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Skeleton System

Rongfu Wang
Peking University First Hospital
China

1. Introductions

Bone and soft tissue disease is kind of detrimental disease and the precise diagnosis and timely therapy is also the clinical doctors' object of a prolonged endeavour. This chapter will introduce the diagnostic and therapeutic methods of bone and soft tissue diseases with nuclear medicine techniques.

The singular advantages of skeletal scintigraphy are high sensitivity in detecting early disease and its ability to survey the entire skeleton quickly and reasonable expense. Most broadly, the uptake of skeletal seeking radiotracers depicts osteoblastic activity and regional blood flow to bone. Any medical condition that changes either of these factors in a positive or negative way can result in an abnormal skeletal scintigram.

Radionuclide distribution has played an important role in understanding normal bone metabolism, in addition to the metabolic effects of pathologic involvement. Radionuclide imaging of the skeleton is being used with increasing frequency in the evaluation of abnormalities involving bones and joints. Several studies have demonstrated that different information can be obtained by radionuclide bone imaging compared with radiography and blood chemistry analysis. Innovations in equipment design and other advances, such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), positron emission tomography/computed tomography (PET/CT), positron emission tomography/magnetic resonance imaging (PET/MR) and hybrid SPECT/CT have been incorporated into the investigation of various musculoskeletal diseases.

The first part of this chapter introduces the mechanism of skeletal radionuclide imaging, which also reviews part knowledge of skeletal anatomy and physiology. The remainder of the chapter discusses radionuclide imaging of the bones and joints, with an emphasis on the applications of the imaging procedures, and the radionuclide therapy of some bone tumors.

2. Mechanism and technique of skeletal radionuclide imaging

Bone scintigraphy is one of the most common investigations performed in nuclear medicine and routinely used in the evaluation of patients with cancer for suspected bone metastases and in various benign musculoskeletal conditions. The uptake of radiotracers in bone is associated with local osteoblastic activity and regional blood flow. More radiopharmaceutical is delivered to hyperemic areas. Either increased blood flow or increased osteogenesis for many types of lesions results in higher tracer uptake than in unaffected or normal parts of the skeleton.

The accumulation of radionuclide in bone is related to both vascularity and rate of bone turn over. Increased blood supply to an area of bone result in increased activity in a blood-pool image (obtained immediately after radiopharmaceutical administration).
The localization of various bone imaging agents is related to exchange with ions in the bone. The process of exchange of an ion native to bone for a labelled, bone-seeking ion is termed heter-ionic exchange. Calcium phosphate is the main inorganic constituent of bone; however, calcium is also found in the form of carbonate and fluoride. Calcium is located in microcystals of hydroxyapatite. Analog elements of calcium, such as strontium-85 (^{85}Sr), are believed to exchange with the calcium. Flurorine-18 (^{18}F) exchanges with hydroxyl ion in the hydroxyapatite. The accumulation of labelled phosphate compounds is probably related to the exchange of the phosphorus groups onto the calcium of hydroxyapatite. Although these mechanisms are not completely understood, the principle of bone imaging is fairly basic. Calcium analogs or phosphate compounds have a low concentration in blood and tissues, and this will supply a good bone-to-soft tissue background ratio.
Radiopharmaceuticals used for bone imaging sometimes can localize in soft tissue areas, demonstrating not only calcification but also infarction, inflammation, trauma, and tumor. The portion of any radiopharmaceutical that does not accumulate in bone and tissue or stays in the circulation is eliminated from the body by various routes, depending on the radiopharmaceutical. ^{85}Sr can be concentrated in the gastrointestinal tract for several days. ^{18}F-fluoride (^{18}F-NaF) and phosphate scans labelled with technetium-99m (^{99m}Tc) demonstrate activity in the kidneys and bladder, since these agents are excreted through the urinary tract.

2.1 Radiopharmaceuticals

Because of different radiopharmaceutical defining the imaging type, it is necessary to introduce some tracers widely used in clinical departments. Radiopharmaceuticals are classified into three goups; single photon emitting agents, positron emitting agents and therapeutic radiopharmaceuticals according to the radiation types.

2.1.1 Single photon emitting agents

SPECT, which is short for single photon emission computer tomography, is the most widely used equipment in departments of nuclear medicine. There are lots of different kinds of single photon emitting radionuclides, however not all of them are suitable for skeleton imaging. The most widely used radionuclide is technetium-99m (^{99m}Tc).
Technetium-99m is a metastable nuclear isomer of technetium-99, symbolized as ^{99m}Tc. Technetium- 99m emits gamma rays which can be detected by SPECT. It is well suited to the role because it emits readily detectable 140 keV (excitation energy) gamma rays, and its half-life for gamma emission is about 6 hr. The short half life of the isotope (in terms of human-activity and metabolism) allows for scanning procedures. The following table (table 1) summarizes its nuclear physics characteristics.
The agents are composed of radiation emitter and chemical or biologic molecules. The Tc-99m-labelled skeletal radiopharmaceuticals are distributed rapidly throughout the extracellular fluid space. For example, ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) is the most famous tracer of skeletal imaging, ^{99m}Tc (V)-2, 3-dimercaptosuccinic acid (^{99m}Tc (V)-DSMA), and ^{99m}Tc-sestamibi (^{99m}Tc-MIBI) are also used in skeletal and soft tissue tumors imaging.

Nuclide symbol	Z(p)	N(n)	isotopic mass (u)	half-life	Decay mode(s)	Daughter isotope(s)
	excitation energy					
^{99m}Tc	43	56	98.9062547(21)	6.0058 hr	IT (99.99%)	^{99}Tc
	140.5 keV				β- (.0037%)	^{99}Ru

Table 1. The nuclear physics characteristics of radionuclide ^{99m}Tc

Upon intravenous injection, the uptake of ^{99m}Tc-MDP appears to be related to bone metabolic activity and to skeletal blood flow. ^{99m}Tc-MDP exhibits a specific affinity for areas of altered osteogenesis. The adsorption is believed to occur primarily to the mineral phase of bone, with little biding to the organic phase. The uptake is significantly higher in amorphous calcium phosphate than in mature crystalline hydroxyapatite, which helps explain the avidity of the tracer for areas of increased osteogenic activity. Localized areas of decreased skeletal accumulation of ^{99m}Tc-MDP may be seen in areas of reduced or absent regional blood flow (i.e. bone infarction) and in areas where the skeleton has been destroyed to the point that no bone matrix elements are present for uptake to occur.

^{99m}Tc (V)-DSMA and ^{99m}Tc-MIBI are usually used in seeking tumors in soft tissues. Also there are reports on the ^{99m}Tc (V)-DSMA scintigraphy as a monitor in the response of bone disease to vitamin D3 therapy in renal osteodystrophy and ^{99m}Tc (V)-DSMA whole body scan in detection of metastases in thyroid medullary cancer.

Gallium-67 (^{67}Ga) is also a single photon emitting radionuclide; it is an iron analogue which avidly binds to iron-binding proteins. It competes for iron sites in transferring and is absorbed by lysosomes and endoplasmic reticulum of white blood cells. It has been used in the evaluation of unknown original fever, chronic inflammations, detection and localization of osteomyelitis and/or disk space infection, etc. The excitation energy of ^{67}Ga is 93.3 keV (36%) and has a life time of 3.26 days. ^{67}Ga scintigraphy has been used to determine the treatment response in soft tissue tumors, such as osteosarcoma.

Thalium-201 (^{201}Tl) is another single photon emitting radionuclide, it has been used in many different SPECT imaging protocols such as myocardial perfusion imaging, skeleton imaging, tumor positive imaging, parathyroid imaging combined with pertechnetate, etc. ^{201}Tl decays by electron capture and gamma emitter with subsequent gamma emission of 68.9 to 80.3 keV (94%) and has a life time of 3.04 days.

Although the role of ^{201}Tl scintigraphy for staging the disease of bone tumor and differentiation of benign from malignant lesions is limited, it has provided important information on the management of patients with bone tumors. ^{201}Tl scintigraphy reflects the disease activity after treatment and it should be used to determine the treatment response and for early diagnosis of recurrence in bone soft tissue tumors.

2.1.2 Positron emitting agents

PET, which is short for positron emission computed tomography, is the most advanced equipment in the field of nuclear medicine even in the area of image science. Lots of kinds of positron emitting radionuclide have been used in practice, such as ^{18}F, ^{11}C (carbon-11), ^{15}O (oxygen-15), ^{13}N (nitrogen-13), etc. The most widely used radionuclide is fluorine-18 (^{18}F) and carbon-11 (^{11}C). The ^{18}F radiolabelled and ^{11}C labelled skeletal radiopharmaceuticals are used in PET imaging, which reflect the bone metabolism. The following table (table 2) summarizes their nuclear physics characteristics.

Nuclide symbol	Z(p)	N(n)	isotopic mass (u)	half-life	Decay mode(s)	Daughter isotope(s)
	excitation energy					
Fluorine-18 ^{18}F	9	9	18.0009380(6)	109.7min	Positron	^{18}O
	0.6335 MeV				β-	
Carbon-11 ^{11}C	6	5	11.011433(10)	20.33 min	β+	^{11}B
	0.96 MeV					

Table 2. The nuclear physics characteristics of positron radionuclide ^{18}F, ^{11}C

^{18}F-2-fluoro-2-deoxy-d-glucose (^{18}F-FDG), ^{18}F sodium fluoride (^{18}F-NaF) and ^{11}C-choline PET imaging is also called bone metabolic imaging. Here we will mention ^{18}F-FDG and ^{18}F-NaF imaging. ^{18}F-FDG (2-fluoro-2-deoxy-d-glucose) is a glucose analogue with a fluorine atom replacing a hydroxyl group in the C-2 position of d-glucose. ^{18}F exchanges with the hydroxyl (OH) ion in the hydroxyapatite. Although the mechanisms are not completely understood, the principal of bone imaging is fairly basic. Radiopharmaceuticals used in bone imaging can localize in soft tissues, demonstrating not only calcification but also inflammation, trauma, and tumor.

2.1.3 Therapeutic radiopharmaceuticals

In the area of therapeutic nuclear medicine, there are lots of applications of different kinds of radiopharmaceuticals. For example, sodium of ^{32}P-phosphate is an FDA-approved radiopharmaceutical indicated for treatment of polycythemia vera, chronic myelocytic leukemia, chronic lymphocytic leukemia, and for palliation of metastatic bone pain. Chromic ^{32}P-phosphate is suspension of ^{32}P used for intracavity installation for treatment of peritoneal or pleural effusions caused by metastatic disease. Phosphorus-32 decays by beta-emission with a half life of 14.3 days. The major toxicity noted is significant marrow suppression in approximately one third of patients receiving this radiopharmaceutical.

Iodine-131 (^{131}I) is the important therapeutic radiopharmaceutical, as a capsule or a solution for oral administration, which decays by beta- emission with subsequent gamma emission of 364 keV (82%) and has a life time of 8 days. Iodine-125 (^{125}I) delivers a higher radiation dose to the patient due to the half life of 60 days and ^{125}I seeds have been used in the therapy of solid tumors.

In skeleton nuclear medicine, some radionuclides are chosen as an effective way for treating the bone pain caused by the bone metastases. ^{89}Sr-chloride (Metastron) has been approved by the FDA for relief of bone pain in cases of painful skeletal metastases. The compound behaves biologically like calcium and localizes in hydroxyapatite crystal by ion exchange. Strontium uptake occurs preferentially at sites of active osteogenesis. This allows primary bone tumors and areas of metastatic involvement to accumulate significantly higher concentration of strontium than surrounding normal bone. ^{89}Sr decays by beta- emission with a half life of 50.6 days.

Another two radiotherapeutic agents, ^{186}Re-HEDP and ^{153}Sm-EDTMP are also used in the area. ^{186}Re decays by beta- and gamma emission with a half life of 90.6 hr and ^{153}Sm decays by beta- emission and has a half life of 46.3 hr. Both of these beta-emitting radionuclides are complex with bone-seeking ligands, which localize by chemisorption. The duration of response is 1-12 months. The main toxicity of these radiotherapeutics is mild transient bone marrow suppression.

2.1.4 Precautions

In pediatric cases the physiology and metabolism is different from adults' and the uptake of radiopharmaceuticals vary greatly, for example the bone uptake in children is up to 80% compared with that of adults at up to 40%. The pediatric dose of radiopharmaceuticals is calculated based on the standard weight method (the pediatric dose=(patient weight in kg×standard adult dose)÷70kg) or body surface area methods. With ^{99m}Tc labelled radiopharmaceuticals, we suggest a 24 to 36 hr breast feeding delay, and ^{67}Ga based products for a 72 hr delay.

In pregnant women, the nuclear medicine examinations are forbidden.

2.2 Technique of skeletal radionuclide imaging

After the radiopharmaceuticals prepared, an emission computed tomography is needed. Tomography is the process of producing a section or slice in a picture of an object. The emission computed tomography (ECT) can produce a picture of the distribution of radiopharmaceuticals administered to the patient. At present the widespread used ECT are SPECT and PET.

2.2.1 Technique of skeleton SPECT imaging

By far the most popular SPECT consists of a rotating Anger camera, which equipped with a large field of view detector, mounted on a 360-degree rotation gantry. Multipledetector SPECT has increased the diagnostic sensitivity and lessened the acquisition time. In skeletal imaging protocols we often chose a low energy and high resolution collimator.

2.2.2 Technique of skeleton PET imaging

PET is one of the exciting tomographic techniques, and provides functional information of blood flow and metabolism. As a positron meets a free electron in the tissue, annihilation occurs and the two 511keV annihilation photons are detected by coupled opposing detectors in coincidence. PET is more sensitivity than SPECT, and differs from SPECT by "electronic collimation".

2.3 Appearance of normal skeleton scintigram

According to the different imaging objects, the nuclear physician chose the proper protocols. Generally speaking, the imaging type are divided into whole body scan, local static bone scan, local bone tomography, dynamic bone scan (i.e. three phase imaging: blood flow phase, blood-pool phase, and delay scan). The whole body bone scan is the most widely used scintigraphy, which reflects the whole skeleton situation.

The appearance of the normal skeletal scintigram should be clear, symmetric and uniform and the uptake of joints, junctions, and scapulas increased. In some older patients the image may have a globally poor quality. The normal image can change dramatically among infancy, childhood, adolescence and mature adulthood. In adults, growth center activity normally becomes equal to activity in adjacent bone, on the contrary more radioactivities in growth center than adjacent bone in childhood. Tracer uptake is greatest in the axial skeleton (spine and pelvis), and relatively less intense uptake in the extremities and skull. The kidneys are routinely visualized in normal subjects and should have less intensity than the adjacent lumbar spine because the urinary system is the excretion pathway of the radiopharmaceuticals. If the kidneys show equal or greater intensity, a renal abnormality or

concomitant drug therapy should be suspected. Here shows a normal skeleton scintigram (Figure 1).

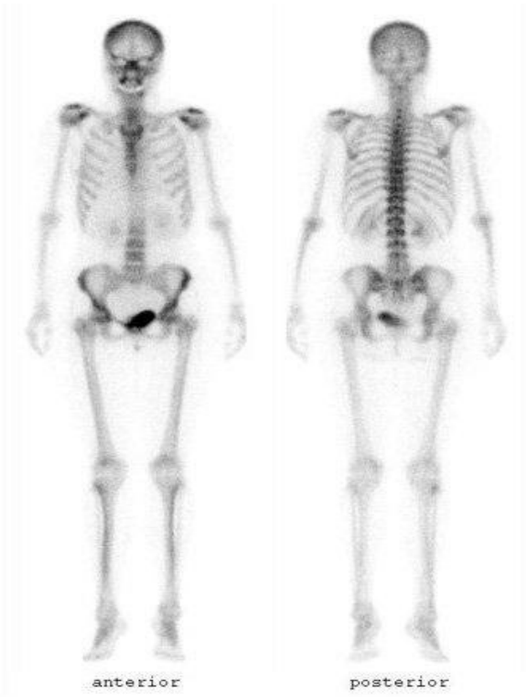


Fig. 1. Normal skeletal scintigram shows the symmetric and uniform activity absorption in anterior and posterior image.

A number of normal variants must be recognized for correct interpretation. Here we list some possible conditions as below.
①Bilaterally increased radionuclide concentration may be normal.
②The anterior aspect of the mandible may appear as a "hot spot" on lateral views of the skull.
③The laryngotracheal cartilages are usually seen in adults probably related to some degree of calcification.
④The thyroid gland can be visualized because of avid accumulation of unbound pertechnetate.
⑤Some mild diffuse asymmetry in paired joints is commonly seen in adults especially in shoulders and correlates with handedness.
⑥Some asymmetry is frequently seen in the sacroiliac joints, and this should be interpreted with caution in patients with scoliosis.

3. Applications of skeletal radionuclide imaging

It is definite that the skeletal radionuclide imaging can present the information of blood flow and osteogenesis of regional area once. There are various abnormalities in skeletal radionuclide imaging, whatever the defects or increased uptake of radionuclide; they can manifest some clue of the lesions. We conclude some abnormal results as below, and describe the details as follow based on the clinical applications.

①Asymmetric focal areas of increased or decreased activity: basically, this type of abnormality can happen in almost every scintigram. Focal increased activity can be associated with more blood flow (caused by hyperaemia, such as trauma, inflammation, etc) and active of osteogenesis (such as bone metastases of prostate cancer).
②"Super scan" is another scintigraphic pattern, with good bone-to-soft tissue background ratio, bone uptake showing brightly, absent or faint visualization of kidney and bladder, an increased uptake in the axial versus appendicular skeleton (appendicular skeleton, distal extremities, facial bones, subtle asymmetries of the rib, skull vault, and proximal long bones, and no soft-tissue uptake apparent at normal intensities). In some patients with breast cancer or prostate cancer the entire axial skeleton becomes diffusely and rather uniformly involved with metastatic disease (Figure 2).

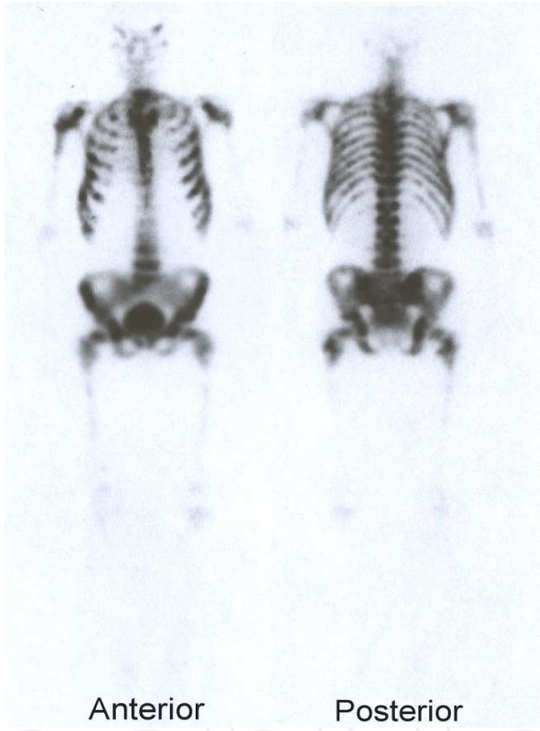


Fig. 2. A patient diagnosed as prostate cancer, the whole body bone scan with ^{99m}Tc-MDP showed "super scan": absent visualization of kidney, increased uptake in the axial versus appendicular skeleton and no soft-tissue uptake apparent at normal intensities.

③Cold areas, which means diminished activity or none distribution of activity, is indicative of osteonecrosis, osteoporosis, osteomalacia, multiple myeloma, radiation or steroid therapy, end-stage cancer patients with diminished metabolism, renal cell carcinoma, thyroid cancer, anaplastic tumors, neuroblastoma.
④"Donut" sign is the typical scintigram of osteonecrosis of the femoral head. The cold area within the femoral head is highly specific and is the earliest scintigraphic evidence of avascular necrosis. Over a period of weeks to months, increased uptake represents revascularization and repair surrounds, and eventually replaces the region of photopenia. The central region of photopenia with surrounding zone of increased uptake is termed as "donut" sign (Figure 3).

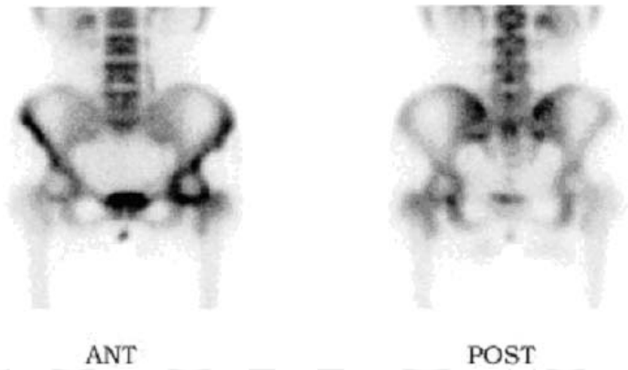


Fig. 3. The image showed "donut" sign in bilateral femoral head (worse in left side than right side), which is the diagnostic evidence of femoral head necrosis resulting from long-time use of dexamethasone.

⑤No uptake in focal areas: patients receive radiation therapy, bone infarct, avascular necrosis, metal prosthesis, bone infiltrated by tumor, poor venous return, edema in extremity may seen cold spot in focal area.
⑥Three phase bone imaging: it is one of the types of imaging protocols, and can help the qualitative diagnosis of some skeletal diseases, such as increased uptake in flow, blood pool, and delays in osteomyelitis cases; increased uptake in flow and blood-pool with mild or no uptake in delays in cellutitis; increased activity in and around joints in flow, blood pool, and delays in arthritis; increased vascular flow, blood pool, and delays focally in primary malignant tumor (Figure 4); increased blood pool and delays, focally intense in benign primary tumor.

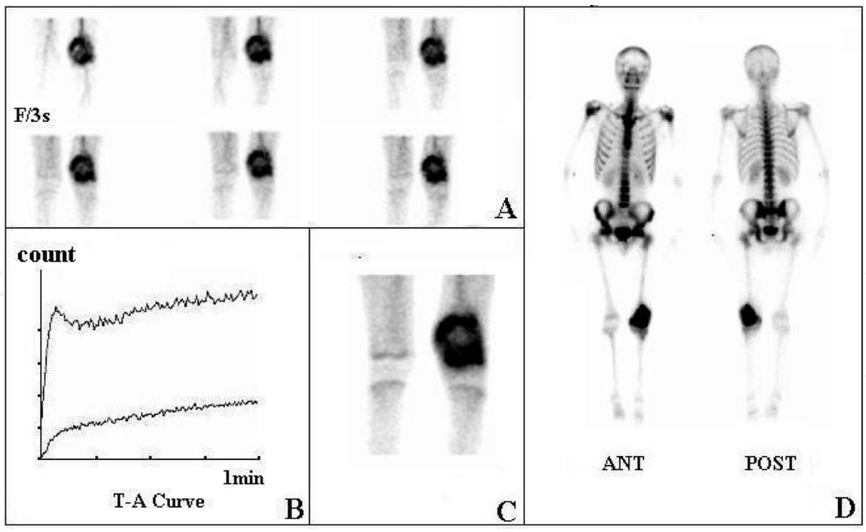


Fig. 4. Three phase bone imaging showed increased activity in left distal femur in blood flow phase (A), blood pool phase (C), and delayed phase (D). Malignant bone tumor: blood supply obviously increased in blood flow phase, vascular extension can be seen. Irregular tracer accumulated in soft tissue, in blood pool phase. Hot spot accumulation can be found on bone in delayed phase. In this case the patient was diagnosed as left femur osteogenic sarcoma by pathological proven finally.

3.1 Metastatic diseases

The most common clinical application of skeletal imaging is in evaluating patients with extraskeletal primary malignancies for the presence of metastatic disease and staging metastatic disease. In many patients the presence of extent of skeletal metastasis directly influences treatment decisions and prognosis. Bone imaging plays an important role in treatment of bone pain and pathological fracture which are common management problems in patients with skeletal metastatic disease.

Anterior and posterior images of the whole body scan are generally obtained. Metastases to bone are common in several primary malignancies, including lung, breast, and prostate carcinomas (Figure 5-6). Metastases to the spine are difficult to detect radiographically, since loss of approximately 50% of the mineral content of the bone must occur before lytic lesions are detected. The usual scintigraphic pattern of skeletal metastatic disease is multiple focal lesions throughout the skeleton, with the greatest involvement generally in the axial skeleton. The area of abnormal radiopharmaceutical deposition represents the edge of the metastatic deposit where osteoblastic repair is attempted.

As metastatic lesions grow in the marrow space, the surrounding bone remodels through osteoclastic (resorptive) and osteoblastic (depositional) activity. The relative degrees of bone resorption and deposition elicited are highly variable among the different types of tumors and sometimes even different locations for the same tumor. The relationship between the two remodelling processes determines whether a metastatic deposit will appear as predominantly lytic or sclerotic or will exhibit a mixed pattern radiographically.

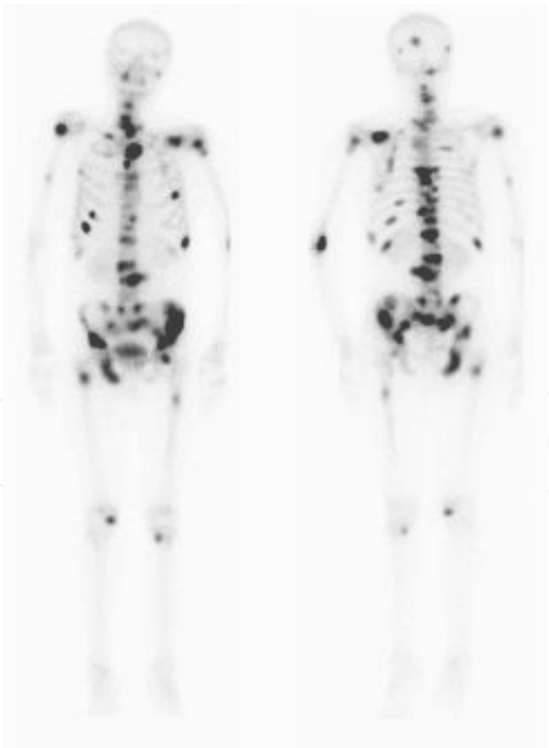


Fig. 5. The image showed multiple hot spot in skull, vertebrae, ribs, pelvis, femur, etc. Combined with the history of prostate cancer and night bone pain, it was concluded as bone metastases of prostate cancer.

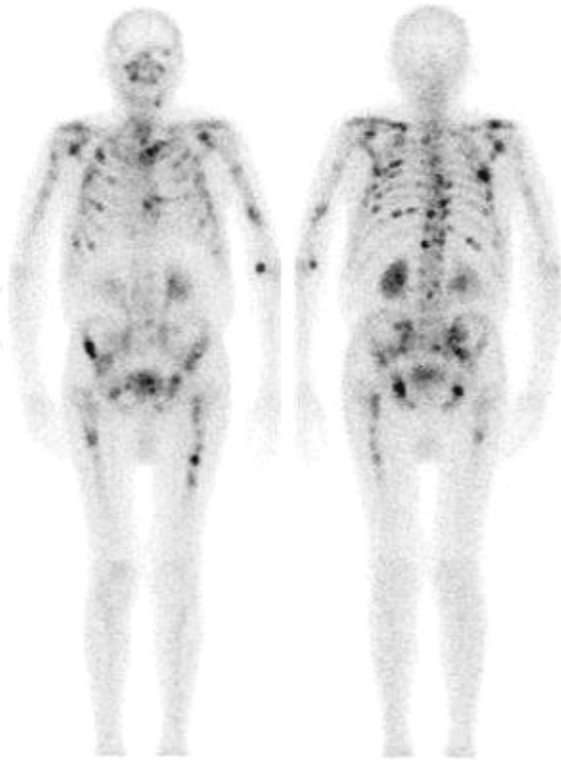


Fig. 6. The image showed multiple focal lesions in bone of patient with breast cancer.

False negative scans have been related to several factors. If the skeleton is diffusely involved with metastatic disease, the focal nature of the lesions might not be apparent. Metastatic lesions may have no associated osteoblastic activity and thus may not be detected by bone scan or may be detected as a photon-deficient area.

3.2 Primary malignant bone tumors

Bone scanning is also used for the evaluation of primary bone neoplasm. Usually the patient has already had radiographs of the primary tumor, but the bone scan offers additional information of that area. The extent of the abnormality on the bone scan is generally not much different from the radiographically apparent lesion. The value of bone scanning in patients with primary bone malignancy lies in the detection of the disease elsewhere.

Uptake of bone-seeking radiopharmaceuticals in primary bone tumors is avid and frequently striking. PET imaging with FDG is being explored for primary bone tumors. FDG uptake correlates with tumor metabolism. Scans can be helpful in localizing sites for biopsy and in assessing response to preoperative radiation and chemotherapy.

^{99m}Tc-MIBI have been used for sarcoma imaging to determine whether tumors are low or high grade and to assess response to therapy. As with FDG, high-grade tumors show higher uptake. Successful radiation therapy or chemotherapy is associated with decreasing uptake. Studies of primary tumor have led to at least one important observation about skeletal tracer uptake. Many tumors elicit marked hyperemia. The increased blood flow is not restricted to the tumor itself but affects the entire watershed distribution of regional flow, most characteristically involving an entire extremity (Figure 7).

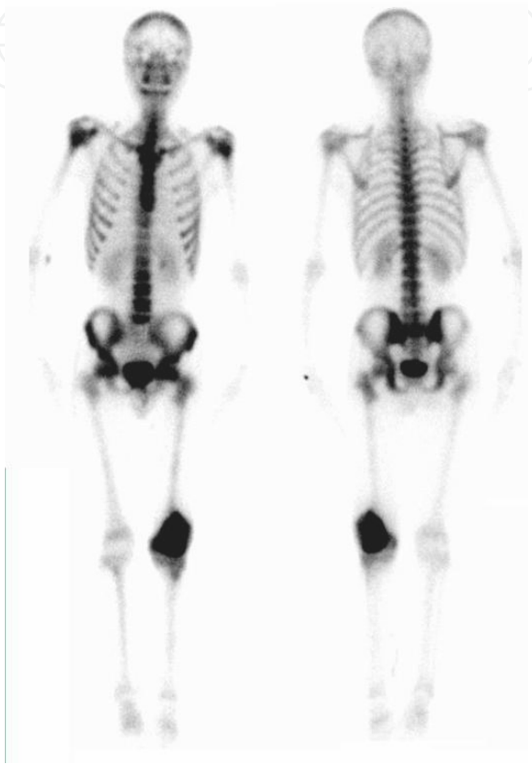


Fig. 7. Anterior and posterior whole body scintigram of a patient with osteosarcoma in the left distal femur. The degree of tracer accumulation in the lesion is striking. Note also the "watershed" phenomenon with increased tracer accumulation in all of the bones of the left lower extremity above and below the lesion. The increased blood flow induced by the osteosarcoma results in increased tracer delivery to the entire limb.

Another primary malignant disease commonly involving bone is multiple myeloma (MM). MM is really a disease of the red marrow space, and the most frequently involved skeletal structures are the vertebrae, pelvis, ribs, and skull (Figure 8). On skeletal scintigram the only finding in MM may be osteopenia. Unless an associated fracture or a focal lesion such as a plasmacytoma is present, skeletal scintigrams are often normal. MRI is an excellent modality for evaluating the marrow space for areas of involvement.

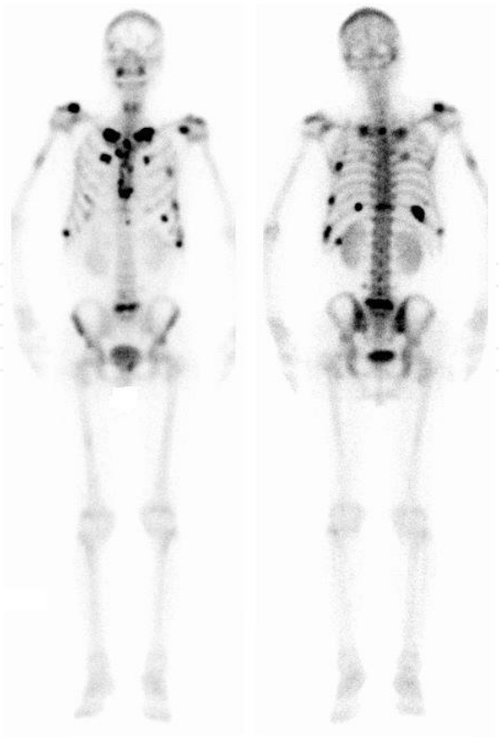


Fig. 8. Multiple myeloma, showed multiple focal accumulation of radioactivity in bone.

3.3 Benign bone tumors

Skeletal imaging is highly sensitive for detecting osteoid osteomas (Figure 9), which can be difficult to find by standard radiography, especially in the spine.

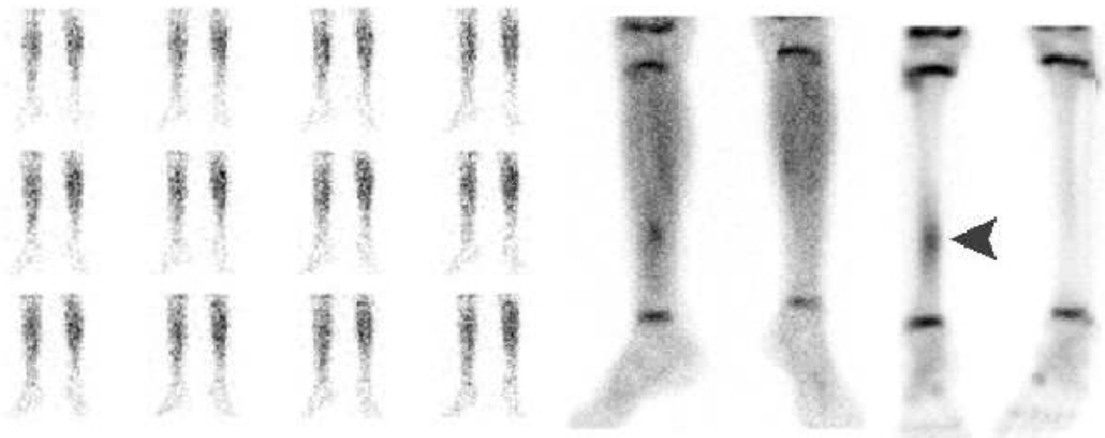


Fig. 9. Three phase bone scan (bottom row) of a 13 years old boy with history of pain and swelling in the right shin. The swelling was localized to the mid shaft of right tibia. Plain x-ray revealed a large area of sclerosis in the mid shaft of right tibia. Bone scan showed normal blood flow phase, high soft tissue uptake in the blood pool phase and a double density hot lesion in delayed image over the mid-shaft of right tibia. Surgical excision of the tumor resulted in total relief of symptoms. Histology confirmed the diagnosis of osteoid osteomas.

3.4 Trauma and athletic injuries

Skeletal trauma is common and presents both an opportunity and a problem in skeletal scintigraphy. As we known, the first choice for suspected bone fracture is radiography, which shows the fracture line and type clearly. But SPECT bone imaging has its own advantages in some aspects. SPECT is a useful adjunct in the course of process such as stress fracture. Normal bone is constantly remodelling, bone resorption and deposition are balanced. When the skeleton is placed under stress the rate of remodelling increases, and that will result in change of activity in bone scintigraphy,

The time a fracture takes to return to normal scintigraphically depends primarily on its location and the degree of damage to the skeleton.

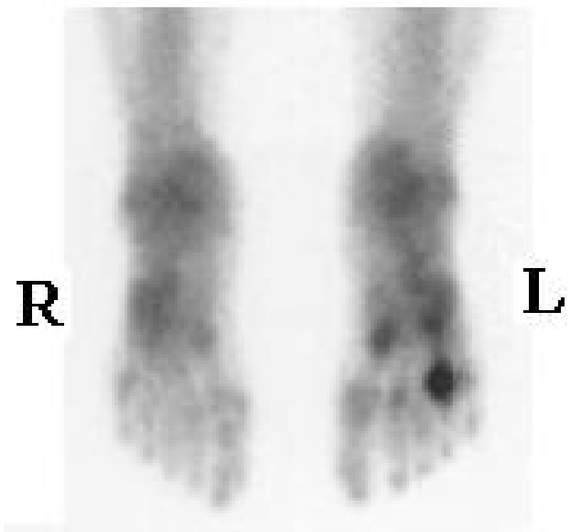


Fig. 10. Occult fracture of the left foot 4th toe, which can not be detected by radiography.

3.5 Osteomyelitis

In addition to being used in the evaluation of malignant disease involving the skeleton, radionuclide bone imaging is helpful in the assessment of several other non-malignant processes, such as patients with suspected osteomyelitis and diskitis. Acute hematogenous osteomyelitis typically begins by seeding of the infectious organism in the marrow space.

A three-phase bone scan is performed by acquiring a rapid blood flow sequence of images over the interested area during agent injection. Early images (blood flow phase) are important in evaluating inflammatory processes. Flow images are performed 40 to 60sec and 2 to 4 sec for each frame. Blood pool images are then immediately obtained for totally 300 to 500 kcounts without moving the patient, and delayed images are taken as necessary. Both osteomyelitis and cellutitis can cause early increased radioactivity accumulation due to an increased vascular response to the affected area. The third phase is routine scanning at 2 to 3 hr after injection. Sometimes there will be a forth phase that can be added 24hr delay. Osteomyelitis demonstrates focally increased activity in the involved bone on both the blood-pool and routine images (Figure 11). Since the use of bone imaging for detecting osteomyelitis, it has been found that several patients do not subsequently develop the typical radiographic changes because the early treatment prevents the development of radiographic abnormalities.

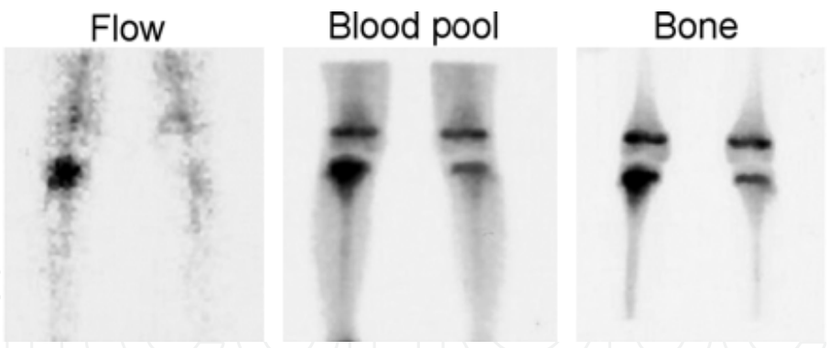


Fig. 11. Plantar view flow image show increased perfusion to the right proximal tibia. Blood-pool image also demonstrate abnormal accumulation in the same area. Delayed image have persistent radiopharmaceutical collection consistent with osteomyelitis. Focal hyerperfusion, focal hyperemia, and focally increased bony activity in the proximal right tibial metaphysic are the classic findings of osteomyelitis.

3.6 Metabolic bone diseases

A number of metabolic conditions can result in marked abnormalities on bone imaging. Although these do not represent important clinical indications for bone imaging, they may be encountered incidentally in other applications, most importantly during metabolic skeletal survey. Hyperthyroidism, primary hyperparathyroidism, renal osteodystrophy, osteomalacia, and hypervitaminosis D all can result in generalized increased tracer uptake throughout the skeleton that has some features in common with the "supers can" seen in metabolic disease(Figure 12). These features are described before, such as increased

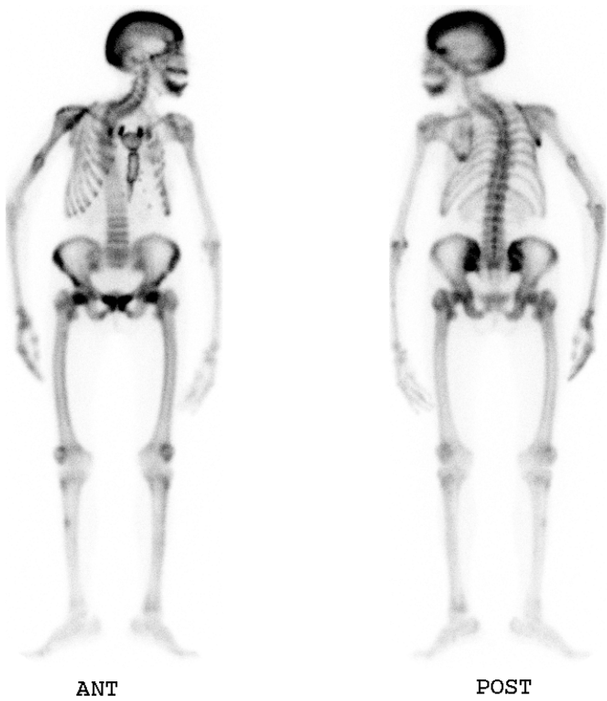


Fig. 12. Supers can in metabolic disease from the patient with hyperparathyroidism

skeleton-to-soft tissue ratio and faint or absent visualization of the kidneys. Increased skull activity, involvement of the long bones of the extremities, and increased periarticular uptake are features that distinguish scan in these conditions from the supers can of metabolic disease.

3.7 Bone marrow disorders

Non-invasive imaging techniques have been used in the past for visualization the functional activity of the bone marrow compartment. Imaging with radiolabelled compounds may allow different bone marrow disorders to be distinguished. These imaging techniques, almost all of which use radiolabelled tracers, such as ^{99m}Tc-nanocolloid, ^{99m}Tc-sulphur colloid (^{99m}Tc-SC), ^{111}In-chloride, and radiolabelled white blood cells (^{99m}Tc-WBC), have been used in nuclear medicine for several decades. The results support that the radiolabelled agents can be alternatives to bone marrow scan.

4. Radionuclide therapy of skeletal tumors

Metastatic bone cancer is a common complication of malignant tumor. It is reported that 20%-75% of cancer patients has developed bone metastases according to necropsy results. Malignant bone pain is still a challenging clinical problem. Pain due to bone metastases will greatly decrease the patient's quality-of-life because of patient's gradual deterioration, local body dysfunction, and mental and physical collapse. Recently, there are several reports on therapy of painful bone metastases by radiotherapy or anticancer drugs showing therapeutic efficacy. The studies, however, were generally heterogeneous trials involving stage of diagnosis, radiopharmaceuticals dosage, combination with other therapeutic modalities and methods of pain assessment. In addition, there are few reports on the study of comparison of radionuclide therapy with chemotherapy for evaluating the therapeutic effectiveness of the patients with painful bone metastases.

4.1 Radionuclide internal-radiation therapy

Radionuclide internal-radiation therapy of severe bone pain due to multiple skeletal metastases has recently achieved successful stage in nuclear medicine, which has been much considered and widespread used. In this chapter we described the principle of treatment of painful disseminated skeletal metastases, therapeutic approaches, evaluation of effective treatment according to our clinical experience in routine clinical treatment and its future applications.

^{89}Sr-chloride (Metastron) has been approved by the FDA for relief of bone pain in cases of painful skeletal metastases. The compound behaves biologically like calcium and localizes in hydroxyapatite crystal by ion exchange. Strontium uptake occurs preferentially at sites of active osteogenesis. This allows primary bone tumors and areas of metastatic involvement to accumulate significantly higher concentrations of strontium than surrounding normal bone. ^{89}Sr decays by beta- emission with a half life of 50.6 days. The conventional dose of ^{89}Sr-chloride is 148 MBq (4mCi), and can be reinjection after three months if necessary. Before administration, a blood regulation test should be checked.

Another two radiotherapeutic agents, ^{186}Re-HEDP and ^{153}Sm-EDTMP are also used in the area. ^{186}Re decays by beta- and gamma emission with a half life of 90.6 hr and ^{153}Sm decays by beta- emission and has a half life of 46.3 hr. Both of these beta-emitting radionuclides are complex with bone-seeking ligands, which localize by chemisorption. The duration of

response is 1-12 months. The main toxicity of these radiotherapeutics is mild transient bone marrow suppression.

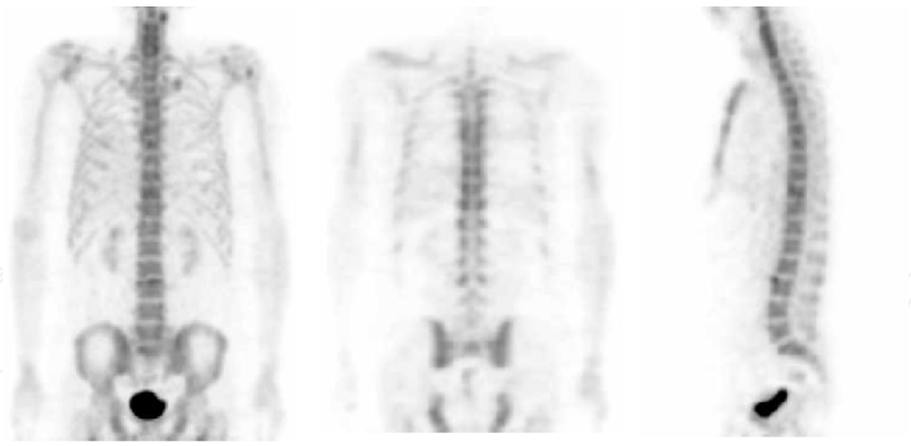
4.2 Radionuclide seed implantation

Radionuclide seed such as ^{125}I、^{103}Pd、^{198}Au implantation has been used in lots of clinical departments. Mostly ^{125}I seeds (Figure 13) have been chosen as the proper one. Iodine-125 delivers a higher radiation dose to the patient due to the half life of 60 days and ^{125}I seeds planted have been used in the therapy of solid tumors.

Fig. 13. ^{125}I seed is used in the therapy of solid tumor by implantation.

5. Recent advances of skeletal radionuclide imaging and therapy

It's well-known that the skeletal radionuclide imaging and therapy will have a prospective development in novel radiopharmaceuticals of skeletal imaging (^{18}F-NaF) (Figure 14) and therapy (heavy ion Carbon-11 and boron neutron capture therapy (BNCT)) and advanced nuclear medicine equipments such as SPECT/CT, PET/CT and PET/MR. In routine clinical practice, a variety of new radiopharmaceuticals have been introduced in recent years. There are three commercial radiopharmaceuticals of Samarium-153-ethylenediaminetetramethylene phosphonic acid (^{153}Sm-EDTMP), Rehnium-188-(Sn)-hydroxyethylene diphosphonate (^{188}Re-HEDP) and Strontium-89 chloride ($^{89}SrCl_2$). $^{89}SrCl_2$ is still the most widely used agent due to a longer physical half life ($T½$ = 50.5 days) and a pure beta-emitter playing an important role in radionuclide internal radiation therapy. ^{188}Re-HEDP ($T½$ = 16.9 hr) obtained from ^{188}W-^{188}Re generator is cheap and convenient in clinical practice routine, with scintigraphic imaging of gamma rays in order to perform individual dosimetric studies, but ^{188}W-^{188}Re generator must be imported from other countries. ^{153}Sm-EDTMP developed by our country is one of the radiopharmaceutical therapeutic agents and has relatively ideal physical, chemical and biological properties similar to ^{188}Re except of slightly longer have-life ($T½$ = 40.4 hr). The 0.103-Mev gamma ray is suitable for imaging in vivo distribution. The benefit of the favourable clinical experience with ^{153}Sm-EDTMP has been reported in several multicenter trials.



a b c

Fig. 14 Normal image of ^{18}F- Fluoride PET（a: 3D projection imaging b: coronal slice iamging: c: sagittal slice imaging）

6. Conclusion

It is important to resolve the problems on skeletal and soft tissue tumors for clinicians to seek for new diagnostic and therapeutic radiopharmaceuticals. Although rapid developments of medical science and great progress have been made recently, there are still some limitations. The clinical applications of radionuclide tracing technique in diagnosis and treatment of skeletal and soft tissue tumor is attached importance to clinical physicians with widely using the technique in clinical routine practice and continuing development of nuclear medicine.

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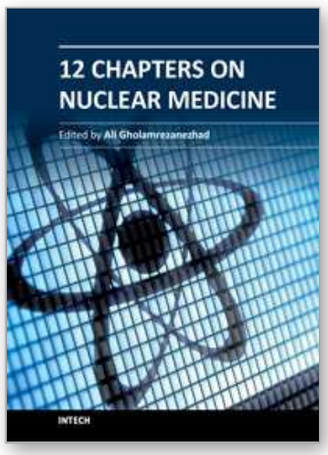

12 Chapters on Nuclear Medicine

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The development of nuclear medicine as a medical specialty has resulted in the large-scale application of its effective imaging methods in everyday practice as a primary method of diagnosis. The introduction of positron-emitting tracers (PET) has represented another fundamental leap forward in the ability of nuclear medicine to exert a profound impact on patient management, while the ability to produce radioisotopes of different elements initiated a variety of tracer studies in biology and medicine, facilitating enhanced interactions of nuclear medicine specialists and specialists in other disciplines. At present, nuclear medicine is an essential part of diagnosis of many diseases, particularly in cardiologic, nephrologic and oncologic applications and it is well-established in its therapeutic approaches, notably in the treatment of thyroid cancers. Data from official sources of different countries confirm that more than 10-15 percent of expenditures on clinical imaging studies are spent on nuclear medicine procedures.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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