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# Clinical Applications of Nuclear Medicine

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Additional information is available at the end of the chapter

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## 1. Introduction

Nuclear Medicine is a medical specialty in which radioactive substances are used for diagnostic and therapeutic purposes. Historically, its major development occurred after the Second World War. After the attack on Pearl Harbor, the United States developed nuclear reactors to produce atomic bombs, which were subsequently dropped on the Japanese cities of Hiroshima and Nagasaki. After the end of the war, the United States was involved in the campaign for application of *Atomic Energy for Peace*, which stimulated implementation of knowledge of nuclear energy for medical applications, among other beneficial actions. There is no doubt that this was the greatest advance in the production and distribution of radionuclides for medical purposes. The first radionuclide for medical applications was iodine-131, and this was followed by several others. Artificial production of technetium for diagnostic purposes was a milestone in the history of nuclear medicine. Today, this radioisotope is used the one most for producing imaging.

In the beginning, the images were documented using rectilinear scanner and subsequently using scintillation cameras or so-called gamma cameras, with images of poor definition. With technological development, improvements to gamma cameras became possible. The acquisition of functional images, which had previously only been done on a two-dimensional plane, became tomographic with three-dimensional reconstruction. This was named Single-Photon Emission Computed Tomography (known as SPECT), and it increased the sensitivity of detecting abnormalities or lesions. More recently, gamma cameras have been coupled with computed tomography (CT) or magnetic resonance imaging (MRI), thereby forming hybrid machines and increasing the effectiveness of identifying lesions or functionally abnormal tissues, at their sites. Technological advances have also been important for

Positron Emission Tomography (known as PET), thereby massively increasing the applicability of this method, especially related to oncologic processes, with molecular imaging.

The diagnostic and therapeutic applications are based on the kind of radiation used. In general, gamma emitters are used for diagnosis, and technetium-99m is the most common agent for this purpose. For therapy, beta radiation emitters such as iodine-131 are the agents most used.

Scintigraphy is a noninvasive imaging diagnosis method using low doses of radiation, it is painless, has reasonable cost and availability, and enables functional or metabolic assessment of organs or structures. Its advantage is clear, especially when the possibility of analysis using other methods is limited. It is based on administration of radiation-emitting substances to patients, with detection by scanning using a scintillation camera. These radioactive substances may migrate to the organs themselves or, when that does not happen, they may bind to other substances, thus forming complexes called radiopharmaceuticals that are taken up by the target organ. There are specific pharmaceuticals for each organ, e.g. MDP, DTPA, sestamibi, etc., thus making it possible to perform bone, renal or cardiac scintigraphy, respectively. The great majority of radiotracers represent the physiology or metabolic activity of some part of the body, but without altering the function of these structures or forming part of the metabolism.

The main characteristic of scintigrams is that they provide information on the functioning and metabolism of organs and structures. Hence, they differ from other imaging methods such as ultrasound, CT scans or MRI, which are anatomical, and thus complement the diagnostic investigation.

From this perspective, it is important to distinguish between the diagnostic approaches for benign or malignant diseases. In benign lesions, the most important information comes from functional assessment of each organ. This may show that the organ function is normal or is deviating from normal, and this is assessed together with the evolution of the disease or the post-intervention changes. Malignancies are assessed based on metabolic activity and findings of active primary or metastatic tumors. Details relating to residual tumors, viable tumors, recurrence, or disease progression are important and can be differentiated. Based on this information, the clinical application of nuclear medicine is to highlight the physiological or metabolic structures or organs involved.

This chapter does not aim to teach the methodology for performing scintigraphy, but to provide some knowledge for professionals who are not specialists in this field, so that the usefulness of this method in relation to various diseases can be seen.

This chapter is divided into applications and therapy using conventional scintigraphy with single-photon emitters.

The radionuclide most used for performing single-photon scintigraphy is technetium 99m, which is a pure gamma radiation emitter, with energy of 140 keV. This is considered to be a low energy level with ideal characteristics for producing images. It can be administered alone or coupled with pharmaceuticals to form complexes with specific characteristics relating to the preferential uptake for various human organs or structures. For each type of scintigraphy,

there is a specific radiotracer uptake mechanism that interfaces with the metabolism or excretion of the organ. In the following, most of the applications of diagnostic nuclear medicine in different systems of the human body are presented. The general precautions to be taken in cases of pregnancy, breastfeeding, breastfed infants and young children, for all the procedures in nuclear medicine, are indicated. This should be discussed on a case-by-case basis.

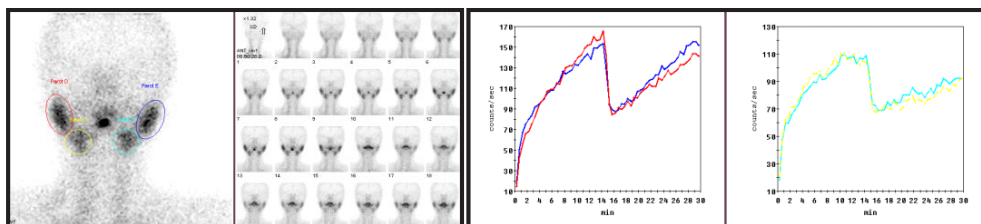
## 2. Gastrointestinal system

Application of nuclear medicine to the gastrointestinal (GI) system is very useful for investigating many diseases. This is a noninvasive and painless examination, with administration of low doses of radiation to patients. It is easy to perform and is indicated for diagnosing and following up gastrointestinal diseases. The long acquisition time for most examinations increases the sensitivity for detecting gastrointestinal abnormalities. Scintigraphy is generally of use for assessing organ function and the kinetics of gastrointestinal transit or excretion.

### 2.1. Salivary gland imaging

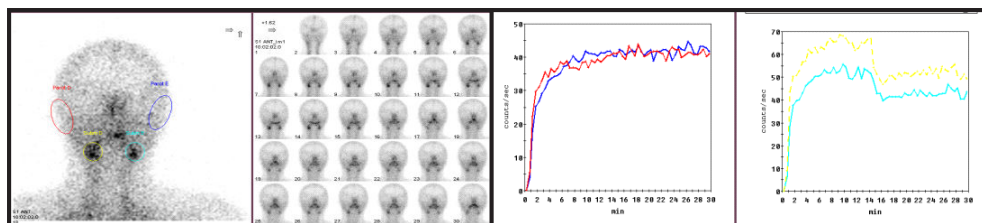
This assesses the function and excretion of the salivary glands, both in the initial diagnosis and in post-treatment follow-up. The main indications include: tumors, cysts, inflammatory or infectious diseases, calculosis and Sjögren's syndrome.

The radioisotope used is pertechnetate, an anion that is concentrated and secreted by the epithelial cells of the salivary glands in the same way as seen with the anions that make up the saliva. Thus, this substance reflects the production and physiological secretion of the saliva. This radiotracer is administered intravenously, and sequential images of the head are acquired for 30 minutes. Over the first ten minutes, increasing concentration of radiotracer in the salivary glands is observed, which represents the function. After administration of citric stimulus, generally using lemon, the excretion phase begins. The uptake peak usually occurs five to ten minutes after starting to administer the radiotracer, and complete excretion begins immediately after the stimulation with lemon (Figure 1).



**Figure 1.** Normal salivary gland imaging. Dynamic images are performed during 30 minutes and citric stimulus is on first fifteen minutes. Region of interest are placed on right and left parotid (red and dark blue) and submandibular (yellow and light blue) glands and time activity curves are created showing quantitative uptake and excretion analyses.

The scintigraphic abnormalities depend on the type and severity of disease. Most tumors present diminished or absence of uptake radiotracer, except for Warthin's tumor. Acute inflammatory and infectious diseases present uptake increased because of the increased vascularization and diminished secretion. Abscesses and cysts do not show any uptake. Patients with Sjögren's syndrome either do not concentrate radioactive material or concentrate very little of it (Figure 2).

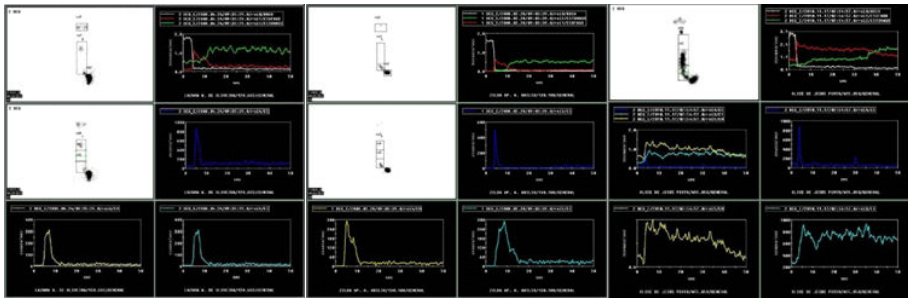


**Figure 2.** Anormal salivary gland imaging. Absence uptake and non excretion in parotid glands confirmed by quantitative curves by region of interest (red and dark blue).

Other agents that are used to assess the salivary glands include gallium-67 and  $^{111}\text{In}/^{99\text{m}}\text{Tc}$ -labeled white blood cells, in cases of inflammatory or infectious diseases.

## 2.2. Scintigraphy on esophageal transit and emptying

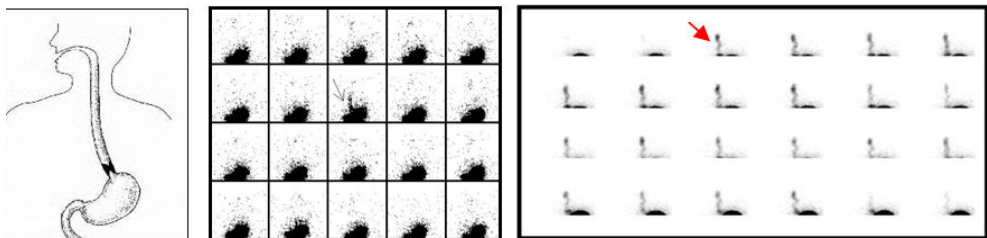
Scintigraphy on the esophageal transit is a noninvasive examination with oral administration of radiotracer that supplies information on esophageal motility, in relation to the duration of esophageal transit and segmental motor abnormalities such as adynamia and lack of coordination. It is indicated for patients with suspected primary or secondary motor disorders, both for diagnosis and for follow-up of therapeutic interventions, in conditions such as achalasia, scleroderma, diffuse esophageal spasm, nutcracker esophagus, diabetic enteropathy, nonspecific motor disorders, Chagas' disease, neoplasm, systemic lupus erythematosus, polymyositis, myasthenia gravis, myotonic dystrophy, esophagitis, alcoholism and others. The radiopharmaceuticals indicated for these assessments are those that are not absorbed by the esophageal mucosa, such as colloids and chelates: technetium- $^{99\text{m}}\text{Tc}$ -sulfur colloid and diethylenetriamine pentaacetic acid (DPTA). The radiopharmaceuticals are administered orally, diluted in 10 ml of water, and deglutition is stimulated every 20 seconds with the patient in either a supine or an upright position. The transit time for the entire esophagus and in its three segments (upper, middle and lower) is quantified and the motor abnormality pattern (adynamia or lack of coordination) is determined (Figure 3).



**Figure 3.** Scintigraphy on esophageal transit. Normal, adynia and adynia with incoordination patterns, respectively.

### 2.3. Investigation of gastroesophageal reflux

Scintigraphy is the most sensitive noninvasive method for detecting gastroesophageal reflux, especially in children. Colloids with low absorption rates in the esophageal and gastric mucosa are used, thereby reflecting the kinetics of the tracer within the digestive system. After oral administration of  $^{99m}\text{Tc}$  colloid, and with a field of view covering the stomach and esophagus, episodes of gastroesophageal reflux are identified and information on the quantity and duration of the reflux and the point that it reaches are obtained (Figure 4). It has the advantage of continuous and more prolonged acquisition, which increases the sensitivity of the method. Other additional information obtained includes assessment of pulmonary aspiration, in the event that the reflux of the ingested material reaches the pulmonary tree.



**Figure 4.** Gastroesophageal reflux scintigraphy. A single episode with a short time, reaching the upper esophageal segment (black arrow) and during a long time (red arrow).

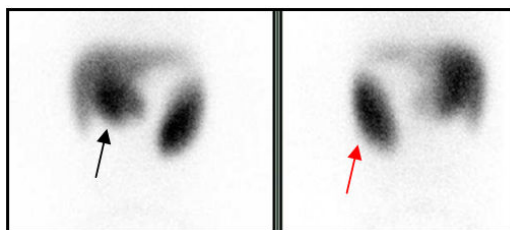
### 2.4. Gastric emptying

This is a noninvasive examination performed after intake of solid foods, liquids or a mixture of these. The emptying time and kinetics of the radiotracer in the stomach depend on the composition of the food ingested. Several pharmacological materials can be labeled with the radioactive substance, and the composition of both the food and the radiotracer depends on

the standard adopted by each laboratory as the reference value. Computer acquisition is required to determine the half-time of emptying and/or percent of emptying and to generate gastric emptying time-activity curves. The main indications include diabetic gastroparesis, anorexia nervosa, gastroesophageal reflux, gastritis, gastric ulcer, duodenal ulcer, Zollinger-Ellison disease, connective tissue disorders and others, along with postsurgical evaluations, vagotomy and gastrectomy.

## 2.5. Liver-spleen imaging

Other imaging methods such as MRI, CT and ultrasound offers better information about the anatomic display of liver and spleen than does this exam. The radionuclide colloid imaging is capitalized by phagocytosis by Kupffer cells of liver and spleen. The uptake and distribution of  $^{99m}\text{Tc}$ -colloid in liver and spleen reflects perfusion and the distribution of functioning reticulendothelial cells. Usually, the information of liver-spleen scan include the size, shape and position, the distribution aspect of activity within the organs, as homogeneity or non-homogeneity, presence of any or many focal defects in activity and relative distribution of colloid among the liver, spleen and bone marrow. Most of the masses seen on MRI, CT or US, which take up  $^{99m}\text{Tc}$  colloid contain Kupffer cells, and are benign. These present with increased hepatic uptake and include: focal nodular hyperplasia (Figure 5), cirrhosis with regenerating nodule, Budd-Chiari syndrome and Superior vena caval obstruction. Masses with decreased hepatic uptake can be benign or malignant. These include: hepatoma, metastasis, cyst, adenoma, hemangioma, abscess, and pseudotumor. The most common causes of focal defects in the spleen include: abscess, cyst, infarct, lymphoma, and hematoma.



**Figure 5.** Liver-spleen scintigraphy. Focal nodular hyperplasia. Anterior and posterior images. Focal uptake increased in liver (black arrow). Spleen increased too (red arrow).

## 2.6. Hepatic blood pool imaging

This exam is indicated for evaluating hemangiomas. These lesions are clusters or large blood filled sinuses. They are usually asymptomatic, and are found as incidental findings during MRI, CT or US performed for others indications. The radiotracer used is  $^{99m}\text{Tc}$ -red blood cells (RBC), injected intravenously. The typical appearance of  $^{99m}\text{Tc}$ -RBC scan is a focal area of decreased perfusion on the first study (flow phase), and in the immediate images because the flow with  $^{99m}\text{Tc}$ -RBC is relatively low compared to the hemangioma. About 1 or 2 hours

later, the radiolabelled cells reach the hemangioma vessels, and then these lesions present as a focal hot spot, with intensity similar to the heart. This method is highly specific to confirm hemangioma.

### **2.7. Gastrointestinal bleeding imaging**

The common causes of lower GI bleeding in adults include neoplasms, inflammatory bowel disease, diverticular disease and angiodysplasia. The GI Imaging is a noninvasive method that provides information especially of lower GI bleeding. The effective therapy for acute GI bleeding depends on accurate localization of the site of bleeding. There are two radiotracer that localize the GI bleeding;  $^{99m}\text{Tc}$ -RBC and  $^{99m}\text{Tc}$ -colloid. The first one is preferred in the investigation of GI hemorrhage, especially in cases of intermittent or slow bleeding, because the radiotracer remains in the intravascular space. Imaging may be performed over a period of 24 hours. The second one is high, specifically to identify the bleeding site, but the sensitivity is low, because it is performed for a short time and the bleeding needs to be present at the moment of scintigraphy.

## **3. Cardiovascular system**

Nuclear medicine examinations play an important role in the noninvasive evaluation of cardiac physiology.

### **3.1. Myocardial perfusion imaging**

Myocardial perfusion imaging (MPI) has high sensitivity to evaluate perfusion in the left ventricular wall and thus indirectly assess coronary flow. The ischemic cascade is the basis and the best justification for the use of nuclear medicine examinations in the evaluation of coronary artery disease.

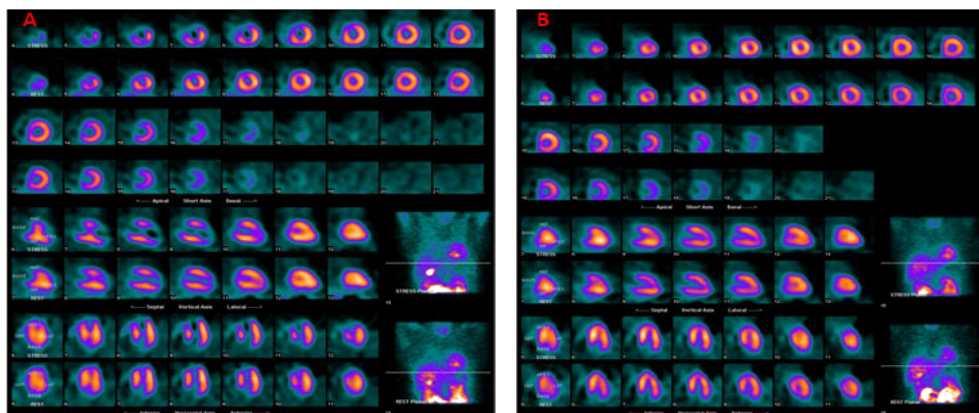
Myocardial perfusion imaging can be performed with thallium-201 chloride and Pharmaceuticals labelled with  $^{99m}\text{Tc}$  (sestamibi, tetrofosmim and teboroxime). To use thallium-201 chloride it is necessary to fast for at least 4 hours. Radiopharmaceuticals labelled with  $^{99m}\text{Tc}$  have advantages and disadvantages when compared to thallium-201 chloride, as best rate of counts and less sensitivity to assess viability, respectively.

The stress phase can be accomplished by exercise or by the use of drugs such as dipyridamole, adenosine, and dobutamine. The sensitivity and specificity of these types of stress are similar.

Clinical applications of the study with thallium-201 chloride are: diagnosis of coronary artery disease, assessing the extent and severity of coronary stenosis, myocardial viability assessment and therapeutic efficacy (CABG and angioplasty).

Radiopharmaceutical labelled with  $^{99m}\text{Tc}$  are usually associated with cardiac monitoring during image acquisition, thus allowing quantitative analysis with motility evaluation of the left ventricular wall and ejection fraction.

Clinical applications of the study using radiopharmaceuticals labelled with  $^{99m}\text{Tc}$  are: a diagnosis of coronary artery disease, risk stratification post-myocardial infarction and therapeutic efficacy (Figure 6).



**Figure 6.** Myocardial perfusion scintigraphy with  $^{99m}\text{Tc}$ -sestamibi. A: Pre-angioplasty: ischemia of the apex and the middle and apical regions of the anteroseptal wall of the left ventricle. B: Post-angioplasty: a study without evidence of myocardial ischemia.

### 3.2. Myocardial viability imaging

The principle objective of myocardial viability assessment is to identify patients eligible for coronary artery bypass grafting (CABG). Several criteria were used to determine the clinical impact of CABG: improvement in regional left ventricular function, in global left ventricular function (ejection fraction), symptoms, functional capacity, in cardiac remodeling and long term prognosis [1].

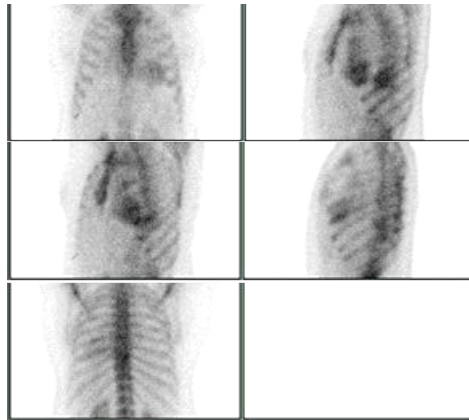
Imaging with thallium-201 chloride and home-redistribution protocol can be used to assess the presence of viable myocardium. Using the protocol stress-rest-reinjection, in addition to similar information, the presence of ischemia can be evaluated.

### 3.3. Myocardial infarction imaging

Currently this study has been little used, due to advances in methods of enzymatic detection of acute myocardial infarction. Radiopharmaceuticals used can be  $^{99m}\text{Tc}$ -pyrophosphate and Antimyosin-Fab-DTPA-In-111.

The maximum uptake of  $^{99m}\text{Tc}$ -pyrophosphate occurs 24 to 72 hours after the event. Planar imaging with  $^{99m}\text{Tc}$  pyrophosphate detect acute transmural with a sensitivity of at least 90% and a specificity of 70% (Figure 7). Tomographic imaging (SPECT) can improve the specificity to around 80%.





**Figure 7.** Imaging of myocardial infarction with  $^{99m}\text{Tc}$ -pyrophosphate.  $^{99m}\text{Tc}$ : transmural infarction in the anterolateral wall of the left ventricle.

Antimyosin has an overall sensitivity of 92% for the detection of acute MI [2].

### 3.4. Multi Gated Acquisition (MUGA)

The objective is to assess the global and regional ventricular function. The radiopharmaceutical used is  $^{99m}\text{Tc}$ -red blood cells (RBC), erythrocytes labeled with  $^{99m}\text{Tc}$ . The parameters evaluated in this study are: motility of the ventricular wall, left ventricular ejection fraction, analysis of phase and amplitude. The clinical indications are: acute myocardial infarction, coronary artery disease, cardiomyopathy, valvular disease, congenital heart disease, therapeutic efficacy assessment and evaluation of cardiotoxic drugs.

### 3.5. Cardiac adrenergic imaging

The sympathetic and parasympathetic innervation of the heart plays an important role in regulating the cardiac function [3]. The activation of sympathetic innervation causes increased heart rate (chronotropic effect), contractility (inotropic effect) and conduction atrio-ventricular [4]. Norepinephrine is produced and stored in presynaptic vesicles in sympathetic nerve terminals [5]. Thus, the radionuclide used for cardiac adrenergic imaging is  $^{123}\text{I}$ -MIBG (metaiodobenzylguanidine) that is a guanethidine analogue which mimics norepinephrine [6]. The clinical indications are: heart failure, cardiomyopathy, cardiac transplantation, ischemia and myocardial infarction and ventricular tachyarrhythmias.

## 4. Pulmonary system

Pulmonary embolism (PE) is an important and treatable illness caused by migration of thrombus to the pulmonary circulation, commonly from the veins of the lower extremities.

Untreated, PE can cause death [7]. The treatment includes oral anticoagulants, heparin and thrombolytic agents. The clinical presentation of PE is variable, from asymptomatic to sudden death, including cough, hemoptysis, chest pain, breathlessness, syncope, palpitations, tachypnoea, cyanosis, tachycardia, pulmonary hypertension and right heart failure. But, these symptoms are not specific of PE, needing more tests to confirm or refuse the PE diagnostic. Recently, Bajc et al, purposed a clinical algorithm for the investigation of patients with suspected PE. If the clinical likelihood of PE is low and the quantitative D-dimer is negative, a diagnosis of PE is unlikely and further investigations are not required. If the clinical likelihood of PE is low and the quantitative D-dimer is positive, further investigations for a range of diagnoses including PE may be required, particularly if the D-dimer level is markedly elevated. If the clinical probability is other than low, it seems more appropriate to skip the D-dimer test and refer the patient directly to the appropriate imaging technique. This may be Ventilation (V) and perfusion (P) imaging ( $V/P_{SCAN}$ ) or multidetector computed tomography of the pulmonary arteries (MDCT) depending on the local availability, medical expertise, and the patient's clinical condition.  $V/PS_{CAN}$  has virtually no contraindications and yields a substantially lower radiation burden than MDCT [8].

A combined ventilation and perfusion study increases the specificity for PE diagnosis. A combined 1-day protocol is preferred. The scan can be with planar lung imaging (anterior, posterior, left and right lateral and left and right posterior oblique) or Spect imaging. In pregnancy only a perfusion scan is recommended.

#### 4.1. Ventilation lung scintigraphy (V)

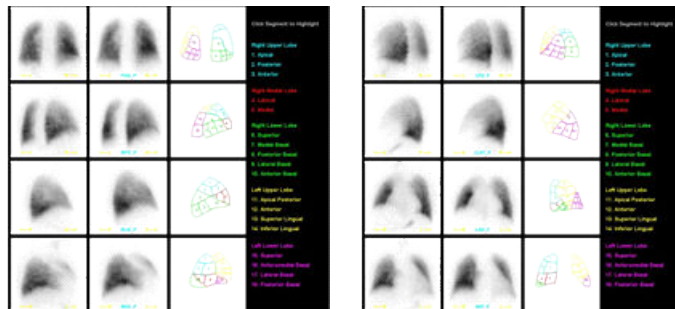
Ventilation studies, in general, are performed after inhalation of inert gases  $^{133}\text{Xe}$  and  $^{81\text{m}}\text{Kr}$ , radiolabelled aerosols  $^{99\text{m}}\text{Tc}$ -DTPA and  $^{99\text{m}}\text{Tc}$ -labelled Technegas. It is performed for mapping regional ventilation.

#### 4.2. Perfusion lung scintigraphy (P)

Perfusion scintigraphy is accomplished by microembolization with radiolabelled particles injected into a peripheral vein. The commercially used particles are MAA, which are labelled with  $^{99\text{m}}\text{Tc}$ . The particle distribution accurately defines regional lung perfusion.

$V/P_{SCAN}$  exploits the unique pulmonary arterial segmental anatomy. Each bronchopulmonary segment is supplied by a single end-artery. In principle, conical bronchopulmonary segments have their apex towards the hilum and base projecting onto the pleural surface. Occlusive thrombi, affecting individual pulmonary arteries, therefore produce characteristic lobar, segmental or subsegmental peripheral wedge-shaped defects with the base projecting to the lung periphery.  $V/P$  mismatch within bronchopulmonary segment(s) defected by PE, ventilation is usually preserved. This pattern of preserved ventilation and absent perfusion within a lung segment gives rise to the fundamental signature for PE diagnosis using  $V/P_{SCAN}$ , known as  $V/P$  mismatch.

Follow-up of PE using imaging is essential to assess the effect of therapy, differentiate between new and old PE on suspicion of PE recurrence and investigate physical incapacity after PE [9].



**Figure 8.** Normal pulmonary scintigraphy. Inhalation and perfusion images are compared. Homogeneous uptake in lungs. Matched findings.

## 5. Genitourinary tract imaging

In nuclear medicine the studies of genitourinary system can be divided into superior and inferior genitourinary tract. Studies evaluating the superior genitourinary tract include the kidneys, allowing evaluation of several characteristics such as blood flow, function, anatomy and integrity of the collection system, aiding in the diagnosis of different pathologies. For the lower genitourinary tract studies are represented by radionuclide cystography and testicular scintigraphy.

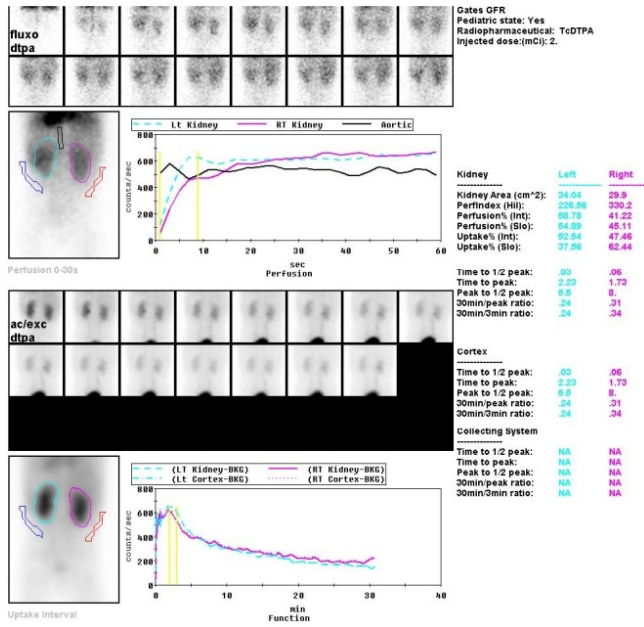
Renal radiopharmaceuticals commonly used to meet the various pathologies are  $^{99m}\text{Tc}$ -MAG3,  $^{99m}\text{Tc}$ -DTPA,  $^{99m}\text{Tc}$ -GHA and  $^{99m}\text{Tc}$ -DMSA, being dependent on the indication of particular characteristics.  $^{99m}\text{Tc}$ -MAG3 has as a main uptake mechanism tubular secretion (98% tubular secretion, 2% of glomerular filtration and extraction fraction of 40-50%). the  $^{99m}\text{Tc}$ -DTPA has as a main uptake mechanism glomerular filtration (100% filtration and extraction fraction of 20%).  $^{99m}\text{Tc}$ -GHA has a mixed uptake mechanism, being, glomerulo-tubular (10-20% tubular secretion and 80-90% glomerular filtration). The  $^{99m}\text{Tc}$ -DMSA is attached to the renal cortical (40-50% cortical binding in 2 hours).

### 5.1. Clinical applications in the superior genitourinary tract

Dynamic renal scintigraphy renogram represents the study commonly used to evaluate the various pathologies associated with superior genitourinary tract.

#### 5.1.1. Obstruction of the genitourinary tract

It is the main indication of renal dynamic studies. The exam is simple, painless, easy to perform and only prior hydration is necessary. It lasts 30 to 50 minutes, and such variation is associated with the use of diuretics (Figures 9 and 10).



**Figure 9.** Dynamic renal scintigraphy with 99mTc-DTPA: flow, normal function and nonobstructive excretory pathways.

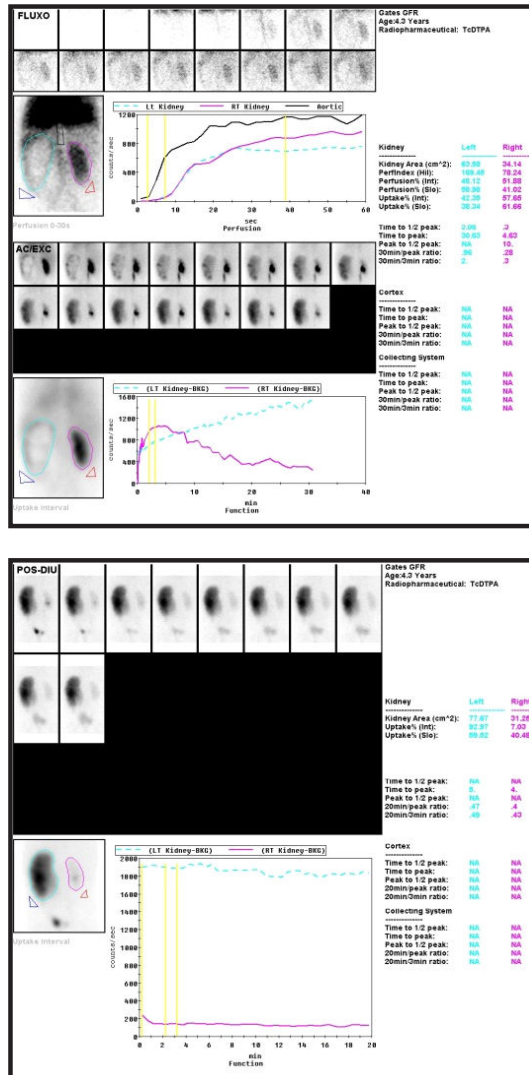
5.1.2. Hypertension of renovascular origin

For this condition, the renal dynamic study is done in two phases: one utilizing a stimulus by angiotensin converting enzyme inhibitor, one hour before administration of the radio-pharmaceutical and the other from the merely studying renal dynamic without stimulus considered study baseline.

According to the pathophysiology of renovascular disease, the standard pattern of diagnosis is an abnormal study with stimulation of the angiotensin converting enzyme inhibitor associated with a normal baseline study.

5.1.3. Renal transplant

In renal transplant, renal dynamic study is mainly used for evaluation of its most common complications such as acute tubular necrosis and rejection. The scintigraphic pattern of acute tubular necrosis and acute rejection are very similar, with preserved or slightly reduced flow and reduced glomerular filtration rate. The time and symptoms are the key to diagnosis. In serial renal studies, the renal graft dysfunction secondary to acute tubular necrosis should improve or remain unchanged, while the rejection demonstrates progressive deterioration. Currently, ultrasound is the method of choice for renal transplant dysfunction [10].



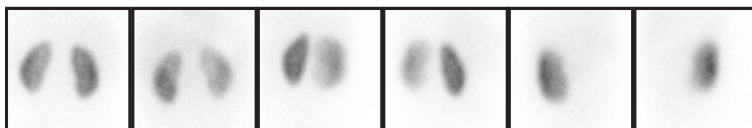
**Figure 10.** Dynamic renal scintigraphy with <sup>99m</sup>Tc-DTPA and use of diuretic: Deficit of flow and left renal function associated with obstructive hydronephrosis.

#### 5.1.4. Acute pyelonephritis and renal scarring

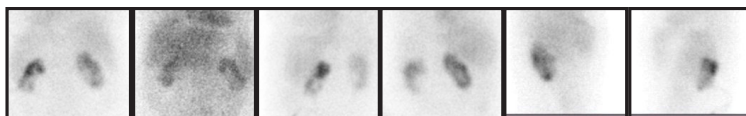
The renal cortical scintigraphy with <sup>99m</sup>Tc-DMSA is the procedure of choice for evaluating acute pyelonephritis and renal scarring. The image acquisition takes place 2 to 3 hours after intravenous administration of the radiopharmaceutical so that attachment occurs at the same cortical. The scintigraphic patterns in acute pyelonephritis are focal involvement of a

single area or multiple areas and diffuse involvement of the kidney. It has 100% sensitivity and specificity above 87% [11].

Renal scarring is a consequence of acute pyelonephritis, which may develop in 37% to 80% of children after an episode of infection [11,12] (Figures 11 and 12).



**Figure 11.** Normal renal scintigraphy with  $^{99m}\text{Tc}$ -DMSA.



**Figure 12.** Renal scintigraphy with  $^{99m}\text{Tc}$ -DMSA, renal scars.

## 5.2. Clinical applications in the lower genitourinary tract

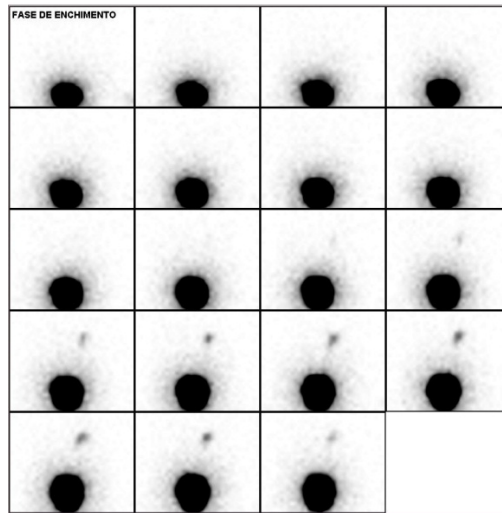
### 5.2.1. Assessment of vesicoureteral reflux

Radionuclide cystography permits visualization of very small volumes of reflux, and is probably more sensitive than contrast cystography [13]. The procedure is performed by infusion of saline and radiopharmaceuticals within the bladder through the catheter, thereby evaluating the presence of reflux (Figure 13).

### 5.2.2. Testicular torsion

Testicular torsion is considered a surgical emergency and the availability of this tissue is mainly related to ischemic time. The testicular ultrasound is a simple method and easily performed for evaluation of this condition, however, in children evaluating the flow can be difficult, testicular scintigraphy is indicated.

The scintigraphic findings depend on the stage of testicular torsion, in the early phase there is a normal flow, reduced or absent and the still image is a slight reduction in uptake of the radiotracer within the testicle, followed by an increase in flow and static image appearance of halo of mildly increased activity around a centrally cold testicle, ending with testicular infarction, in which there is an increased flow rate and persistent halo of increased activity around a cold center.



**Figure 13.** Radionuclide cystography: right vesicoureteral reflux.

## 6. Musculoskeletal system

### 6.1. Bone scintigraphy

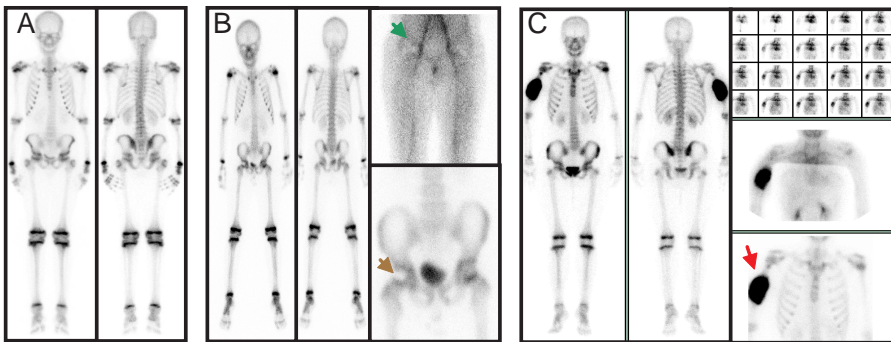
Bone scintigraphy identifies single or multiple focal or diffuse areas with increased osteoblastic activity, which reflects local bone remodeling. It is a highly sensitive examination for detecting such abnormalities, but its specificity is limited. It needs to be analyzed in conjunction with other imaging examinations. It is indicated for both adults and children, but should be interpreted differently for these two groups, given that the normal distribution of radiopharmaceutical in the skeleton differs between adults and children, particularly because of the presence of physiological osteoblastic activity in the growth cartilage of children. These bone scans are based on the principle of phosphonate uptake in bone tissue, especially in blastic lesions. For example, from this principle, the presence of osteoblastic metastases from breast tumors or prostate tumors can be seen, among others. Likewise, changes typical of benign diseases such as bone infections, inflammatory activity of rheumatic diseases, and prosthesis complications like loosening, infection, etc., can be seen.

The radiopharmaceutical used most, which is called  $^{99m}\text{Tc}$ -methylene diphosphonate ( $^{99m}\text{Tc}$ -MDP), binds to the amorphous phase of hydroxyapatite crystals by means of chemoadsorption. It is administered intravenously as a bolus. Images can be acquired immediately afterwards when information on the blood supply and vascular permeability is important, like in cases of infectious or tumor growth processes. They may also only be acquired later on, after 2-3 hours of injection, with acquisition of whole-body images in the anterior and posterior projections, in order to acquire information on osteoblastic activity. It is worth em-

phasizing that this examination shows low sensitivity to predominantly lytic pathological conditions or to conditions with low bone remodeling, except in cases associated with significant osteoblastic abnormalities, such as in investigations of associated fractures, for example, in patients with multiple myeloma. The great advantage of this method is that it assesses the whole body in a single examination with high sensitivity, and it guides other examinations that are more specific.

#### 6.1.1. Clinical applications for children

Based on informations above, the mean indications of bone scan include: primary benign or malignant bone tumors and bone metastases; acute osteomyelitis versus soft-tissue inflammation; subacute and chronic osteomyelitis; septic arthritis as a complication of osteomyelitis; and aseptic arthritis; aseptic necrosis (Legg-Calvé-Perthes disease) and sickle cell disease; equivocal radiographic findings after trauma; stress fractures; occult fractures; child abuse; multiple trauma; complications of fractures and therapy; and Sudeck's atrophy; surgery-guided by bone scintigraphy, like as osteoid osteoma; bone dysplasia; Camurati-Engelmann disease; evaluations on skeletal involvement (brown tumors); and hyperparathyroidism; arthritis and bone pain [14]. Scintigraphies in children are showed in figure 14.



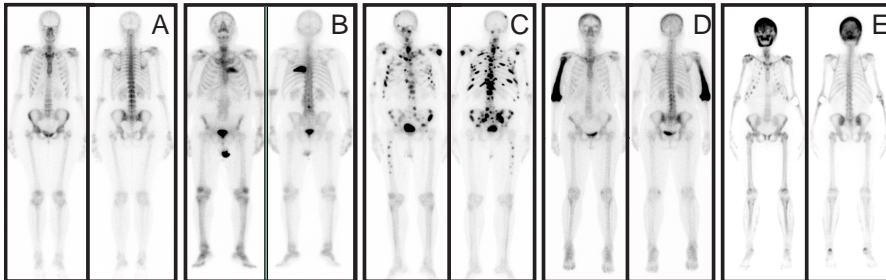
**Figure 14.** Bone scintigraphy in children. A. normal scan: Symmetric uptake on the skeletal and presence of physiological osteoblastic activity in the growth cartilage. B. Acute phase of avascular necrosis in right femoral head. Vascular permeability decreased (green arrow) and photopenic area (brown arrow) in right femoral head. C. Three phase bone scan. Osteosarcoma in the right humerus. Flow, vascular permeability and osteoblastic activity increased in right humerus (red arrows).

#### 6.1.2. Clinical applications for adults

A little difference is observed between the children's and adults' indications of bone scan. In this last group, the pathologies include: primary and metastatic bone tumors: staging, follow-up and post-therapy evaluation; distribution of osteoblastic activity prior to radiometabolic therapy ( $^{89}\text{Sr}$ ,  $^{153}\text{Sm-EDTMP}$  and  $^{186}\text{Re-HEDP}$ ); osteomyelitis; Paget's disease, osteoporosis and hyperparathyroidism; arthropathy, low back pain and sacroiliitis; fibrous



dysplasia and other rare congenital conditions; stress fractures, shin splints, occult fractures; avascular necrosis and loose or infected joint prosthesis [15] (Figure 15).



**Figure 15.** Bone scintigraphies in adults. A. Normal scan: symmetric uptake on the skeletal. B. Single bone metastasis on left rib. C. Multiple bone metastasis. Multiple focal uptake on skull, scapulas, ribs, spine, pelvis and right femur. D. Monostotic Paget Disease on right humerus. Intense uptake on right humerus. E. Hyperparathyroidism. Intense uptake on skull and focal uptake on ribs.

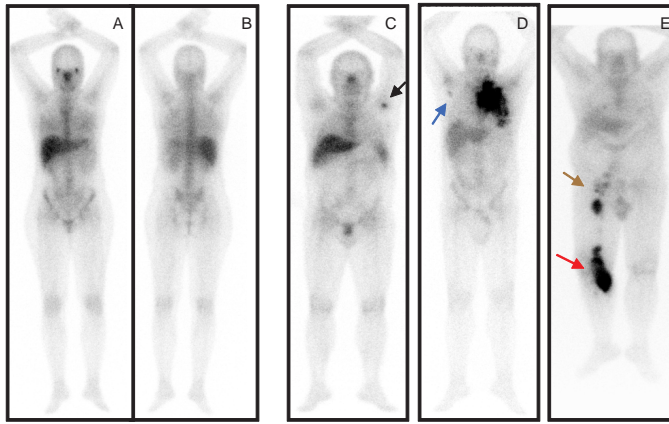
## 7. Scintigraphy with gallium-67 citrate

Because of the characteristics of gallium-67 uptake in tissues, this radiotracer can be used in relation to neoplastic diseases, especially lymphomas, and in cases of chronic inflammatory or infectious processes, such as those in fever of unknown origin or in patients with acquired immunodeficiency.

The radiotracer is administered intravenously 48 hours before producing whole-body initial images in the supine position, in the anterior and posterior projections. Delayed images, produced at least from 72 hours and up to 5 days after injection, may be needed to differentiate normal colonic activity from lesions in the abdomen. This allows clearance of nonspecific activity from the body, and enhancement of the target in relation to the background in the images. The technologist or physician should give the patient a thorough explanation about the examination. Food and liquid restrictions are not mandatory. Bowel preparation is optional. In patients with constipation, oral laxatives prior to imaging may decrease the activity in the bowel. In this case, laxatives should be given on the day before gallium-67 scintigraphy (at least 18 hours prior to scanning). Gallium-67 scanning should be avoided within 24 hours of blood transfusion or gadolinium-enhanced MRI, which could interfere with gallium-67 biodistribution. It is also advisable to wait 3-4 weeks after chemotherapy before performing follow-up imaging.

Management of patients with lymphoma is very useful, especially in intermediate or high-grade tumors. Low-grade lymphomas may not uptake gallium-67 and therefore may not benefit from this method. Although anatomical diagnostic methods such as CT and MRI are superior to gallium-67 for initially staging the patients, an initial examination using gallium-67 is important because it serves as the basis for post-therapy monitoring of patients and

indicates which patients may benefit from this method. If the tumor does not concentrate gallium-67 in the first examination, this radiotracer should not be used for the follow-up. For lymphomas that concentrate gallium-67, this tool becomes very useful for assessing the response to the treatment, since gallium accurately assesses tumor viability and the extent of the disease, indicates the prognosis and, especially, is important for restaging, given that the anatomical changes that occur after the treatment make it difficult to interpret anatomical images. Other tumors that may benefit from this method are lung cancer, head and neck tumors, hepatocellular carcinoma, germ cell tumors, neuroblastomas, sarcomas, multiple myelomas and melanomas. These tumors present avidity for gallium-67, but the use of this imaging method in these tumors is not well defined (Figure 16).



**Figure 16.** Whole body scan with gallium 67. A. normal scintigraphy. B. Lymphoma with lymphonodopathy. Uptake in left axillary lymphonode. C. Lymphoma with lymphonodopathy in right axillary, supraclavicular and mediastinal chain and left lung. D. Lymphoma in inguinopelvic lymphonode and soft tissue in right leg.

In addition, gallium-67 has been used to detect infections or inflammations such as osteomyelitis, sarcoidosis and myocarditis, and to evaluate interstitial lung disease and examine patients with acquired immunodeficiency syndrome (AIDS). It has been suggested that gallium-67 may be clinically useful for assessing adults presenting fever of unknown origin because of the possibility of locating pathological uptake (both malignant and benign).

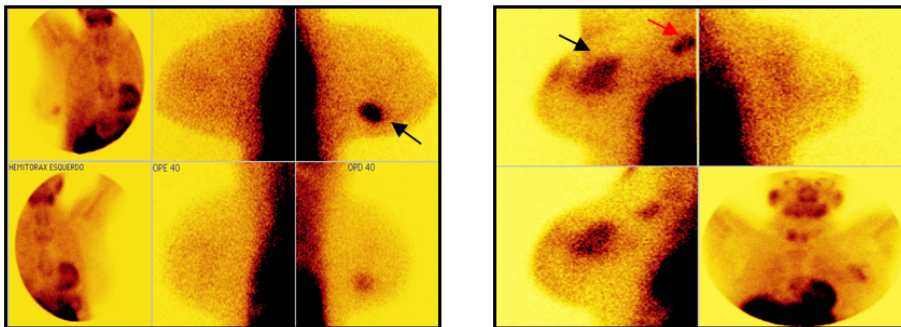
Precautions need to be taken in relation to cases of suspected or confirmed pregnancy. If diagnostic procedures are performed on such patients, a clinical decision weighing the benefits against the possible harm from carrying out the procedure is necessary. Moreover, if diagnostic procedures are performed on breastfeeding mothers, the breastfeeding should be discontinued.

Because of the high radiation exposure, children aged less than 14 years should not undergo gallium-67 scintigraphy, except when there is clear evidence of malignancy.

In laboratories with PET/CT the gallium scintigraphy was replaced by  $^{18}\text{F}$ -FDG in the pathologies described above, because of the best accuracy of the PET.

## 8. Scintimammography

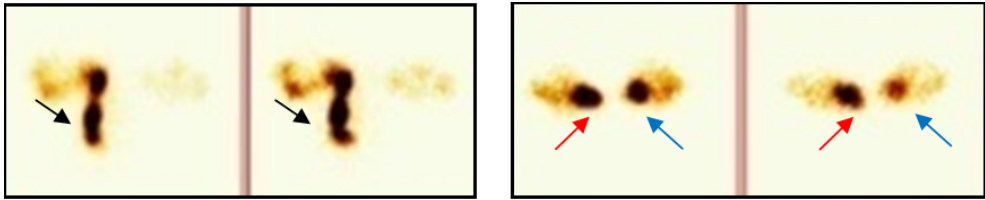
Scintimammography was approved by the FDA in 1987 as a complementary examination for use when mammography is indeterminate in investigating malignant breast tumors. It is not used for screening, although new technologies for the equipment have improved the accuracy of this method. On the other hand, it is now indicated when mammography presents limitations in investigating tumor processes, such as in cases of dense breasts, asymmetrical density, architectural distortion acquired after the procedures or belonging to the breast, detection of tumor viability or recurrence, and very small breasts, particularly in men when breast compression cannot be performed. Lymph node status is also assessed, although with low sensitivity.  $^{99\text{m}}\text{Tc}$ -Sestamibi (a cation with affinity for malignant tumor processes) is used, with summing of factors such as negative transmembrane potential, activity, mitochondrial density, cell count and cell mitotic activity.



**Figure 17.** Scintimammography. Breast carcinoma in right and left side (black arrows) and lymphonodal metastase (red arrow).

## 9. Dacryoscintigraphy

This examination is indicated for cases of epiphora. It is a simple and easy-to-perform examination, with administration of microdrops of pertechnetate in the epicanthus of the eyes. In a normal examination, the radiotracer is expected to progressively pass through the palpebral fissure, lacrimal canaliculi, lacrimal sac, nasolacrimal ducts and nasal cavity. The retention or obstruction patterns do not show progression of the radiotracer.



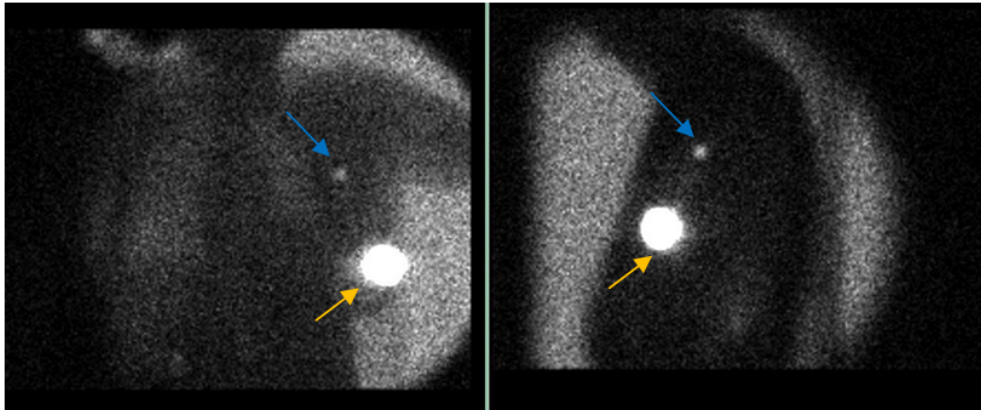
**Figure 18.** Dacrioscintigraphy. Normal exam. Radiotracer reaches right nasal cavity (black arrows). Total retention in bilateral lacrimal sacs. Right lacrimal sac (red arrows) and left lacrimal sac (light blue arrows).

## 10. Radioguided procedures

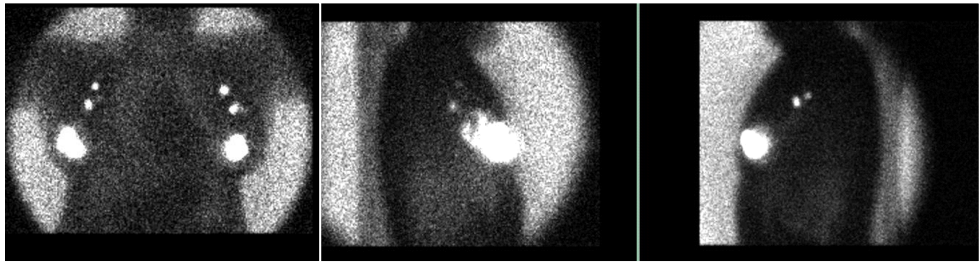
Radioguided procedures were introduced in the 80s, and are based on the search of concentrated lesions of radioactive material guided by a small detector. There are three types of procedures: the search for occult and/or radioguided lesion (ROLL), the search of sentinel lymph node (SLN), and the association of the two methods (SNOLL).

ROLL are lesions with difficult to be found when is necessary to be located for biopsy. The main indications are: nonpalpable breast lesions, like a small lesions, deep lesions or microcalcifications; for biopsy of parathyroid, osteoma, bone metastasis and so on.

SNL is the first lymph node to be reached by neoplasms cells from the primary tumor. When the lymph node was not metastatic, the second lymph nodes are not. Then, the total lymphadenectomy can be avoided (Figure 19 and figure 20).



**Figure 19.** Breast lymphoscintigraphy. Anterior and left lateral images. After injection of radiopharmaceutical substance in left breast (yellow arrows) and SLN in left axillary lymphatic chair (light blue arrows).



**Figure 20.** Bilateral breast lymphoscintigraphy. Two sentinel lymph nodes are identified in left and in right axillary lymphatic chain.

## 11. Therapy

### 11.1. Therapy with radioiodine

Radioiodine therapy consists of oral administration of iodine-131 to treat benign and malignant diseases of the thyroid. Iodine-131 is a beta-emitting radionuclide with a physical half-life of 8.1 days. The main gamma rays have energy of 364 keV and the beta radiation has maximum energy of 0.61 MeV, mean energy of 0.192 MeV and tissue reach of 0.8 mm. Because of cellular damage it is necessary to have some precautions.

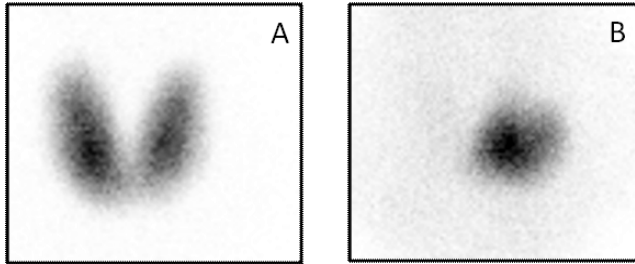
Mean absolute contraindications include: Pregnancy: Female patients of fertile age should ideally undergo a pregnancy test 72 hours or less before radioiodine therapy. Occasionally, when the patient's history clearly demonstrates that there is no possibility of pregnancy, the test may not have to be done; Breastfeeding: Patients who are breastfeeding have to be advised to postpone radioiodine therapy until lactation ceases. This has the aim of minimizing the radiation absorbed by the breast. Lactation ceases between four and six weeks after delivery when there is no breastfeeding, and four to six weeks after the end of breastfeeding. This milk should not be stored.

Mean relative contraindications are: Urinary incontinence that is difficult to manage: The physician should obtain confirmation of the patient's urinary incontinence in order to take the necessary measures to avoid contamination through the urine; uncontrollable hyperthyroidism; active exophthalmia.

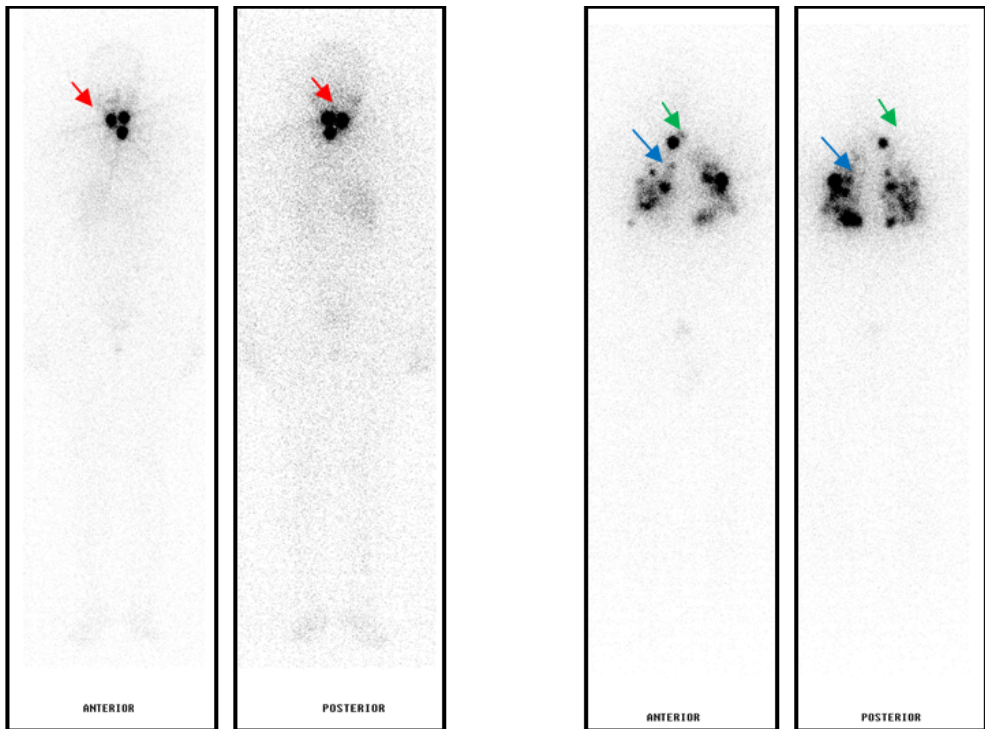
The clinical indications for benign disease of thyroid including: hyperthyroidism: Graves' disease, toxic multinodular goiter and autonomous nodules; non-toxic multinodular goiter: therapy with iodine-131 has been successfully used to reduce non-toxic multinodular goiter [15,16](Figure 21).

And for malignant thyroid diseases, specially for: well-differentiated neoplasms of the thyroid that synthesize thyroglobulin. In these cases, iodine-131 has been used to ablate the remains of the thyroid after total thyroidectomy, and to treat residual cancer and metastatic

disease after total thyroidectomy. Cerebral metastases have to be assessed carefully, since there is a risk of bleeding and cerebral edema. In general, the more invasive the cancer is, the bigger the dose will be.



**Figure 21.** Thyroid scintigraphies. A. Graves' Disease. Diffuse thyroid uptake. B. Plummer's Disease. Nodular uptake on left thyroid lobe with suppression of the gland.

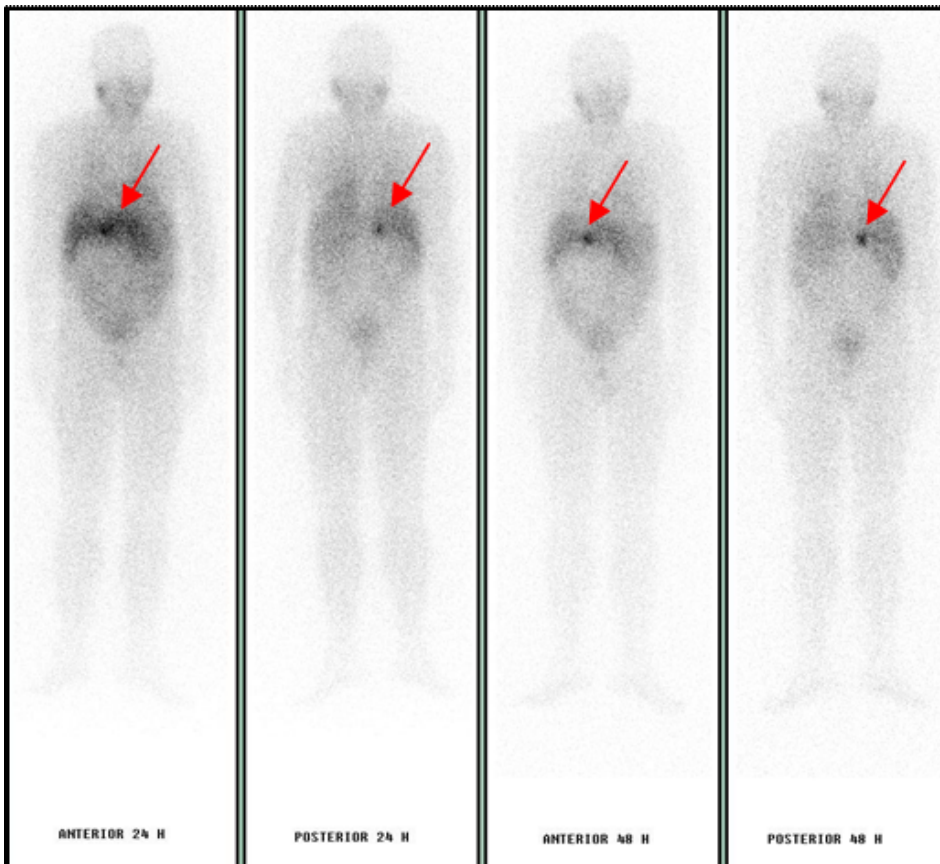


**Figure 22.** Whole body scan post radioiodine therapy. Radiiodine on thyroid tissue and on cervical lymphodes (red arrows). In another patient, notice lymphonode (green arrows and lung (light blue arrows) metastasis.

### 11.2. $^{131}\text{I}$ -meta-iodobenzylguanidine therapy ( $^{131}\text{I}$ -mIBG)

This consists of  $^{131}\text{I}$ -mIBG intravenous infusion, selectively accumulated by neuroectodermal tissue, including tumours of neuroectodermal origin. Uptake occurs by active via and passive diffusion. mIBG is a meta isomer of the guanethidine derivative iodobenzylguanidine, stored within cytoplasmic storage granules and  $^{131}\text{I}$ .

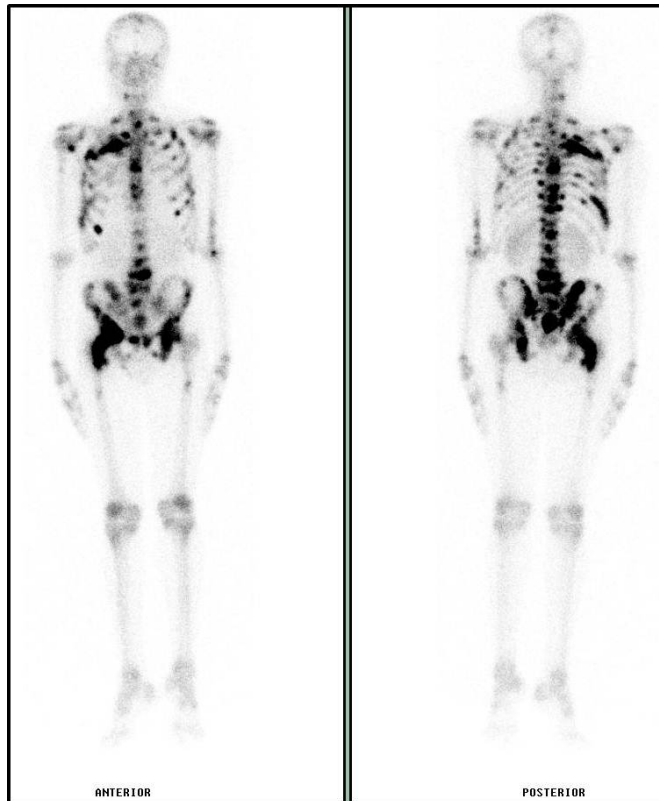
Common indications include: neuroectodermal tumours derived from the primitive neural crest, and showing uptake and retention of labeled mIBG, especially in inoperable or malignant pheochromocytoma (Figure 23), inoperable or malignant paraganglioma, inoperable or malignant carcinoid tumour Stage III or IV neuroblastoma, inoperable, malignant medullary thyroid cancer.



**Figure 23.** Pheochromocytoma. Focal uptake in posterior abdomen aspect (red arrows). Late images are better to identify the lesion.

### 11.3. Treatment of refractory metastatic bone pain

Bone pain is a common symptom of metastatic disease in cancer, experienced with various intensities during the development of their disease, generally in the terminal phases. In addition to other therapies, such as analgesics, bisphosphonates, chemotherapy, hormonal therapy and external beam radiotherapy, bone-seeking radiopharmaceuticals are also used for the palliation of pain from bone metastases (Figure 24). Substantial advantages of bone palliation radionuclide therapy include the ability to simultaneously treat multiple sites of disease with a more probable effect in earlier phases of metastatic disease. The tissue destruction is also based on beta-emitting radionuclide. This therapy consists of intravenous administration of  $^{89}\text{Sr}$ -chloride in aqueous solution,  $^{153}\text{Sm}$ -EDTMP or  $^{186}\text{Re}$ -HEDP that reaches the osteoblastic or mixed metastasis from prostate, breast, lung or any other tumor with osteoblastic presentation. Caution is necessary because this therapy develops myelotoxicity. Usually the bone pain decreased after two weeks depending on the radionuclide administered [17].



**Figure 24.** Bone scan. Bone metastasis. Multiple focal uptake on skeletal,



## 12. Conclusion

In conclusion, the information about the nuclear medicine applications, based on metabolic and functional evaluations, make this method a co-adjutant of the others anatomic exams on investigation of many pathologies, without competition with them and being preferred on the functional lesion follow up, metastasis screening and viable tumor issue.

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