
5. Merrick MV, Beales JS, Garvie N, Leonard RC. Evaluation and skeletal metastases. Br J Radiol. Sep 1992;65(777):803-6.
6. Aitchison FA, Poon FW, Hadley MD, et al. Vertebral metastases and an equivocal bone scan: value of magnetic resonance imaging. Nucl Med Commun. Jun 1992;13(6):429-31.
7. Evans AJ, Robertson JF. Magnetic resonance imaging versus radionuclide scintigraphy for screening in bone metastases. Clin Radiol. Aug 2000;55(8):653; discussion 653-4.
8. Gosfield E 3rd, Alavi A, Kneeland B. Comparison of radionuclide bone scans and magnetic resonance imaging in detecting spinal metastases. J Nucl Med. Dec 1993;34(12):2191-8.
9. Steiner RM, Mitchell DG, Rao VM, Schweitzer ME. Magnetic resonance imaging of diffuse bone marrow disease. Radiol Clin North Am. Mar 1993;31(2):383-409.
10. Algra PR, Bloem JL, Tissing H, et al. Detection of vertebral metastases: comparison between MR imaging and bone scintigraphy. Radiographics. Mar 1991;11(2):219-32.
11. Frank JA, Ling A, Patronas NJ, et al. Detection of malignant bone tumors: MR imaging vs scintigraphy. AJR Am J Roentgenol. Nov 1990;155(5):1043-8.
12. Kattapuram SV, Khurana JS, Scott JA, el-Khoury GY. Negative scintigraphy with positive magnetic resonance imaging in bone metastases. Skeletal Radiol. 1990;19(2):113-6.
13. Royal College of Radiologists: Making the Best Use of a Department of Clinical Radiology: Guidelines for Doctors, ed 4. London, RCR Publications, 1998, p 13
14. Genant HK, Bautovich GJ, Singh M, Lathrop KA, Harper PV. Bone-seeking radionuclides: an in vivo study of factors affecting skeletal uptake. Radiology 1974; 113:373-382.
15. Galasko CSB. The pathological basis for skeletal scintigraphy. J Bone Joint Surg Br 1975; 57:353-359.
16. McAfee JG, Reba RC, Majd M. The musculoskeletal system. In: Wagner HN,

Jr, Szabo Z, Buchanan JW, eds. Principles of nuclear medicine. 2nd ed. Philadelphia, Pa: Saunders, 1995; 986-1012.

17. Salmon JM, Kilpatrick SE. Pathology of skeletal metastases. Orthop Clin North Am. Oct 2000;31(4):537-44, vii-viii.

18. Clines GA, Guise TA. Molecular mechanisms and treatment of bone metastasis. Expert Rev Mol Med. Mar 6 2008;10:e7.

19. Citrin DL, Tormey DC, Carbone PP. Implications of the 99mTc diphosphonate bone scan on treatment of primary breast cancer. Cancer Treat Rep 1977; 61:1249-1252.

20. Fon GT, Wong WS, Gold RH, Kaiser LR. Skeletal metastases of melanoma: radiographic, scintigraphic, and clinical review. AJR Am J Roentgenol 1981; 137:103-108.

21. Galasko CS, Doyle FH. The detection of skeletal metastases from mammary cancer: a regional comparison between radiology and scintigraphy. Clin Radiol 1972; 23:295-297.

22. Hage WD, Aboulafia AJ, Aboulafia DM. Incidence, location, and diagnostic evaluation of metastatic bone disease. Orthop Clin North Am 2000; 31:515-528.

23. Palmer E, Henrikson B, McKusick K, Strauss HW, Hochberg F. Pain as an indicator of bone metastasis. Acta Radiol 1988; 29:445-449.

24. Bibbo C, Patel DV, Benevenia J. Perioperative considerations in patients with metastatic bone disease. Orthop Clin North Am 2000; 31:577-595.

25. Thrall JH, Ziessman HA. Skeletal system. In: Thrall JH, Ziessman HA, eds. Nuclear medicine: the requisites. 2nd ed. St Louis, Mo: Mosby, 2001; 110-144.

26. Stokkel MPM, Valdes Olmos RA, Hoefnagel CA, Richel DJ. Tumor and therapy associated abnormal changes on bone scintigraphy: old and new phenomena. Clin Nucl Med 1993; 18:821-828.

27. Coombes RC, Dady P, Parsons C, et al. Assessment of response of bone metastases to systemic treatment in patients with breast cancer. Cancer 1983; 52:610-614.

28. Coleman RE, Mashiter G, Whitaker KB, Moss DW, Rubens RD, Fogelman I. Bone scan flare predicts successful systemic therapy for bone metastases. J Nucl Med 1988; 29:1354-1359.

29. Holtzhausen L, Noakes TD: Stress fracture of the sacrum in two distance runners. Clin J Sport Med 1992;2:139-142.

30. Matin P. The appearance of bone scans following fractures, including immediate and long-term studies. J Nucl Med 1979; 20:1227-1231.

31. Murray IPC. Bone scintigraphy in trauma.Implications of the 99mTc diphosphonate bone scan on treatment of primary breast cancer. Cancer Treat Rep 1977; 61:1249-1252.

32. Fon GT, Wong WS, Gold RH, Kaiser LR. Skeletal metastases of melanoma: radiographic, scintigraphic, and clinical review. AJR Am J Roentgenol 1981; 137:103-108.

33. Galasko CS, Doyle FH. The detection of skeletal metastases from mammary cancer: a regional comparison between radiology and scintigraphy. Clin Radiol 1972; 23:295-297.

34. Hage WD, Aboulafia AJ, Aboulafia DM. Incidence, location, and diagnostic evaluation of metastatic bone disease.

Orthop Clin North Am 2000; 31:515-528.

35. Palmer E, Henrikson B, McKusick K, Strauss HW, Hochberg F. Pain as an indicator of bone metastasis. Acta Radiol 1988; 29:445-449.

36. Bibbo C, Patel DV, Benevenia J. Perioperative considerations in patients with metastatic bone disease. Orthop Clin North Am 2000; 31:577-595.

37. Thrall JH, Ziessman HA. Skeletal system. In: Thrall JH, Ziessman HA, eds. Nuclear medicine: the requisites. 2nd ed. St Louis, Mo: Mosby, 2001; 110-144.

38. Stokkel MPM, Valdes Olmos RA, Hoefnagel CA, Richel DJ. Tumor and therapy associated abnormal changes on bone scintigraphy: old and new phenomena. Clin Nucl Med 1993; 18:821-828.

39. Coombes RC, Dady P, Parsons C, et al. Assessment of response of bone metastases to systemic treatment in patients with breast cancer. Cancer 1983; 52:610-614.

40. Coleman RE, Mashiter G, Whitaker KB, Moss DW, Rubens RD, Fogelman I. Bone scan flare predicts successful systemic therapy for bone metastases. J Nucl Med 1988; 29:1354-1359.

41. 41. Holtzhausen L, Noakes TD: Stress fracture of the sacrum in two distance runners. Clin J Sport Med 1992;2:139-142.

42. 42. Matin P. The appearance of bone scans following fractures, including immediate and long-term studies. J Nucl Med 1979; 20:1227-1231.

43. 43. Murray IPC. Bone scintigraphy in trauma. In: Murray IPC, Ell PJ, eds. Nuclear medicine in clinical diagnosis and treatment. 2nd ed. Edinburgh, Scotland: Churchill Livingstone, 1998; 1241-1267.

44. Aburano T, Yokoyama K, Taki J, Nakajima K, Tonami N, Hisada K. Tc-99m MDP bone imaging in inflammatory enthesopathy. Clin Nucl Med 1990; 15:105-106.

45. Intenzo CM, Wapner KL, Park CH, Kim SM. Evaluation of plantar fasciitis by three-phase bone scintigraphy. Clin Nucl Med 1991; 16:325-328.

46. Rupani HD, Holder LE, Espinola DA, Engin SI. Three-phase radionuclide bone imaging in sports medicine. Radiology 1985; 156:187-196.

47. Holder LE, Michael RH. The specific scintigraphic pattern of "shin splints in the lower leg": concise communication. J Nucl Med 1984; 25:865-869.

48. Galasko CSB, Weber DA. Avascular necrosis. In: Galasko CSB, Weber DA, eds. Radionuclide scintigraphy in orthopaedics. Edinburgh, Scotland: Churchill Livingstone, 1984; 200-209.

49. DeSmet AA, Dalinka MK, Alazraki N, et al. Diagnostic imaging of avascular necrosis of the hip. Radiology 2000; 215 (suppl):247-254.

50. Ulmer JL, Mathews VP, Elster AD, et al. MR imaging of lumbar spondylolysis: the importance of ancillary observations. AJR Am J Roentgenol. Jul 1997;169(1):233-9

51. Ulmer JL, Elster AD, Mathews VP, Allen AM. Lumbar spondylolysis: reactive marrow changes seen in adjacent pedicles on MR images. AJR Am J Roentgenol. Feb 1995;164(2):429-33.

52. Mofidi A, Tansey C, Mahapatra SR, Mirza HA, Eisenstein SM. Cervical spondylolysis, radiologic pointers of stability and acute traumatic as opposed to chronic spondylolysis. J Spinal Disord Tech. Aug 2007;20(6):473-9.

53. Krupski W, Majcher P, Tatara MR. Computed tomorgaphy diagnostic of lumbar spondylolysis. Ortop Traumatol Rehabil. Oct 30 2004;6(5):652-7.

54. Palestro CJ, Torres MA. Radionuclide imaging of orthopedic infections. Semin Nucl Med 1997; 27:334-345.

55. Love C, Tomas MB, Marwin SE, Pugliese PV, Palestro CJ. Role of nuclear medicine in diagnosis of the infected joint replacement. RadioGraphics 2001; 21:1229-1238.

56. McAfee JG. Radionuclide imaging in metabolic and systemic skeletal diseases. Semin Nucl Med. 1987 Oct;17(4):334-49.

57. Kanis JA. Paget's disease of bone (osteitis deformans). In: Goldman L, Bennett JC, eds. Cecil textbook of medicine. 21st ed. Philadelphia, Pa: Saunders, 2000; 1413-1416.

58. Wellman HN, Schauwecker D, Robb JA, Khairi MR, Johnston CC. Skeletal scintimaging and radiography in the diagnosis and management of Paget's disease. Clin Orthop 1977; 127:55-62.

59. Rausch JM, Resnick D, Goergen TG, Taylor A. Bone scanning in osteolytic Paget's disease: case report. J Nucl Med 1977; 18:699-701.

60. Ali A, Tetalman MR, Fordham EW, et al. Distribution of hypertrophic pulmonary osteoarthropathy. AJR Am J Roentgenol 1980; 134:771-780.

61. Fournier RS, Holder LE. Reflex sympathetic dystrophy: diagnostic controversies. Semin Nucl Med 1998; 28:116-123.

62. Kozin F, Soin JS, Ryan LM, Carrera GF, Wortmann RL. Bone scintigraphy in the reflex sympathetic dystrophy syndrome. Radiology 1981; 138:437-443.

63. Heck LL. Extraosseous localization of phosphate bone agents. Semin Nucl Med 1980; 10:311-313.

64. Silberstein EB, Elgazzar AH, Fernandez-Ulloa M, Nishiyama H. Skeletal scintigraphy in non-neoplastic osseous disorders. Henkin RE, Bloes MA, Dillehay GL, et al. Nuclear medicine. St Louis, Mo: Mosby, 1996; 1141-1197.

65. Buring K. On the origin of cells in heterotopic bone formation. Clin Orthop 1975; 110:293-302.

66. Silberstein EB, DeLong S, Cline J. Tc99m diphosphonate and sulfur colloid uptake by the spleen in sickle disease: interrelationship and clinical correlates: concise communication. J Nucl Med 1984; 25:1300-1303.

67. Blair RJ, Schroeder ET, McAfee JG, Duxbury CE. Skeletal muscle uptake of bone seeking agents in both traumatic and non-traumatic rhabdomyolysis with acute renal failure (abstr). J Nucl Med 1975; 16(P):515-516.

68. Ashwani Sood A, Seam RK, Sethi S, Gupta M. Diffuse hepatic and Splenic: Tc-99m MDP tracer uptake in case of multiple myeloma. Indian Journal Nuclear Medicine

69. MacDonald J. Idiopathic Hepatic Uptake of 99mTc Methylene Diphosphonate: A Case Report Journal of Nuclear Medicine Technology Volume 29, Number 1, 2001 32-36

70. Omojola MF, Cockshott WP, Beatty EG. Osteoid osteoma: an evaluation of diagnostic modalities. Clin Radiol. 1981 Mar;32(2):199-204

71. Eftekhari F. Imaging assessment of osteosarcoma in childhood and adolescence: diagnosis, staging, and evaluating response to chemotherapy. Cancer Treat Res. 2009;152:33-62.