Single-Photon-Emitting Radiopharmaceuticals

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Learning Objectives

- Learn the general definition of "radiopharmaceutical" and "radiolabeling."
- Learn the main physical and chemical characteristics of radionuclides emitting γ-rays commonly employed for single-photon imaging, including ^{99m}Tc, ^{111}In, ^{123}I, ^{131}I, ^{201}Tl, and ^{67}Ga.
- Distinguish the different mechanism(s) of localization of the most important radiopharmaceuticals employed in conventional nuclear medicine imaging.
- Understand the favorable physical characteristics of ^{99m}Tc for gamma camera imaging and of the ^{99}Mo/^{99m}Tc generator for distribution logistics.
- Become familiar with the wide spectrum of available radiopharmaceuticals commonly used in clinical practice for gamma camera imaging, with special attention to their clinical indications and in vivo pharmacokinetics.
- Become familiar with the estimates of radiation dosimetry to normal tissues/organs for each diagnostic radiopharmaceutical.
- Understand the concept of "molecular target" and of "theranostics."

2.1 Overall Background

Nuclear medicine images depict anatomic, functional, and metabolic processes in tissue. To create these images, specific compounds called radiopharmaceuticals are administered to the patient. A radiopharmaceutical generally consists of a biochemical core, which confers certain biological properties that dictate its biodistribution. This biochemical core is chemically linked to the radionuclide emitting the radioactive signal that can be detected from outside the body, usually in the form of γ-rays (also called "photons"); in some cases, it is the ionic form per se of the radionuclide that determines its biodistribution.

Imaging with single-photon-emitting radionuclides (radioisotopes of elements) produces both planar images and single-photon emission computed tomography (SPECT) using a gamma camera. Radiopharmaceuticals labeled with positron-emitting radionuclides are used for positron emission tomography imaging (as described in Chap. 3 of this book "Positron-emitting radiopharmaceuticals"), while radiopharmaceuticals emitting predominantly β- or α-particles are used for therapeutic purposes (as described in Chap. 4 of this book).

Radiopharmaceuticals consisting of only the radionuclide in its ionic form usually concentrate in specific target tissues/organs because either they are radioisotopes of a naturally occurring element of biologic interest (such as thyroid imaging with $^{123}I^-$ or $^{131}I^-$—which undergoes the same physiologic distribution as nonradioactive native iodine-127) or they share chemical similarities/analogies with native elements of biologic interest (such as the $^{201}Tl^+$ ion—mirroring the physiologic distribution of the native K^+ ion). For more complex radiopharmaceuticals, the radionuclide is linked to the main core/carrier molecule through a chemical process denominated "radiolabeling."

The diagnostic information provided by scintigraphic images derives from the specific distribution of a radiopharmaceutical within the body, usually injected intravenously (less often by inhalation, orally, interstitially, intracavitarily, or intra-arterially).

The main parameters derived from serial scintigraphic images are delivery and clearance of the tracer from the organ or tissue. Pathophysiologic changes induce modifications of these parameters (especially retention and/or the absence of retention of the radiopharmaceutical in the tissue/organ under examination).

The radionuclides most frequently used for diagnostic applications in conventional nuclear medicine are the isotopes of technetium, iodine, indium, gallium, and thallium. Their main physical characteristics are summarized in Table 2.1.

Table 2.1 Main physical characteristics of radionuclides used for single-photon imaging, arranged according to increasing half-life of physical decay

Radionuclide	Decay $T_{1/2}$	Energy of major photon emissions (keV)
^{99m}Tc	6.0 h	141 (89%)
^{123}I	13.2 h	159 (83%); 528 (1%)
^{111}In	2.80 days	171 (90%); 245 (94%)
^{201}Tl	3.04 days	68–82 (88%); 135 (3%); 167 (10%)
^{67}Ga	3.26 days	93 (39%); 185 (21%); 300 (17%)
^{133}Xe	5.25 days	81 (36.5%)
^{131}I	8.0 days	284 (6%); 365 (82%); 637 (7%)
^{51}Cr[a]	27.7 days	5 (20%); 320 (10%)
^{125}I[a]	59.9 days	27 (14%); 31 (26%); 36 (7%)

[a]Not useful for actual external imaging in humans; used for specific application involving counting of biological samples with well-type γ-counters

Radiopharmaceuticals labeled with ^{99m}Tc are used for about 85% of diagnostic in single-photon imaging. This radionuclide is widely employed clinically because:

- It can be obtained from commercial ^{99}Mo/^{99m}Tc generators in local radiopharmacies.
- Many kits are available to produce the radiopharmaceutical on-site with readily available equipment.
- The metastable radionuclide produces a 140 keV photon in 88% of its nuclear decays (a conversion electron is produced in 12%).
- Its γ-energy (140 keV) is favorable for detection by gamma cameras (whose detectors have excellent efficiency for γ-energies between 100 and 200 keV).
- Its relatively short half-life of 6 h represents a good compromise between the quality of images and radiation burden to the patient.

Biological-metabolic alterations typically occur at an early stage of disease prior to morphologic alterations in shape, size, structure, or motion of the tissue/organ. On the other hand, this high sensitivity of nuclear medicine investigations for early changes is rarely matched by equally high specificity for a given disease. For instance, the increased metabolism of glucose in a particular region of the body can indicate the presence of neoplastic cells with high proliferative activity, but it may also indicate a condition of intense inflammation due to infection or immunologic attack.

Since radiopharmaceuticals are typically used in very small mass amounts (in the order of micro-, nano-, or picomoles), they generally do not cause any disturbance of the biological system under investigation (except for possible radiobiological effects due to the radioactive emission).

Quality control procedures applied to nonradioactive drugs are applicable to radiopharmaceuticals. Quality control tests that ensure the purity, potency, product identity, biologic safety, and efficacy of radiopharmaceuticals are mandatory for their clinical use. Moreover, because of the radiation component, radionuclidic and radiochemical purity must also be tested. The equipment and procedures necessary for these quality control tests are described in details in Chaps. 39 and 40 of this book (for single-photon emitting and for positron-emitting radiopharmaceuticals, respectively).

The quantity of radioactivity administered varies according to the procedure. Examinations based on the use of ionizing radiation must be optimized so as to deliver a radiation dose "as low as reasonably achievable" (ALARA) consistent with the diagnostic goal.

Metabolism, biodistribution, and excretion of drugs are different in children from those in adults; the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) have developed pediatric dosage cards that take into account the age and body weight for determining the activity of radiopharmaceuticals for administration to children [1].

The chemical and physical characteristics of a radiopharmaceutical are the main factors determining its accumulation and retention in normal and diseased tissues of the organism. This chapter classifies radiopharmaceuticals according to radionuclide used for labeling and to the main mechanism(s) of tissue localization responsible for the specific distribution properties of the imaging agent.

Key Learning Points

- Radiopharmaceuticals usually consist of a combination of a biologic directing agent and of a radionuclide emitting photons that can be detected outside the body using gamma cameras for imaging.
- The diagnostic information provided by radiopharmaceuticals derives from their specific distribution within the body in physiologic and pathologic conditions.
- Alterations occurring at the molecular level detectable by functional imaging typically occur at an early stage of disease, prior to morphologic alterations in shape, size, structure, or motion of the tissue/organ.
- The most common radionuclide used for single-photon imaging is ^{99m}Tc; other radionuclides employed in conventional nuclear medicine include ^{131}I, ^{123}I, ^{111}In, ^{67}Ga, and ^{201}Tl.
- Since radiopharmaceuticals are typically used in very small mass amounts, they generally do not cause any disturbance to patients, except for possible radiobiological effect.
- Quality control procedures applied to nonradioactive drugs must be applied also to radiopharmaceuticals.
- The quantity of radiopharmaceutical used in a specific procedure should be "as low as reasonably achievable" (ALARA), especially in pediatric patients.
- Radiopharmaceuticals can be classified according to the radionuclide used for labeling and to the main mechanism(s) of tissue localizations.

2.2 General Localization Mechanisms for Single-Photon-Emitting Radiopharmaceuticals

Localization of most radiopharmaceuticals is not limited to one simple mechanism but also depends on the mode of administration and delivery to the tissue. For some radiopharmaceuticals there is more than one single localization mechanism involved.

The principle of *compartmental localization or dilution* is at the basis of the applications of nondiffusible radiopharmaceuticals. This definition refers to the situation where the molecules of interest are distributed in an enclosed volume (called a compartment). In case of uniform radiopharmaceutical dispersion, the principle of compartmental dilution is exploited for calculation of the whole-body erythrocyte mass (red blood cells labeled with ^{51}Cr) or of whole-body plasma volume (^{125}I-radioiodinated serum albumin). These methods are based on the principle of dilution of a known amount of radioactive substance in an unknown distribution volume; in particular, by measuring the degree of dilution (i.e., change in concentration) of the amount of radioactivity administered, it is possible to calculate the volume in which the radiopharmaceutical has been diluted.

Red blood cells labeled with a radionuclide (e.g., ^{99m}Tc) also allow to record in vivo images of the heart at systole and diastole and to measure chamber volume at the end of diastole and systole determinig the left ventricular ejection fraction.

In some other conditions, there can be an abnormal leakage of contents from the compartment. For instance, scintigraphy with ^{99m}Tc-labeled red blood cells can identify the site of gastrointestinal bleeding as an area of increased radioactivity accumulation at some point in the gastrointestinal lumen—where the radiolabeled erythrocytes do not normally accumulate. Similarly, scintigraphy with a radiopharmaceutical that normally undergoes hepatobiliary clearance and excretion (e.g., ^{99m}Tc-mebrofenin) can visualize abnormal biliary leakage into the abdominal cavity, e.g., after biliary surgery.

In other conditions, images can show, within a certain tissue/organ, areas of radioactive concentration that are reduced with respect to the surrounding (supposedly normal) tissue/organ. Such areas are often the result of an obstruction in a compartmental space. For instance, ventilation lung scintigraphy after inhalation of the radioactive gas xenon-133 can indicate the presence of an obstruction in the lung airways as an area of reduced/absent radioactivity accumulation in the bronchi/bronchioles beyond the point of obstruction.

Macroaggregated albumin (MAA) particles, ranging in diameter from 10 to 90 μm (with >90% of particles ranging from 10 to 40 μm), can be radiolabeled (usually with ^{99m}Tc) and injected intravenously to depict the distribution of regional pulmonary blood flow. The particles become *mechanically trapped* in the capillary bed of the lungs, thus enabling to utilize the principle of microembolization to identify the regions of pulmonary parenchyma with normal perfusion. Regions with reduced perfusion (typically in case of thromboembolic disease) are depicted as areas with decreased/absent radioactivity.

The mechanical trapping mechanism is also used for the preliminary evaluation of liver perfusion before trans-arterial radionuclide therapy with ^{90}Y-labeled microspheres in patients with inoperable liver malignancies; in this case, ^{99m}Tc-MAA is injected directly into the arterial branches of the hepatic artery.

The mechanism of *chemisorption* is used in bone scans. For example, ^{99m}Tc-labeled diphosphonates accumulate at the surface of newly formed calcium hydroxyapatite crystals and in the amorphous bone mineral matrix; their uptake is increased in areas with increased new bone formation (e.g., fracture healing, infection, primary and metastatic tumors) (Fig. 2.1). Chemisorption is quite strong, intermediate between *chemical* covalent binding and hydrogen binding (*adsorption*); hence the term *chemisorption* is used. In addition to chemisorption on the bone surfaces, there can also be chemisorption onto calcium phosphate crystals in dystrophic calcium deposits that precipitate in certain soft tissues, e.g., as a consequence of severe hyperparathyroidism and hypercalcemia.

Autologous radiolabeled leukocytes localize at sites of infection based on chemotactic signals. The *chemotaxix* is the characteristic movement or orientation of an organism or cell (including leukocytes) along a chemical concentration gradient either toward or away from the chemical stimulus and tipically occurs in the sites of inflammation and infection, involving immune cells, blood vessels, and molecular mediators.

Phagocytosis is the process whereby microparticles are internalized from the extracellular space into cells, a process that is especially active in macrophages. Although macrophages are ubiquitous cells, they are concentrated mostly in the reticuloendothelial system, especially in the liver, spleen, bone marrow, and lymph nodes, as well as at sites of infection/inflammation. Phagocytosis is facilitated by several properties of the particles, such as size between 2.5 nm and 1 μm, negative charge, and possible opsonization by a class of macromolecules that include the complement fractions C3, C4B, and C5, as well as some α- and β-globulins. Phagocytosis is responsible for the accumulation of ^{99m}Tc-labeled particles in the nanocolloidal size range (e.g., albumin nanocolloids or sulfur colloid preparations) at different sites depending on the route of administration. In fact, these radiocolloids can be used for imaging the liver, spleen, and bone marrow following systemic administration (i.e., an i.v. injection). On the other hand, radiocolloids injected interstitially migrate through the lymphatic system. This mechanism is the basis of lymphoscintigraphy, a preliminary step to, e.g., radioguided sentinel lymph node biopsy.

Many radiopharmaceuticals accumulate in cells through *transmembrane transport mechanisms* (either passive or active transport). While passive transport does not require any energy expenditure and only involves diffusion of a substance from areas of high concentration to areas of low concentration (concentration gradient), on the other hand,

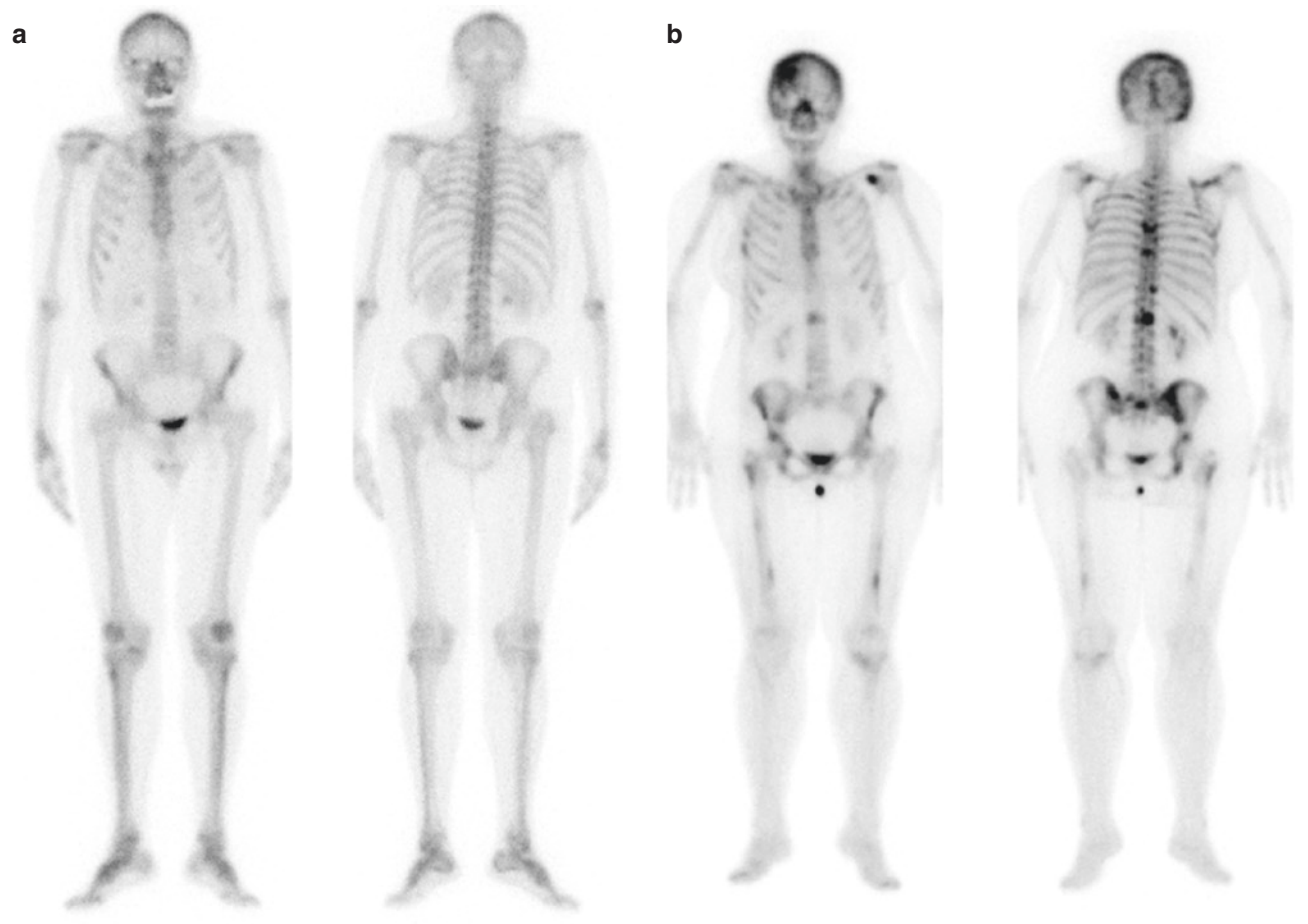

Fig. 2.1 Examples of planar whole-body acquisitions of bone scintigraphy with ^{99m}Tc-MDP. (**a**) Normal pattern of skeletal scintigraphy showing physiologic turnover of the mineral matrix of the bone, without any areas of abnormally increased tracer uptake. (**b**) The presence of numerous focal areas with markedly increased tracer uptake throughout the skeleton in a patient with multiple skeletal metastasis

active transport requires energy (in the form of ATP or an electrochemical gradient of Na^+ or H^+) for the system to function.

Passive transport generally occurs by diffusion, i.e., when a substance moves from an area of high concentration to an area of low concentration. A substance, typically lipophilic, crosses the phospholipid bilayer of cell membranes. Simple diffusion is influenced by pH/ionization state. In fact, many molecules may exist in either a neutral state or as a charged ion, depending on pH. Hence, a molecule may be able to diffuse across a membrane in its non-ionized lipophilic form but cannot diffuse across the same membrane in its ionized hydrophilic form. Membranes have small pores that limit the size of molecules that can cross the membrane (molecular weight <80 kDa). It follows that passive diffusion is nonselective, not competitively inhibited by similar molecules, and not subject to saturation.

An example of simple diffusion as a mechanism of radiopharmaceutical uptake is represented by ^{99m}Tc-labeled myocardial perfusion agents (either ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin) that cross cell membranes following both a concentration gradient and an electrochemical gradient. These positively charged molecules are attracted by molecules or by structures in the cell that are negatively charged. Since diffusion is not a unidirectional process, intracellular accumulation typically involves some additional mechanism(s) of retention. In the case of ^{99m}Tc-tetrofosmin, the radiopharmaceutical binds to intracellular polar metabolites or complex carriers of the cytosolic components, while ^{99m}Tc-sestamibi binds to the cell membrane of mitochondria. This process results in stable intracellular binding and minimizes washout of the tracer.

The tracers used to image cerebral perfusion, ^{99m}Tc-exametazime (^{99m}Tc-HMPAO) or ^{99m}Tc-bicisate (^{99m}Tc-ECD), are electrochemically neutral compounds. Due to their lipophilicity, these uncharged molecules cross the blood-brain barrier by passive diffusion following a concentration gradient. Once in the intracellular space, the radiopharmaceuticals undergo an enzymatic process (or chemical transformation) that renders them hydrophilic,

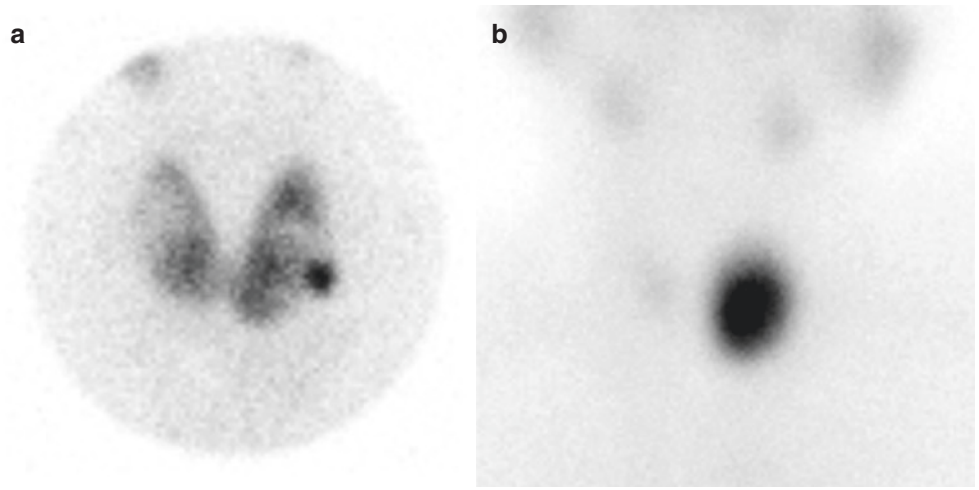

Fig. 2.2 Examples of different thyroid conditions visualized by scintigraphy. (**a**) Scintigraphy with ^{123}I-iodide: multinodular goiter with both bilateral "cold" and "hot" nodules (*image obtained using a pinhole collimator*). (**b**) Scintigraphy with ^{99m}Tc-pertechnetate: single "hot" nodule of the left thyroid lobe with complete inhibition of the remaining parenchyma uptake, typical of hyperfunctioning thyroid adenoma (*image obtained using a parallel-hole, high-resolution collimator, zoom factor 2*)

therefore not capable of passively diffusing back to the extracellular space. This is therefore a process of "biochemical trapping" that causes radiopharmaceutical retention into the neurons.

When transmembrane diffusion of a substance involves a specific carrier system, the phenomenon is called *facilitated diffusion*. Such carriers are generally selective and can be competitively inhibited by an excess amount of similar molecules; in general, the process is also subject to saturation, when all the sites that activate transport are occupied.

Facilitated diffusion is the process responsible for transport of the glucose analog [^{18}F]FDG into cells. A series of glucose transporters, GLUT1-GLUT5, are responsible for carrying glucose (or its analog 2-fluorodeoxyglucose) across the cell membrane (see also Chap. 3 of this book). Once inside the cells, an enzyme that physiologically initiates intracellular metabolism of glucose (hexokinase) converts [^{18}F]FDG into [^{18}F]FDG-6-phosphate; this compound cannot enter the glycolytic pathways that glucose-6-phosphate follows, thus remaining trapped inside the cells. Also nonpolar lipophilic anionic radiopharmaceuticals used for hepatobiliary scintigraphy (derivatives of ^{99m}Tc-iminodiacetic acid) accumulate in hepatocytes through transmembrane carriers present on the hepatocyte cell surface; inside the hepatocytes, they are then conjugated and excreted into the bile.

Active transport generally uses energy-dependent carriers that transfer molecules against a concentration gradient, i.e., from an area of low concentration to an area of high concentration. It is selective, can be competitively inhibited, and can be saturated.

A well-known example of active transport is the uptake of iodide in the thyroid gland. Radioisotopes of iodine in ionic form ($^{123}I^-$, $^{124}I^-$, $^{125}I^-$, $^{131}I^-$) and other anions ($^{99m}TcO_4^-$) are transported into thyroid cells via the so-called Na^+/I^- symporter (NIS); these radiopharmaceuticals are employed for morphofunctional evaluation of the thyroid gland (Fig. 2.2). High concentrations of iodide in the blood, such as those resulting from, e.g., recent administration of iodinated X-ray contrast media, competitively inhibit thyroid uptake of these thyroid-imaging agents.

Another example of active transport is the transmembrane transfer of the ionic form of radioactive potassium or its analog ($^{201}Tl^+$) facilitated by the Na^+/K^+ transmembrane pump. This pump system is active in all cells, to maintain the high intracellular concentration of potassium. Tl^+ has an ionic radius similar to K^+ and is able to fit in the Na^+/K^+ pump. Uptake in the myocardium reflects myocardial perfusion and viability.

The kidney has two mechanisms for transferring drugs from the blood into the urine: (1) *glomerular filtration* is a special case of diffusion involving the transit of molecules through pores, or channels, regulated by hydrostatic or osmotic pressure gradients and by molecular size (a tracer which is filtered, such as ^{99m}Tc-DTPA, is used clinically to measure the glomerular filtration rate), and (2) *tubular secretion* is a special case of active transport out of glands directly into the renal tubules. A tracer that utilizes both mechanisms, such as ^{99m}Tc-mertiatide (^{99m}Tc-MAG3), undergoes partial glomerular filtration, followed by tubular secretion, resulting in a higher concentration in the kidney.

An additional mechanism of cellular interaction is based on the expression receptors on the surface of cell membranes. Over 50 different classes of receptors have been identified, and their number is continuously increasing. Radioactive drugs accumulating into cells through a *receptor-mediated mechanism* compete with the endogenous receptor-specific ligands for binding to their respective receptor; therefore, the diagnostic or therapeutic use of these radiopharmaceuticals is based on their high binding specificity (in the nanomolar range) which, due to the limited availability of binding sites, mainly depends on specific activity of radiopharmaceutical preparation. Specific activity of radiopharmaceuticals is defined as the radioactivity of a given per unit mass. In low specific activity radiopharmaceuticals, the amount of unlabeled tracer is high, thus possibly resulting in saturation of the binding sites with the nonradioactive drug and consequent poor image quality. Single-photon radiopharmaceuticals accumulating in tissues/organs through a receptor-mediated mechanism include analogs of somatostatin (such as ^{111}In-pentetreotide or ^{99m}Tc-EDDA/HYNIC-TOC, used to investigate neuroendocrine tumors), ^{99m}Tc-mannosyl-DTPA-dextran (a receptor-targeted agent injected interstitially for lymphatic mapping that binds avidly to the CD206 receptors for mannose on the surface of macrophages and dendritic cells in lymph nodes), and ^{123}I-ioflupane, a chemical derivative of cocaine that binds to presynaptic dopamine transporters (primarily located in the caudate and *putamen*) and is used to investigate patients with movement disorders (Fig. 2.3). Many other radiopharmaceuticals are based on the receptor-mediated localization mechanism, most of them labeled with positron-emitting radionuclides.

Radiolabeled antibody preparations have been developed to recognize specific target epitopes expressed on the cell surface of tissues either physiologically or following malignant transformation of cells. Accumulation of such radiopharmaceuticals at certain sites of interest (tumor tissues) is therefore based on an *immunological mechanism*. Radiolabeled monoclonal antibodies (or molecularly engineered fragments, such as fab, fab′, and fc) are directed against epitopes expressed on the surface of neoplastic cells or glycoproteins in the tumor stroma (extracellular matrix). Antibody imaging can be used for therapy or diagnosis. When radiolabeled antibodies are employed for radioimmunotherapy of tumors, they are usually labeled with radionuclides emitting β-particles with suitable energies (as better detailed in Chap. 4 of this book "Radiopharmaceuticals for therapy"). When antibodies are used for diagnosis, they are labeled with the positron-emitting radionuclide ^{68}Ga or single-photon-emitting ^{111}In or ^{99m}Tc.

Finally, there is a heterogeneous group of radiopharmaceuticals that localize at specific sites (either extracellular or intracellular) because they behave as ligands that bind with high (and avid) *chemical affinity* to specific components either in the extracellular space (e.g., the β-amyloid fibrils typical of Alzheimer's disease) or in the intracellular space (such as mitochondria, employed for imaging, e.g., myocardial blood flow). Agents targeting intracellular components must be lipophilic to diffuse into cells (or cross the blood-brain barrier). Once in the cell, the agents need to either bind to some intracellular component or undergo a reaction that reduces the lipophilicity to trap the molecule in the cell. Many of these imaging agents are derived from dyes used for staining histological preparations.

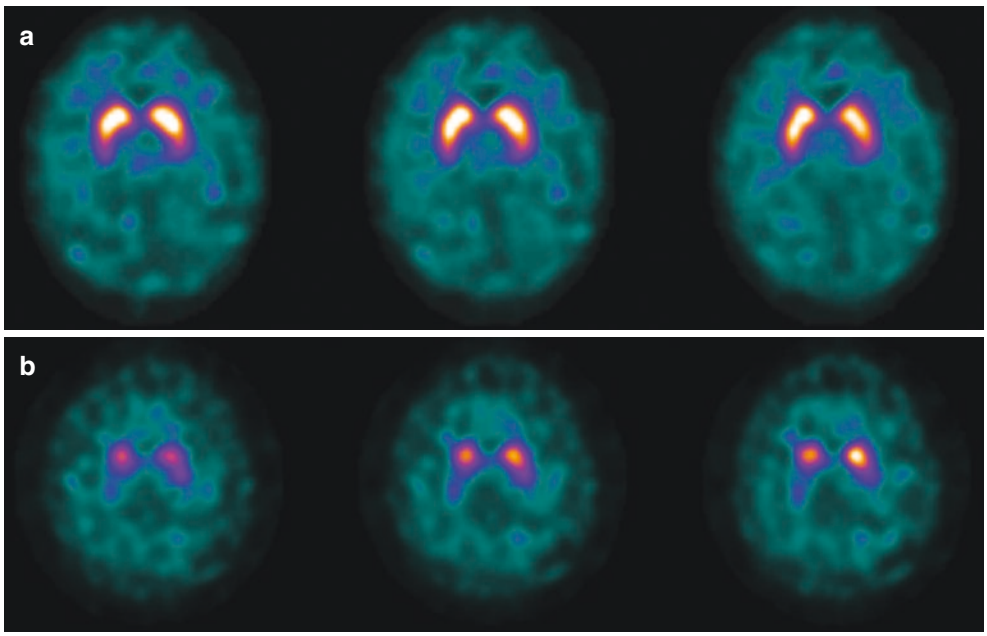

Fig. 2.3 Axial SPECT images obtained at different levels during receptor brain scintigraphy with ^{123}I-ioflupane. (**a**) Physiologic pattern of uptake by the presynaptic dopamine transporters, with normal bilateral visualization of basal ganglia. (**b**) Scintigraphy in a patient with Parkinson's disease, showing an abnormal pattern of reduced and asymmetrical uptake in the basal ganglia

Key Learning Points

- Localization of most radiopharmaceuticals is not limited to one simple mechanism but also depends on the mode of administration and delivery to tissues.
- For some radiopharmaceuticals, there is more than one single localization mechanism involved.
- The main principles of radiopharmaceutical accumulation include compartmental dilution of nondiffusible radiopharmaceuticals, leakage of compartmental localization, mechanical trapping, chemisorption, chemotaxis, phagocytosis, transmembrane transport (including active transport and passive transport—either simple or facilitated diffusion), filtration, secretion, receptor-mediated mechanism, immunological mechanism, and chemical affinity.

2.3 ^{99m}Tc-Labeled Radiopharmaceuticals

The ^{99}Mo/^{99m}Tc generator makes this transition metal almost ideal for diagnostic nuclear medicine. A radioisotope generator is a system where a "parent" radionuclide with a relatively long half-life decays into a "daughter" radionuclide generally with a shorter half-life. The parent radionuclide is generally bound in an insoluble form to the stationary phase of a chromatographic column, while the daughter radionuclide is eluted from the column. There is usually an optimal interval of time between elutions to allow generation of a sufficient amount of radioactive daughter. ^{99}Mo/^{99m}Tc generators can be easily transported over long distances to hospitals; the in situ produced ^{99m}Tc is available in the chemical form of ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$) that can be used for scintigraphic imaging as such (e.g., for thyroid scintigraphy, salivary scintigraphy, detection of ectopic gastric mucosa in Meckel's diverticulum) or for instant labeling of different kits to produce other radiopharmaceuticals.

Most of the ^{99}Mo utilized for the ^{99}Mo/^{99m}Tc generators had been produced through purification of products from nuclear fission of highly enriched uranium fission products. Recently, due to threats from terrorists, alternative approaches to produce ^{99}Mo, through the use of a linear accelerator of low-enriched uranium targets, have gained favor.

^{99}Mo decays with a physical half-life of 2.75 days, mainly with the emission of high-energy β-particles and of γ-rays with a wide energy spectrum; the end product of ^{99}Mo decay is ^{99m}Tc.

The ^{99}Mo/^{99m}Tc generator consists of an ion exchange chromatographic column. The "parent" radionuclide (^{99}Mo, which is insoluble in water or in physiological saline) is firmly bound in the form of molybdate to a chromatography anion exchange resin, which constitutes the stationary phase of the system usually designed as a small glass column (about 40 mm long and less than 10 mm wide). ^{99m}Tc is generated during the continuous decay of ^{99}Mo, and it is periodically removed from the column by elution of the column with physiological saline. ^{99m}Tc is produced in the chemical form of ^{99m}Tc-pertechnetate anion ($^{99m}TcO_4^-$); the chloride ions present in the saline solution exchange with the $^{99m}TcO_4^-$ ions in the column, thus permitting their elution in physiological saline.

The regeneration process proceeds exponentially, and in about one half-life (6 h), 50% of the ^{99m}Tc is regenerated. After 24 h ^{99}Mo and ^{99m}Tc reach a new balance, and the generator is ready to be eluted again. However, since ^{99}Mo has decayed in the meantime, the amount of ^{99m}Tc obtained with the second elution will be about 70% of the amount obtained with the prior elution.

Two types of generators are currently available commercially, known as "wet" and "dry" generators, respectively. The wet generators have a large reservoir of saline permanently attached to the inlet. Each elution pulls liquid from the column by a vacuum in an evacuated vial attached to the outlet of the chromatography column, this liquid being replaced by an equal volume of saline from the reservoir. Thus, the column remains full of saline between two elution procedures. In a dry generator, elution is performed with a set volume of saline provided each time by attaching a vial to an inlet to the generator. Similarly as with the wet generator, saline is pulled through the column by a vacuum provided by an empty evacuated vial attached to the outlet of the chromatography column. The liquid pulled through the column is followed by an additional volume of air to effectively remove most of the liquid from the column. This will not render the column completely free of liquid, but the bulk of the saline will be pulled away from the column.

Each ^{99m}Tc-labeled radiopharmaceutical is chemically defined as a "coordination complex," i.e., a compound formed by a central transition metal (coordination center) bonding with "coordinate covalent bonds" to other surrounding molecules, defined as "ligands or complexing agents." Technetium is the transition metal, while ligands can be single atoms such as chlorine, bromine, oxygen, or nitrogen or larger molecules such as ammonia, water, carbon monoxide, and amino acids. The fundamental requirement for a ligand to be labeled with ^{99m}Tc is to possess an appropriate set of atoms able to firmly coordinate to the metallic center.

In a complex, the metal is capable of forming more than one bond with as many ligands as the coordination number. For example, technetium can form complexes with coordination numbers of 4, 5, 6, or 7 (most commonly 5 and 6).

An important property of the coordination complex is its molecular geometry. Each complex can assume a particular

geometric conformation, the transition metal remaining in the center. Octahedral and pyramidal geometries are those more frequently found in the technetium complexes.

Another important parameter that characterizes a coordination complex is the electrical charge, determined by the metal oxidation state. The higher the charge, the greater the hydrophilicity. An uncharged complex is usually the most lipophilic.

$^{99m}TcO_4^-$ is a coordination compound with a very compact structure with tetrahedral geometry and oxidation state +7. Pertechnetate, the highest possible oxidation state for this metal, is also a very stable chemical species in aqueous solution. Thus, in order to label any given molecule with $^{99m}TcO_4^-$, the oxygen atoms bound to the metal must be removed through a reducing agent and must be replaced with new ligand-coordinated atoms. During this process, the oxidation state of technetium is reduced to values lower than +7. The stannous ion (Sn^{2+}) is generally used as a reducing agent, being added in aqueous solution as a chloride salt ($SnCl_2$) in such small amounts that it does not alter solubility of the preparation or cause toxicity to the patient. The oxygen atoms are removed from $^{99m}TcO_4^-$ through the formation of $Sn(OH)_4$ and other similar compounds. The atom of technetium is now ready to coordinate with a specific binder or a chelating agent that has been pre-attached to the molecule to be labeled. The binder must have a high technetium coordinating ability, in order to ensure stability of the ^{99m}Tc-labeled radiopharmaceutical and prevent it from recombining with the oxygen atoms in aqueous solution and thus return back to the anion pertechnetate or form technetium dioxide (TcO_2), a secondary compound of oxygen that tends to form colloidal particles.

2.3.1 ^{99m}Tc-Sodium Pertechnetate

^{99m}Tc-sodium pertechnetate ($Na^{99m}TcO_4$, present as the $^{99m}TcO_4^-$ ion in solution at physiological pH) is obtained directly after ^{99}Mo/^{99m}Tc generator elution with physiological saline.

After i.v. administration, the pertechnetate ions circulate in the blood partly in their free form and partly bound to plasma proteins; because of their small size, free ions easily leave the vascular compartment and migrate to the interstitial fluids. As their concentration in blood diminishes, other $^{99m}TcO_4^-$ ions are released from their binding to plasma proteins. Therefore, visualization of the vascular space observed in early scintigraphic acquisitions declines gradually over time.

Pertechnetate ions are concentrated in tissues due the activity of anion pumps in the thyroid, stomach, salivary glands, intestine, choroid plexus, and kidney. ^{99m}Tc-Pertechnetate (Fig. 2.4) is commonly used for thyroid scintigraphy, for the search of ectopic gastric mucosa, and for salivary gland scintigraphy.

The anion pump responsible for localization in the thyroid is called the Na^+/I^- symporter (NIS). NIS is a transmembrane protein consisting of 643 amino acids arranged in 13 domains with extracellular amino-terminal and intracellular carboxy-terminal (molecular weight ranging between 79 and 90 kDa, depending on the degree of glycosylation). The pertechnetate ion mimics the iodide ion, since $^{99m}TcO_4^-$ is similar in terms of mass, size, and charge density; however, once inside the thyroid cell, $^{99m}TcO_4^-$ does not undergo subsequent organification as iodide does to participate in the synthesis of thyroid hormones. NIS is located on the basolateral membrane of thyroid cells, and it is able to simultaneously transport sodium and

Key Learning Points

- The ^{99}Mo/^{99m}Tc generator is an ion exchange chromatographic column where the "parent" radionuclide (^{99}Mo) with a relatively long half-life (2.75 days) decays into the "daughter" radionuclide (^{99m}Tc) with a shorter half-life (6 h) and becomes available for elution in the chemical form of ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$).
- "Wet" and "dry" generators are currently available commercially.
- ^{99m}Tc-Pertechnetate is a transitional metal suitable for scintigraphic imaging as such or for radiolabeling of different ligands to produce a variety of "coordination complexes," in virtue of its tetrahedral geometry and oxidation state +7.

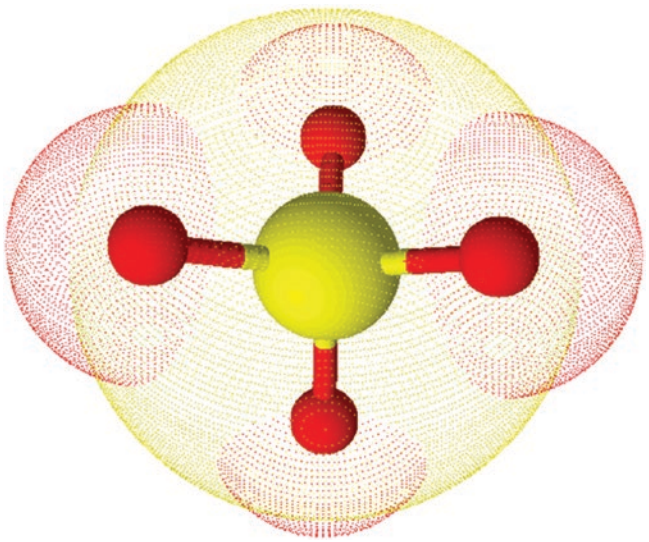

Fig. 2.4 Tridimensional chemical structure of the ^{99m}Tc-pertechnetate anion ($^{99m}TcO_4^-$). Color codes: *yellow* = ^{99m}Tc; *red* = O

iodide (with a stoichiometric ratio of 2:1) from the extracellular space into thyroid cells. Expression of this protein is regulated, among other minor mechanisms, mostly by the thyroid-stimulating hormone (TSH, which upregulates the process) and by the concentration of iodide in extracellular fluids (which downregulates the process). Extraction of iodine from plasma and its concentration in thyroid cells is a saturable and active process that takes place against an electrochemical gradient (resulting in an intracellular concentration of iodine 20- to 40-fold higher than in plasma) and requires energy, which is supplied by the Na^+/K^+-dependent ATPase system.

For the *search of ectopic gastric mucosa in Meckel's diverticulum*, ^{99m}Tc-pertechnetate is employed because of its physiologic secretion by the gastric mucosa. In fact, technetium is a member of Group 7A of the periodic table of elements, and it is reasonable to assume that gastric concentration of pertechnetate might be similar to that of chloride (since chlorine is a member of Group 7B). This assumption is supported by the correlation observed between acid output and pertechnetate clearance. It has also been demonstrated that ^{99m}Tc-pertechnetate is secreted also by the mucous epithelial cell [2].

^{99m}Tc-Pertechnetate is the radiopharmaceutical of choice for the *scintigraphy of the salivary glands* because of its chemical-physical analogy with the anions physiologically present in saliva (mainly iodide) excreted by salivary glands. The concentration mechanism for pertechnetate in the human salivary glands is typical of an active ion transport system located in cells of the striated ducts as well as in acinar cells.

$^{99m}TcO_4^-$ ions do not pass the intact blood-brain barrier (due to the hydrophilicity of the charged molecule). Pertechnetate does, however, concentrate in the choroid plexus. ^{99m}Tc-Pertechnetate has been used in the past for the *scintigraphic evaluation of the integrity of the blood-brain barrier* (which is disrupted in brain tumors, meningitis, brain abscess, and vascular accidents). From a clinical perspective, pertechnetate imaging to detect the integrity of the blood-brain barrier has been replaced by magnetic resonance and CT imaging.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-pertechnetate are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.013 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Upper large bowel 0.056 mGy/MBq
  - Colonic wall 0.041 mGy/MBq
  - Stomach 0.026 mGy/MBq

Key Learning Points

- ^{99m}Tc-Pertechnetate mimics the iodide ion of the anion pumps (Na^+/I^- symporter).
- ^{99m}Tc-Pertechnetate as such is commonly used for thyroid scintigraphy, for the search of ectopic gastric mucosa, and for salivary gland scintigraphy.

2.3.2 ^{99m}Tc-Bisphosphonates

^{99m}Tc-Bisphosphonates, also called ^{99m}Tc-diphosphonates, are employed for bone scintigraphy because of their high uptake in the skeleton and rapid clearance from blood and soft tissue after i.v. injection.

The molecules are called bisphosphonates because they have two phosphonate ($PO(OH)_2$) groups in their chemical structure (Fig. 2.5). The P-C-P bond between the two phosphates, which is similar to the P-O-P structure of native pyrophosphate, makes the molecule extremely resistant to hydrolysis by the enzyme phosphatase and to acidic conditions. Slightly different chemical forms of radiolabeled bisphosphonates are available. The most commonly used diphosphonates (Fig. 2.6) are methylene diphosphonate (^{99m}Tc-medronate or ^{99m}Tc-MDP), hydroxymethylene diphosphonate (^{99m}Tc-oxidronate or ^{99m}Tc-HMDP), hydroxyethylene diphosphonate (^{99m}Tc-HDP), and dicarboxypropane diphosphonate (^{99m}Tc-DPD). The agents are substantially equivalent regarding lesion detectability; minor differences are reported among the different radiopharmaceuticals regarding the rate of clearance from the blood, justifying different imaging times after injection to obtain the best bone-to-soft tissue ratio.

^{99m}Tc-Bisphosphonates accumulate at sites of bone mineral rearrangement by chemisorption on the surface of newly formed hydroxyapatite crystals. Bone remodeling is an integral component of the osteoblastic reaction associated with most tumors metastatic to the bone, as well as primary bone tumors, infection in the bone, and response to trauma. Some tumors (e.g., renal cell carcinoma) cause primarily osteolytic lesions. Pure osteolytic lesions may be difficult or impossible to detect on bone scans.

Uptake of the radiopharmaceutical in the bone is also directly correlated with local vascularization, although not in a linear relationship; in fact, a three- to fourfold increase in blood flow enhances uptake by only 30–40%. Furthermore, a reduction of the sympathetic tone has vasodilator effects on capillary blood flow, thus increasing radiopharmaceutical

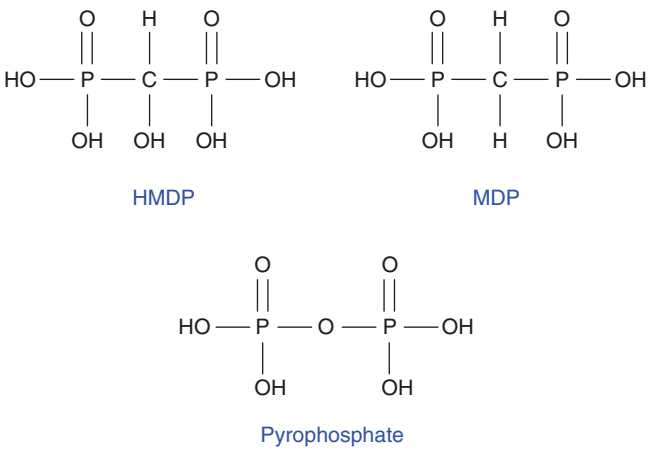

Fig. 2.5 Chemical structure of HMDP, MDP, and native pyrophosphate

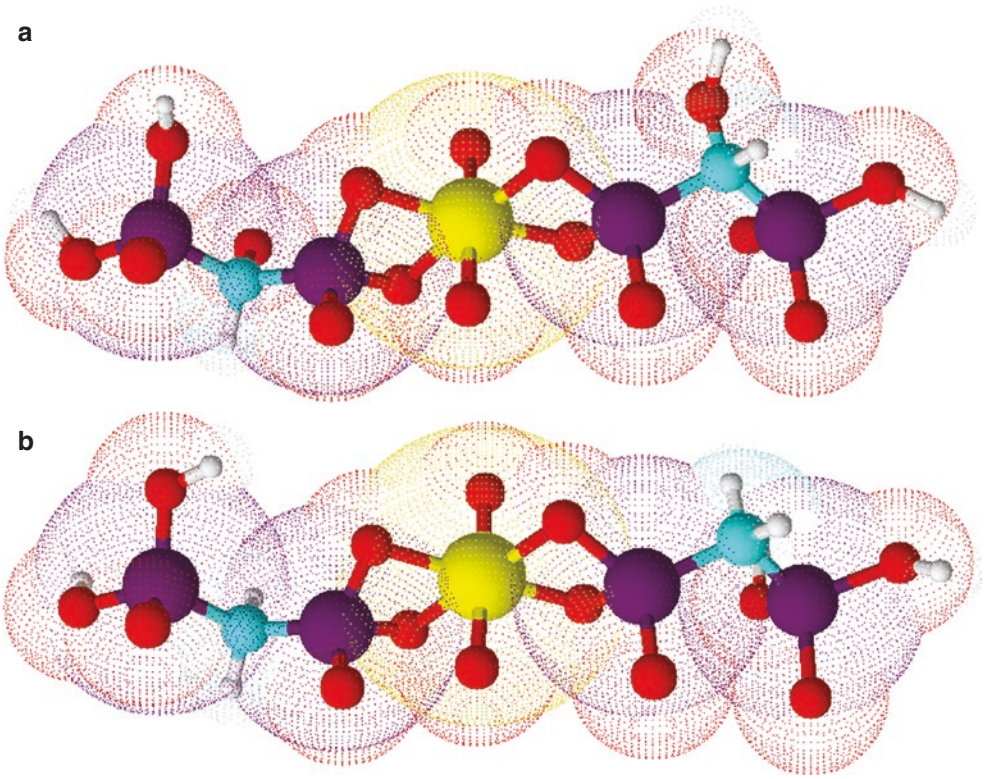

Fig. 2.6 Tridimensional chemical structure of ^{99m}Tc-labeled bisphosphonates employed for bone scintigraphy. (**a**) ^{99m}Tc-HMDP. (**b**) ^{99m}Tc-MDP. Color codes: *yellow* = ^{99m}Tc; *red* = O; *white* = H; *purple* = P; *light blue* = C

uptake, as observed in the case of reflex sympathetic dystrophy, sympathectomy, thrombosis, or hemiplegia.

After i.v. administration, the radiopharmaceutical rapidly diffuses into the extracellular space, and uptake in bone begins immediately. About 10% of the initial activity remains in the circulation 30 min after injection, decreasing to about 1% by 4 h after administration. The mechanism of radiopharmaceutical clearance from the body is through renal excretion, with about 50% of the intact radiopharmaceutical being excreted in the first 6 h after injection. The scan is usually performed 2–3 h after administration, when an optimal target/background ratio is achieved.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-bisphosphonates derivatives are reported below, normalized to unit of administered activity:

- Effective dose 0.0049 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Urinary bladder wall 0.047 mGy/MBq
  - Bone surface 0.034 mGy/MBq
  - Kidney 0.0072 mGy/MBq

Key Learning Points

- ^{99m}Tc-Bisphosphonates (or diphosphonates) accumulate at sites of bone mineral rearrangement by chemisorption on the surface of newly formed hydroxyapatite crystals.
- These compounds are commonly used for bone scintigraphy.

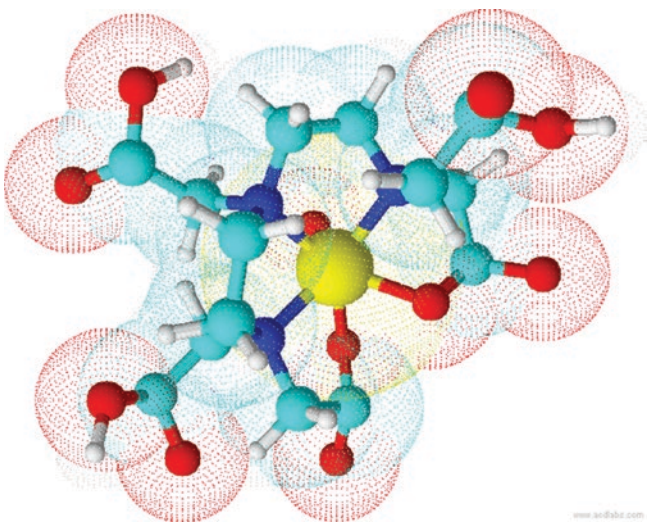

Fig. 2.7 Tridimensional chemical structure of ^{99m}Tc-DTPA. Color codes: *yellow* = ^{99m}Tc; *red* = O; *white* = H; *light blue* = C; *blue* = N

2.3.3 ^{99m}Tc-Diethylene Triamine Penta-Acetic Acid (^{99m}Tc-DTPA)

^{99m}Tc-DTPA is a ^{99m}Tc-chelated compound with a molecular weight of about 500 Da and a negative electrical charge (Fig. 2.7); this small molecule is therefore able to easily diffuse in the extracellular fluids. It is excreted unmodified through the kidneys through glomerular filtration, and it is not subject to tubular secretion and/or reabsorption.

Introduced in clinical practice in 1970 [4], ^{99m}Tc-DTPA is still one of the most commonly used radiopharmaceuticals for dynamic renal scintigraphy, which provides information about renal perfusion, glomerular function, and urinary tract obstruction. It is readily available, has relative low cost, and, above all, clinical benefits with good reproducibility.

Because of a relatively low binding to plasma proteins (3–5%), accumulation of ^{99m}Tc-DTPA in the urine reflects glomerular filtration. Quantitative analysis of the data acquired during dynamic renal scintigraphy with ^{99m}Tc-DTPA allows calculation of the glomerular filtration rate (GFR), the main parameter of renal function. Nevertheless, despite its very low plasma protein binding, ^{99m}Tc-DTPA tends to yield slightly lower GFR values than the reference values obtained by measuring inulin clearance.

Besides its use for the evaluation of renal function and flow through the urinary tract, ^{99m}Tc-DTPA has been employed as an inert, low-molecular-weight tracer for lung ventilation studies. When inhaled as an aerosol, ^{99m}Tc-DTPA is not absorbed from the lung but remains in the alveolus, reflecting the distribution of ventilation (see section on "Lung ventilation radiopharmaceuticals" further below).

Because of its inability to cross the intact blood-brain barrier, ^{99m}Tc-DTPA has also been used for scintigraphic evaluation of cerebral perfusion, especially to confirm brain death (by recording a dynamic planar first-pass acquisition in the first 60–120 s after administration of an i.v. bolus containing up to 740 MBq) as well as the integrity of the blood-brain barrier (static acquisition about 1 h after administration).

Specific investigations on the cerebrospinal fluid dynamics, such as cysternoscintigraphy or ventriculoscintigraphy, are possible after intrathecal administration of ^{111}In-DTPA (through the lumbar or suboccipital route). These investigations aim to identify possible obstructions or pathological leak of the cerebrospinal fluid (e.g., otorrhea or rhinorrhea) and arachnoid or porencephalic cysts, in the case of hydrocephalus or brain malformation. When delayed acquisitions extending up to 3 days are required, DTPA should be labeled with ^{111}In, which has a longer physical half-life more suitable for delayed imaging.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-DTPA are reported here below, normalized to unit of administered activity:

- Effective dose 0.0049 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Urinary bladder wall 0.062 mGy/MBq
  - Uterus 0.0079 mGy/MBq
  - Kidney 0.0044 mGy/MBq

Key Learning Points

- ^{99m}Tc-DTPA is a small chelated compound with negative electrical charge able to easily diffuse in the extracellular fluids.
- It is excreted unmodified through the kidneys through glomerular filtration, and it is not subject to tubular secretion and/or reabsorption, so its main use is for dynamic renal scintigraphy and GFR calculation.
- It has also been employed for lung ventilation, brain perfusion, and cysternoscintigraphy or ventriculoscintigraphy.

2.3.4 ^{99m}Tc-Mercapto-Acetyl-Triglycine (^{99m}Tc-MAG3)

Also known as ^{99m}Tc-betiatide or ^{99m}Tc-mertiatide, ^{99m}Tc-MAG3 contains, in addition to a coordinating structure able to bind ^{99m}Tc, an ionic carboxyl group (COOH) and a carbonyl group (C=O) (Fig. 2.8) binding to specific receptors located primarily in the distal part of proximal tubular cells and to a lesser extent in the early part of the distal tubule. This radiopharmaceutical undergoes partial glomerular filtration and active tubular secretion; it is therefore characterized by high renal extraction and fast blood clearance. ^{99m}Tc-MAG3 is commonly employed for dynamic renal scintigraphy [5]. Compared to the tubular excretion agent ^{131}I-hippuran (see further below), it has a γ-ray energy emission more favorable for gamma camera imaging and more favorable radiation dosimetry; advantages versus ^{123}I-hippuran include much lower cost and wider availability.

Following i.v. injection, ^{99m}Tc-MAG3 rapidly distributes in the extracellular fluids and is then cleared from the blood mainly by tubular secretion (>90%), without undergoing tubular reabsorption; the remaining amount of ^{99m}Tc-MAG3

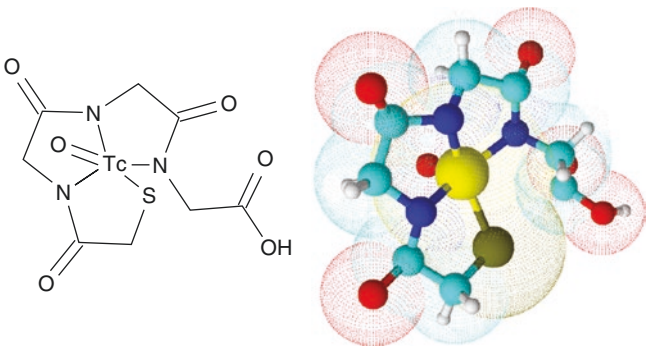

Fig. 2.8 Chemical and tridimensional structure of ^{99m}Tc-MAG3. Color codes: *yellow* = ^{99m}Tc; *red* = O; *white* = H; *light blue* = C; *blue* = N; *olive green* = S

is cleared through glomerular filtration, despite a high fraction of plasma protein binding (80%). There is also a minor fraction of excretion through the hepatobiliary tract, mediated by uptake in hepatocytes that is independent from renal function and mainly attributable to the lipophilic properties of ^{99m}Tc-MAG3. Some of the minimal quantities (1–2%) of impurities formed during radiolabeling accumulate in the liver and also undergo hepatobiliary excretion.

Because of its high first-pass renal extraction (around 60%) due to the active tubular secretion mechanism, ^{99m}Tc-MAG3 is particularly appropriate for use in pediatric-age patients, in the evaluation of the transplanted kidney, and in subjects with impaired renal function. In these cases, the high extraction fraction results in good images with a high target-to-background ratio with low injected activity.

Thanks to the properties of this tracer, quantitative analysis of the data acquired during dynamic renal scintigraphy allows calculation of the tubular extraction rate (TER), an important parameter of renal function.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-MAG3 are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.0017 mSv/MBq (urinary bladder emptied 30 min after administration)
- Tissues/organs with the highest values of absorbed dose:
  - Urinary bladder wall 0.11 mGy/MBq
  - Uterus 0.012 mGy/MBq
  - Lower large bowel wall 0.0057 mGy/MBq

Key Learning Points

- ^{99m}Tc-MAG3 (or betiatide or mertiatide) is a chemical compound undergoing partial glomerular filtration and active tubular secretion.
- This radiopharmaceutical is characterized by high renal extraction, and it is commonly employed for dynamic renal scintigraphy and tubular extraction rate (TER) calculation.

2.3.5 ^{99m}Tc-Dimercaptosuccinic Acid (^{99m}Tc-DMSA)

^{99m}Tc-DMSA is a chelated radiopharmaceutical used for renal parenchymal imaging (static renal scintigraphy), which provides information on morphology (malformations, ectopies, agenesis), cortical function, and renal injuries or infections.

The precise intrarenal handling of ^{99m}Tc-DMSA is still debated. Uptake can occur by tubular reabsorption across either the luminal membrane or directly by extraction from the blood of the peritubular capillaries via the basocellular membrane.

Following i.v. injection, ^{99m}Tc-DMSA initially distributes in the extracellular fluid, with temporary retention in the liver and spleen. About 90% of the radiopharmaceutical circulates in the blood bound to plasma proteins, which prevents its glomerular filtration (limited to 2–3% of total injected activity). Its kidney extraction is 5% at each passage, and 1 h postinjection, approximately 50% of the administered activity is firmly retained in the proximal renal tubular cells (mainly in the cytoplasm), with a 22:1 cortex/medulla uptake ratio. Maximum renal cortical uptake of the radiopharmaceutical is reached at about 3 h. Static renal scintigraphy acquired 1–3 h after injection provides excellent imaging of the renal cortex. Washout of ^{99m}Tc-DMSA is slow, so that 6 h after administration about 35% of injected activity is still retained in the renal cortex. Very late images (6–24 h) are generally acquired only in the event of urinary tract obstruction; at this time point, image quality is still suboptimal, due especially to the late concentration of ^{99m}Tc-DMSA in the liver, with an inverse proportion to renal uptake and function. About 50% of the injected activity is still bound to the renal tubules 24 h after administration.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-DMSA are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.0088 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Kidney 0.18 mGy/MBq
  - Urinary bladder wall 0.018 mGy/MBq
  - Spleen 0.013 mGy/MBq

Key Learning Points

- ^{99m}Tc-DMSA is a chelated radiopharmaceutical with high renal extraction and intraparenchymal retention commonly employed for static renal scintigraphy.
- The precise intrarenal handling of ^{99m}Tc-DMSA is still debated.

2.3.6 ^{99m}Tc-Radiocolloids

A “colloid” is defined as a homogeneous mixture in which one substance of microscopically dispersed insoluble particles is suspended throughout another substance (liquid or gas). To qualify as a colloid, the mixture must be one that does not settle or would

take a very long time to settle appreciably. Unlike those in a suspension, colloidal particles cannot be separated out by ordinary filtering or by centrifugation. The dispersed substance alone is called the colloid. Therefore, from the biological point of view, a colloid includes all particles ranging from 1 nm to about 4 μm that are found in the body fluids. These particles are generally due to debris of microorganisms, fragments of cells produced during the physiologic processes of tissue renewal, or products of intestinal absorption (especially fat). Colloids are generally removed from circulation by phagocytosis, except for products of intestinal absorption that undergo their physiological metabolism in the liver or at other metabolic sites.

Originally introduced to perform hepatosplenic scintigraphy and bone marrow scintigraphy (after systemic i.v. administration), their most common current use is for lymphoscintigraphy. Following its intradermal or subcutaneous administration, a colloidal tracer is usually cleared from the injection site by lymphatic drainage, allowing visualization of lymph nodes protecting that tissue. In patients with breast cancer, melanoma, or penile tumors, it has become a standard of clinical practice to biopsy the first lymph node (called the sentinel node) draining the region of the tumor.

Radiopharmaceuticals with colloidal properties include several types of preparations. The most widely used radiocolloids are ^{99m}Tc-nanocolloidal human albumin, ^{99m}Tc-sulfur colloid, and ^{99m}Tc-antimony trisulfide. Additional radiocolloids employed for lymphoscintigraphy (depending on local availability) include ^{99m}Tc-rhenium sulfide nanocolloid, ^{99m}Tc-sulfide nanocolloid, ^{99m}Tc-stannous phytate, ^{99m}Tc-tin colloid, and ^{99m}Tc-microaggregated human albumin [6]. Despite important differences in the size range of the radiolabeled particles (that dictate variable rates of clearance from the site of interstitial injection) (Fig. 2.9), a choice of a certain radiocolloid preparation over others is based more on local availability than on differences in diagnostic performance (e.g., the success rate in sentinel lymph node identification for radioguided sentinel lymph node biopsy, SLNB). It should be noted that smaller-sized particles migrate faster from the site of interstitial injection through the lymphatic channels, a feature that is more favorable for investigating the pattern of lymphatic circulation, e.g., in patients with edema of the limbs. However, small particles are not efficiently retained in the first lymph node they encounter along a certain pathway of lymphatic drainage (i.e., the sentinel lymph node), and they progress in part to visualize other lymph nodes along the same pathway; this feature complicates the gamma-probe-guided intraoperative search of sentinel lymph node(s). On the other hand, larger particles are retained more efficiently in the sentinel lymph node, but at the expense of a slower migration speed from the site of interstitial injection.

^{99m}Tc-Nanocolloidal human albumin is most frequently used in Europe and represents a good compromise between the speed of migration and lymph node retention. The size of its particles ranges from 5 to 100 nm, with at least 95% of human albumin

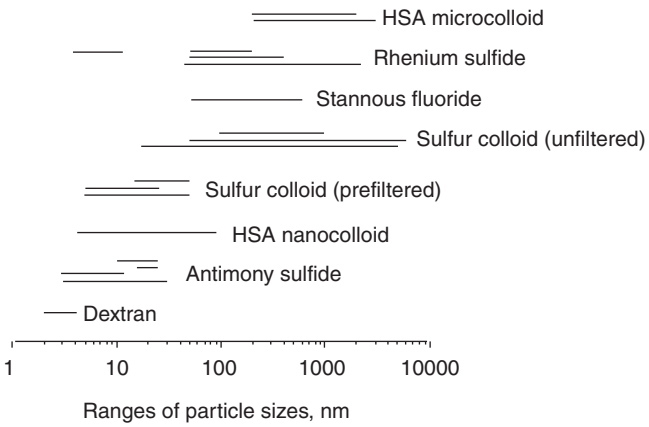

Fig. 2.9 Schematic representation of the ranges of particle sizes (in nm) constituting the main radiocolloids employed for lymphoscintigraphy; the logarithmic scale is used to compensate for the wide range in sizes (*reproduced with permission from Erba PA, Bisogni G, Del Guerra A, Mariani G. Methodological aspects of lymphoscintigraphy: radiopharmaceuticals and administration. In: Mariani G, Manca G, Orsini F, Vidal-Sicart S. Valdés Olmos RA, eds. Atlas of Lymphoscintigraphy and Sentinel Node Mapping – A Pictorial Case-Based Approach. Milan: Springer; 2013: pp 17–26*)

colloidal particles with a diameter ≤80 nm, which easily migrate through the lymphatic system but are not totally retained in the sentinel node. Lymphoscintigraphy will therefore usually display multiple lymph nodes along a certain lymphatic route, an occurrence that can complicate the intraoperative search for the "true" sentinel lymph node using the gamma probe.

^{99m}Tc-Sulfur colloid is commonly used in the USA; the range of particle sizes is quite wide (15–5000 nm) depending on the preparation method, with an average size ranging from 305 to 340 nm. The filtered colloidal form of ^{99m}Tc-sulfur colloid (particle size ranging from 100 to 220 nm) is used for lymphoscintigraphy. In this case radiocolloids are retained in the sentinel lymph node more efficiently than ^{99m}Tc-nanocolloidal human albumin, although their migration is quite slow, so that a longer time can be required to complete lymphoscintigraphy.

^{99m}Tc-Antimony trisulfide, used mostly in Canada and Australia, has a range of particle size of 3–30 nm. It migrates quite fast from the injection site through the lymphatic system; however, it is less efficiently retained in the sentinel node, so that several lymph nodes can typically be visualized along a single lymphatic draining channel.

The use of radiocolloids for liver, spleen, and bone marrow imaging relies on the fact that, following i.v. administration, these radiopharmaceuticals are cleared from the circulation through phagocytosis taking place in macrophages of the endothelial-lymphatic system, which are particularly abundant in the liver, spleen, and reticuloendothelial system of the bone marrow.

Lymphoscintigraphy is the first phase of radioguided SLNB. Along the route of lymphatic drainage from the site

of injection around the tumor, radiocolloids reach lymph nodes. The first lymph node is called the sentinel lymph node; this is the lymphatic station where tumor cells possibly entering lymph vessels and migrating along the route of lymphatic drainage encounter the first lymph node (or nodes) of the lymphatic basin draining that specific tumor region.

Different parameters such as specific injection site, particle size, and pathophysiology of local lymphatic circulation affect the speed of lymphatic drainage of radiocolloids. Small particles are drained to the extent of about 40–60%, whereas the larger particles are retained preferentially at the injection site. For instance, when using ^{99m}Tc-nanocolloidal albumin, lymph node activity reaches a plateau within 2 h after injection, approximately 3% of the injected activity being retained in all visualized nodes.

The ideal radiopharmaceutical for sentinel lymph node biopsy should allow rapid visualization of the first lymph node draining from the tumor/injection site and prolonged retention in the sentinel node, possibly without further migration to higher echelon nodes. In principle, radiocolloids with relatively large-sized particles (between 200 and 300 nm) have efficient retention in the first lymph node encountered along the migration route, with very little progression to higher echelon nodes. Nevertheless, particles of this size migrate quite slowly from the injection site.

Since the speed of migration of radiocolloids injected interstitially is inversely related to particle size, some compromise must be found between the speed of lymphatic migration and the degree of phagocytosis of the colloidal particles in lymph nodes. Given the different sizes of radiocolloids successfully used for lymph node mapping, the choice is usually based on local availability.

Radiocolloids can also be used as nonabsorbable ^{99m}Tc-labeled radiopharmaceutical for gastroenteric scintigraphy, including esophageal transit and gastric emptying imaging after oral administration. In this case the radiocolloids are generally suspended in some liquid, semisolid, or solid food (such as water, jelly, or eggs, respectively). Since radiocolloids cannot be absorbed within the gastrointestinal tract, it is possible to obtain functional images of the oral, esophageal, and gastric lumen enabling investigation of swallowing disorders, dysmotilities, or gastroparesis, according to the principle of compartmental localization.

An additional use of radiocolloids such as ^{99m}Tc-nanocolloidal human albumin has been described, i.e., as inert, small-sized particles for lung ventilation studies, by means of a special nebulizer producing a radioactive droplet aerosol [7].

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-labeled colloids 100–1000 nm in size (including sulfur colloid, tin colloid, microaggregated albumin, and phytate) are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.0091 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Spleen 0.074 mGy/MBq
  - Liver 0.071 mGy/MBq
  - Gallbladder wall 0.02 mGy/MBq

The main radiation dosimetry estimates to patients following intra-tumoral administration in breast cancer patients of ^{99m}Tc-labeled small colloids (<100 nm, including nanocolloidal albumin and antimony sulfide) 18 h prior to surgery are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.002 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Myocardium 0.0071 mGy/MBq
  - Remaining breast tissue 0.0064 mGy/MBq
  - Lung 0.0063 mGy/MBq

The main radiation dosimetry estimates to patients following oral administration of solid food labeled with ^{99m}Tc-colloids are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.024 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Colonic wall 0.10 mGy/MBq
  - Small bowel wall 0.061 mGy/MBq
  - Gastric wall 0.059 mGy/MBq

Key Learning Points

- Radiocolloids are very small particles (1 nm to 4 μm) that are found in the body fluids, generally due to debris of microorganisms, fragments of cells, or products of intestinal absorption.
- Several types of ^{99m}Tc-labeled colloids exist, with different origins and particle sizes.
- Radiocolloids administered intravenously have been used to perform hepatosplenic scintigraphy and bone marrow scintigraphy.
- As nonabsorbable radiopharmaceutical after oral administration, they are employed for gastroenteric scintigraphy (esophageal transit and gastric emptying imaging) and, as inert small-sized particles, for lung ventilation scintigraphy.
- The most common current use of radiocolloids is lymphoscintigraphy after intradermal or subcutaneous administration in the search of the so-called sentinel lymph node in patients with different types of solid cancers.

2.3.7 ^{99m}Tc-Mannosyl-DTPA-Dextran (^{99m}Tc-Tilmanocept)

^{99m}Tc-Tilmanocept is a noncolloidal receptor-targeted radiopharmaceutical approved by the FDA and EMA for sentinel lymph node mapping in patients with different types of solid cancers (including breast cancer, cutaneous melanoma, and squamous cell carcinoma of the oral cavity).

This small-sized macromolecule (average diameter 7 nm) consists of a dextran backbone with multiple units of DTPA (for labeling with ^{99m}Tc) and mannose residues, each covalently attached to the dextran backbone. The uptake mechanism of this radiopharmaceutical in lymph nodes does not depend on the particle size but on avid binding to the CD206 receptors for mannose expressed on the surface of macrophages and dendritic cells in lymph nodes.

The advantages of this novel radiopharmaceutical include rapid clearance from the injection site, high sentinel lymph node extraction, and high retention in sentinel lymph node, with consequent low migration to second-echelon lymph nodes.

The main radiation dosimetry estimates to patients following peritumoral injection of ^{99m}Tc-tilmanocept in patients with breast cancer are reported here below, normalized to unit of administered activity:

- Effective dose 0.3 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Breast (injection site) 1.65 mGy/MBq
  - Ovaries 0.187 mGy/MBq
  - Kidney 0.186 mGy/MBq

The main radiation dosimetry estimates to patients with melanoma following intradermal injection of ^{99m}Tc-tilmanocept in patients with cutaneous melanoma are reported here below, normalized to unit of administered activity:

- Effective dose 0.22 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Ovaries 0.299 mGy/MBq
  - Kidneys 0.278 mGy/MBq
  - Testes 0.104 mGy/MBq

Key Learning Points

- ^{99m}Tc-Tilmanocept is a small-sized macromolecule with high avidity for binding with the CD206 receptors for mannose expressed on the surface of macrophages and dendritic cells in lymph nodes.
- This radiopharmaceutical is used for sentinel lymph node mapping in patients with different types of solid cancers.

2.3.8 ^{99m}Tc-Macroaggregated Albumin (^{99m}Tc-MAA)

^{99m}Tc-MAA consists of irregular-shaped heat-denatured human albumin particles with varying sizes (range between 15 and 100 μm, no particles greater than 150 μm). This radiopharmaceutical is employed for perfusion lung scintigraphy after i.v. injection of approximately 100,000–400,000 radiolabeled particles (minimum 60,000).

After intravenous administration, over 90% of the ^{99m}Tc-MAA particles are trapped by microembolization in the pulmonary capillaries and precapillary arterioles because of their large size, with a pattern of anatomic distribution that mirrors regional lung perfusion. The particles are then removed from the pulmonary bed with an effective half-life of 1.5–3 h, through enzymatic degradation and mechanical movement of the lung; smaller particles produced during degradation enter the circulation taking on nanocolloidal characteristics, undergoing phagocytosis by macrophages of the reticuloendothelial system.

Upon i.v. administration, the ^{99m}Tc-MAA particles obstruct only a very small fraction of pulmonary vessels (<0.1%), which is negligible from the hemodynamic point of view since there are over 280 billion pulmonary capillaries and 300 million precapillary lung arterioles. Particles in size >150 μm would occlude arterioles of greater caliber with possible undesirable effects.

In patients with known pulmonary hypertension or right-to-left heart shunt, the number of ^{99m}Tc-MAA particles should be reduced to 100,000–200,000. In infants and children, the number of administered ^{99m}Tc-MAA particles should be further reduced as a function of age and body weight.

^{99m}Tc-MAA is also used for a particular procedure of radioguided surgery, radioguided occult lesion localization (ROLL). For this specific application, a small amount/volume of the radiopharmaceutical is injected under imaging guidance (often ultrasound, rarely CT) directly into the lesion to be surgically removed. Because of their size, the ^{99m}Tc-MAA particles remain into the lesion and do not undergo clearance via lymphatic drainage. The lesion is then located and excised intraoperatively under guidance with a gamma-detecting probe, according to the same detection principles as those of radioguided SLNB.

^{99m}Tc-MAA can be injected also during an angiographic session directly into the hepatic artery (or a segmental branch). This procedure is very important for treatment planning prior to trans-arterial radioembolization therapy with ^{90}Y- or ^{166}Ho-labeled microspheres in patients with primary or metastatic liver malignancies. In fact, the procedure allows assessment of possible shunt(s) of the intra-arterially injected particles to the pulmonary and/or gastrointestinal circulation.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-MAA are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.011 mSv/MBq
- Tissues/organs with the highest values of absorbed dose
  - Lung 0.066 mGy/MBq
  - Liver 0.016 mGy/MBq
  - Myocardium 0.0096 mGy/MBq

Key Learning Points

- ^{99m}Tc-MAAs are macroaggregates of denatured human albumin, with particles ranging in size between 15 and 150 μm.
- After i.v. injection, they are trapped by microembolization in the pulmonary capillaries and precapillary arterioles because of their large size and are therefore commonly employed for perfusion lung scintigraphy.

2.3.9 ^{99m}Tc-Hexa-Methyl-Propylene-AmineOxime (^{99m}Tc-HMPAO)

The molecular structure of ^{99m}Tc-HMPAO (also known as ^{99m}Tc-exametazine) shows Tc^{+5} to have five coordinate groups, with an oxo-group at the apex and four nitrogen atoms at the corners of the base of a square pyramid (Fig. 2.10).

This radiopharmaceutical has been developed primarily to perform brain perfusion scintigraphy. SPECT acquisition is mandatory, as it allows the evaluation of changes in regional cerebral blood flow (rCBF) that characterize certain clinical conditions such as Alzheimer's disease and other forms of dementia and cerebrovascular diseases in general. Although PET radiopharmaceuticals are currently preferred for characterization of patients with the dementias, ^{99m}Tc-HMPAO still plays an important role for rCBF assessment in nuclear medicine centers where a PET scanner is not available.

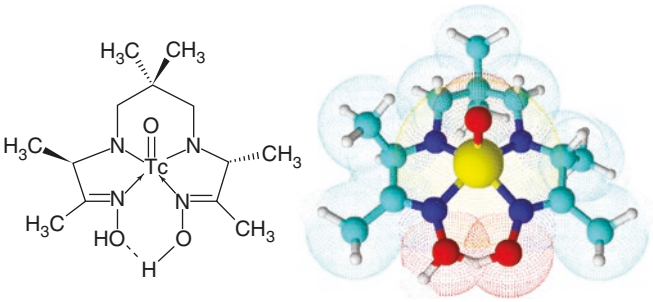

Fig. 2.10 Chemical and tridimensional structure of ^{99m}Tc-HMPAO. Color codes: *yellow* = ^{99m}Tc; *red* = O; *white* = H; *light blue* = C; *blue* = N

^{99m}Tc-HMPAO has been used also as a brain-specific tracer to perform brain death scintigraphy acquiring both early dynamic flow images and delayed SPECT images to ensure definitive absence of cerebral blood flow.

In clinical practice ^{99m}Tc-HMPAO is currently used predominantly for in vitro labeling of autologous leukocytes for scintigraphic visualization of infectious foci (see Chap. 46 of this book "Current practical guidelines for the most common nuclear medicine procedures" for details on how to radiolabel autologous leukocytes with ^{99m}Tc-HMAO).

As a neutral, low-molecular-weight, and lipophilic compound, ^{99m}Tc-HMPAO easily crosses the blood-brain barrier by simple diffusion following its concentration gradient from blood to the extravascular spaces and further on from the extracellular to the intracellular compartment. Because of this property and also by virtue of the efficient renal and hepatobiliary clearance (which remove 40% and 20%, respectively, of the administered activity), the radiopharmaceutical is rapidly cleared from circulating blood after intravenous administration.

After diffusion across the cell membrane, ^{99m}Tc-HMPAO undergoes the action of the enzyme esterase, which transforms it from a lipophilic to a hydrophilic substance that cannot diffuse back from the intracellular to the extracellular space; the hydrophilic form of ^{99m}Tc-HMPAO remains therefore trapped within neurons. This process is at the base of the prolonged retention of ^{99m}Tc-HMPAO in the brain with a distribution pattern that is proportional to rCBF at the time of tracer administration. Uptake in the brain reaches a maximum of 4–6% of injected activity within 1 min, with very little decline of activity over the following 24 h. For this reason, SPECT acquisition can start over a rather flexible time frame (usually 30–60 min after injection but even at delayed time points if necessary), during which no significant changes in ^{99m}Tc-HMPAO concentration occur.

It should be noted that, after reconstitution of the labeling kit, ^{99m}Tc-HMPAO is chemically stable for only 30 min and it should therefore be administered (or used for leukocyte labeling) within this time frame. Therefore, the radiopharmaceutical should be reconstituted only after the venous access has been set in place, in order to avoid delays in administration that may hamper reliability of the scan.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-HMPAO are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.0093 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:

- Kidney 0.034 mGy/MBq
- Thyroid 0.026 mGy/MBq
- Urinary bladder wall 0.023 mGy/MBq

Key Learning Points

- ^{99m}Tc-HMPAO (or exametazime) is a neutral, low-molecular-weight, and lipophilic compound able to cross the blood-brain barrier and to accumulate in the intracellular space.
- It is commonly employed to perform brain perfusion SPECT and for in vitro labeling of autologous leukocytes.

2.3.10 ^{99m}Tc-Ethylenediylbis-Cysteine-Diethylester (^{99m}Tc-ECD)

^{99m}Tc-ECD (also known as ^{99m}Tc-bicisate) is a neutral lipophilic complex that crosses the intact blood-brain barrier rapidly and enters the intracellular space of the brain, where it is retained for a long time. Only the stereoisomer l,l-ECD undergoes an intracellular enzymatic process that converts it into a polar species that is trapped in the human brain. Thus, only purified l,l-ECD is used for ^{99m}Tc-ECD formulation (Fig. 2.11). The ^{99m}Tc-ECD molecule has the core structure of $Tc{=}ON_2S_2$, with a coordination number of 5, consisting of two cysteine residues linked by an ethylene bridge. The resulting neutral complex has a square pyramidal molecular geometry, with the Tc=O group at the apex of the pyramid.

The only clinical indication for the use of this radiopharmaceutical is brain perfusion scintigraphy for assessing regional cerebral perfusion abnormalities and brain death.

Similarly to ^{99m}Tc-HMPAO, ^{99m}Tc-ECD crosses the blood-brain barrier and neuronal cell membrane with a mechanism of passive diffusion following a concentration gradient. After its entry into the cells, ^{99m}Tc-ECD is transformed into the negatively charged compound ^{99m}Tc-ethylenediyl-bis-L-cysteine monoethyl ester complex (or ^{99m}Tc-ECM) through a pH-dependent esterification enzymatic process that inactivates the lipophilic component. This transformation prevents ^{99m}Tc-ECM from crossing the cell membrane back to the extracellular space.

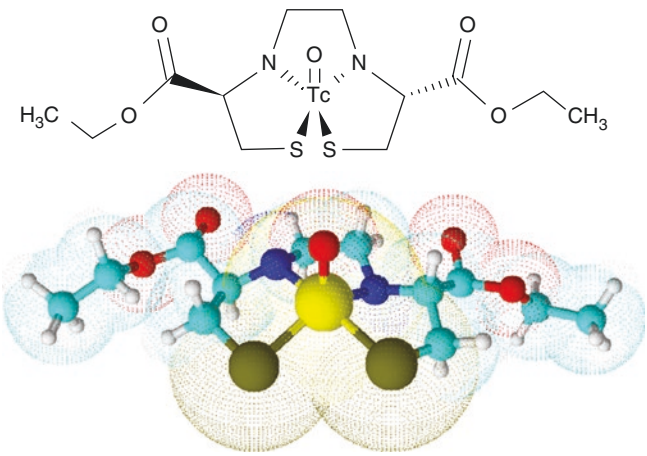

Fig. 2.11 Chemical and tridimensional structure of ^{99m}Tc-ECD. Color codes: *yellow* = ^{99m}Tc; *red* = O; *white* = H; *light blue* = C; *blue* = N; *olive green* = S

Brain uptake is very rapid, about 5% of injected activity concentrating in the brain within the first 2–3 min after administration and only 5% of injected activity remaining in the circulation 1 h after administration. Since the removal from the central nervous system is very slow, brain concentration does not vary for at least 6 h after injection. For best image quality, acquisitions should be performed 30–60 min after injection in order to achieve the optimal target-to-background ratio.

About 50% of injected activity is excreted through the kidneys within the first 2 h, while at 24 h urinary excretion is about 75%. The wall of the urinary bladder constitutes therefore the critical organ; such relatively high radiation burden can significantly be reduced by frequently emptying the bladder.

At variance with ^{99m}Tc-HMPAO, the ^{99m}Tc-ECD complex is very stable after reconstitution of the labeling kit; the radiopharmaceutical can therefore be injected up to about 8 h after reconstitution, if stored at a temperature below 25 °C.

When comparing ^{99m}Tc-ECD to ^{99m}Tc-HMPAO for brain perfusion imaging, some differences should be noted between the two radiopharmaceuticals regarding in vitro stability, retention mechanism, and dosimetry. Differences in the retention mechanisms may account for somewhat different patterns of distribution in specific disorders. For instance, in patients with subacute stroke ^{99m}Tc-ECD distribution seems to reflect metabolic activity more closely, whereas ^{99m}Tc-HMPAO is better correlated with cerebral perfusion. In conclusion, either of the two tracers can be used, but they are not fully interchangeable.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-ECD are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.0077 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Urinary bladder wall 0.05 mGy/MBq
  - Gallbladder wall 0.028 mGy/MBq
  - Colonic wall 0.021 mGy/MBq

Key Learning Points

- ^{99m}Tc-ECD (or bicisate) is a neutral lipophilic complex able to cross the blood-brain barrier and enter the intracellular space of the brain.
- This radiopharmaceutical is employed for brain perfusion SPECT.

2.3.11 ^{99m}Tc-Hexakis-2-Methoxy-2-Isobutyl-Isonitrile (^{99m}Tc-Sestamibi)

^{99m}Tc-Sestamibi is a positively charged lipophilic radiopharmaceutical, consisting of a central atom of technetium linked to six octahedral ligands (Fig. 2.12).

After i.v. administration, ^{99m}Tc-sestamibi diffuses rapidly in the extracellular spaces and then crosses cell membranes by passive diffusion (because of its lipophilicity) following both a concentration gradient and an electrical gradient driven by the negatively charged intracellular space. After entering into cells, ^{99m}Tc-sestamibi rapidly accumulates in the mitochondria, which are particularly abundant in cells with enhanced energy demand, such as cardiomyocytes and parathyroid adenoma cells. Its uptake and retention depend on regional blood flow, cell viability, cell membrane potential, and mitochondrial density/activity. Since this radiopharmaceutical is retained in mitochondria with a very slow washout rate, no significant redistribution takes place; there is no evidence of any metabolism of this radiopharmaceutical.

After intravenous injection, ^{99m}Tc-sestamibi is rapidly cleared from the blood, with only 8% of the administered activity remaining in the circulation 5 min postinjection. This tracer concentrates predominantly in the muscles (including the myocardium, with a biological half-life of approximately 6 h), liver, and kidneys, with a smaller amount accumulating in the salivary glands and thyroid. When ^{99m}Tc-sestamibi is injected during an exercise stress test, its uptake in the heart and skeletal muscles increases considerably due to the redistribution of cardiac output during exercise (decreased perfusion of the splanchnic bed and increased perfusion of the exercising muscles). In the resting state, the main pathway for excretion is via the hepatobiliary system to the gastrointestinal tract (33% at 48 h), with some additional excretion via the kidneys (27% at 24 h). Most of the injected activity is excreted within 48 h.

Originally introduced into the clinical routine for myocardial perfusion scintigraphy [8] ^{99m}Tc-sestamibi is used also for parathyroid scintigraphy and for scintimammography.

Localization of ^{99m}Tc-sestamibi in the parathyroid tissue is a function of metabolic activity, since this agent accumulates preferentially in mitochondria-rich tissues, as typically is a hyperfunctioning parathyroid tissue [9]. Although ^{99m}Tc-sestamibi accumulates also in the normal thyroid parenchyma, its washout rate from the hyperfunctioning parathyroid cells is much lower than from the thyroid gland. This differential retention kinetics seems to be related to downregulation in the parathyroid tissue of the P-glycoprotein system, which is responsible for the efflux of various compounds (including ^{99m}Tc-sestamibi) from the intracellular to the extracellular space. For parathyroid scintigraphy using ^{99m}Tc-sestamibi as a single tracer, images are recorded about 15 min postinjection, and at 2–3 h postinjection; differential washout rate of the radiopharmaceutical allows detection of hyperfunctioning parathyroid tissue (Fig. 2.13).

Although the precise mechanisms responsible for ^{99m}Tc-sestamibi uptake in breast tumors (as in other cancer cells) are still not completely clarified, they most likely depend on regional blood flow, plasma and mitochondrial membrane potential, angiogenesis, and overall tissue metabolism. For scintimammography, ^{99m}Tc-sestamibi imaging was first performed using standard gamma cameras and imaging tables adapted to allow for prone imaging [10], whereas high-resolution small-field-of-view gamma cameras specifically designed for breast imaging have more recently been introduced.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-sestamibi are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.009 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Gallbladder wall 0.039 mGy/MBq
  - Kidney 0.036 mGy/MBq
  - Colonic wall 0.024 mGy/MBq

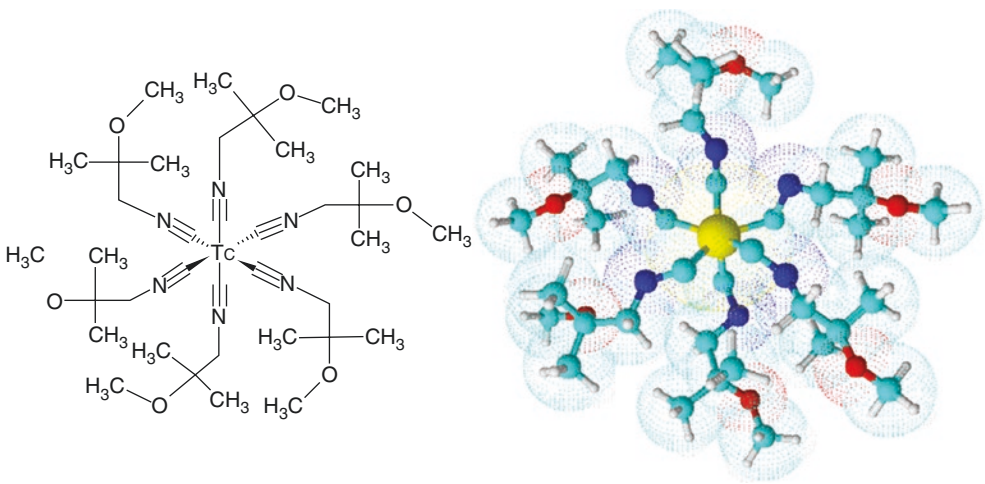

Fig. 2.12 Chemical and tridimensional structure of ^{99m}Tc-sestamibi. Color codes: *yellow* = ^{99m}Tc; *red* = O; *white* = H; *light blue* = C; *blue* = N

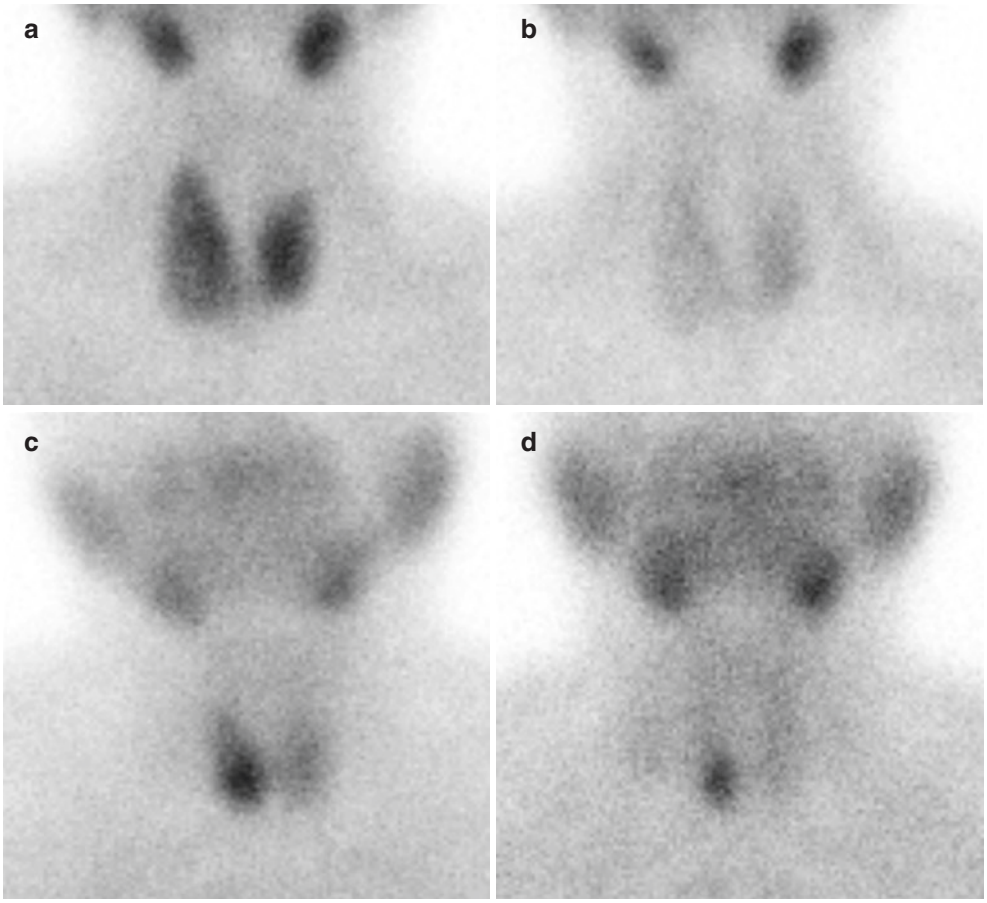

Fig. 2.13 Examples of dual-phase parathyroid scintigraphy with ^{99m}Tc-sestamibi (early image on the left, delayed image on the right). (**a**) No abnormal areas of focally increased ^{99m}Tc-sestamibi uptake on both early and delayed imaging. (**b**) Focal area of increased ^{99m}Tc-sestamibi uptake at the lower pole of the right thyroid lobe visualized both on early imaging (where also the thyroid parenchyma exhibits some tracer uptake) (**c**) on delayed imaging (where most of the activity has cleared from the thyroid parenchyma) (**d**); the area with slow ^{99m}Tc-sestamibi washout corresponds to an adenoma of the right lower parathyroid gland

Key Learning Points

- ^{99m}Tc-Sestamibi is a positively charged lipophilic compound, able to enter into cells by passive diffusion and be retained mostly in the mitochondria.
- In addition to its routine use for myocardial perfusion scintigraphy, it is also employed for parathyroid scintigraphy and for scintimammography.

2.3.12 ^{99m}Tc-6,9-Bis(2-Ethoxyethyl)-3,12-Dioxa-6,9-Diphospha-Tetradecane (^{99m}Tc-Tetrofosmin)

^{99m}Tc-Tetrofosmin is a positively charged lipophilic technetium phosphine whose molecular structure is characterized by a core of four atoms of phosphor-binding ^{99m}Tc, stabilized by two oxygen atoms (O=Tc=O) (Fig. 2.14).

The localization properties of ^{99m}Tc-tetrofosmin are similar as those of ^{99m}Tc-sestamibi; after entering into cells by passive diffusion following a concentration gradient and an electrical gradient, ^{99m}Tc-tetrofosmin is retained intracellularly mostly bound to cytosol proteins.

Myocardial uptake of ^{99m}Tc-tetrofosmin (as well as that of ^{99m}Tc-sestamibi) is proportional to blood flow up to about 2 mL/min per gram, which is twice the resting level, reaching a plateau at higher flow rates.

Following systemic intravenous administration, less than 5% of the administered activity remains in the circulation 10 min postinjection. About 65% of the administered activity is excreted within 48 h, 40% in the urine and 25% through the hepatobiliary tract. The hepatic clearance of ^{99m}Tc-tetrofosmin is more rapid than that of ^{99m}Tc-sestamibi, thus allowing earlier myocardial imaging.

^{99m}Tc-Tetrofosmin is employed almost exclusively for myocardial perfusion scintigraphy [11], whereas, its use for parathyroid scintigraphy is much less frequent than that of

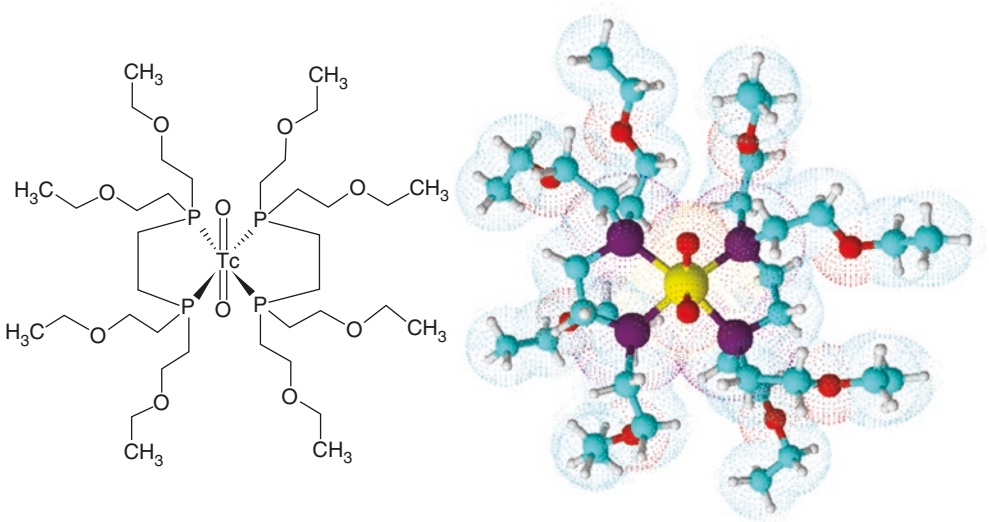

Fig. 2.14 Chemical and tridimensional structure of ^{99m}Tc-tetrofosmin. Color codes: *yellow* = ^{99m}Tc; *red* = O; *white* = H; *light blue* = C; *purple* = P

^{99m}Tc-sestamibi, mostly due to the fact that its kinetics of washout from the thyroid parenchyma is not so much different from the washout rate from hyperfunctioning parathyroid tissue.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-tetrofosmin are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.008 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Gallbladder wall 0.036 mGy/MBq
  - Colonic wall 0.024 mGy/MBq
  - Urinary bladder wall 0.017 mGy/MBq

Key Learning Points

- ^{99m}Tc-Tetrofosmin is a positively charged lipophilic compound able to enter into cells by passive diffusion and be retained mostly bound to cytosol proteins.
- It is mainly employed for myocardial perfusion scintigraphy.

2.3.13 ^{99m}Tc-Labeled Iminodiacetic Acid (IDA) Derivatives (^{99m}Tc-IDA)

Radiopharmaceuticals belonging to this group are analogs of lidocaine consisting of lipophilic anions with very low affinity for plasma proteins. Based on variable N-substitution of IDA, they are named according to the type of substitute. The main compounds of this group are diethyl-IDA, diisopropyl-IDA, *p*-isopropyl-IDA, *p*-butyl-IDA, and mebrofenin. In clinical practice, mainly ^{99m}Tc-mebrofenin (i.e., *N*-(3-bromo-2,4,6-trimethylphenylcarbamoylmethyl)-iminodiacetic acid) and ^{99m}Tc-diisopropyl-IDA are used.

These derivatives are used for hepatobiliary function imaging, as they allow scintigraphic evaluation of overall hepatocyte function, conjugation capability, and kinetics of biliary excretion. Following i.v. injection, hepatocytes rapidly extract these radiopharmaceuticals from circulating blood against an electrochemical and concentration gradient, thanks to non-sodium-dependent carriers located on the bloodstream side of the cell membrane; this mechanism is similar to the mechanism that bilirubin, bile acids, and other anions metabolized in the liver undergo. Binding of ^{99m}Tc-IDA derivatives with the bilirubin receptors is about 15-fold greater than that for bilirubin. Therefore, it is possible to perform the examination in the presence of high bilirubin blood values. However, based on our experience, when the bilirubin is >10 mg/dL, hepatobiliary visualization is poor. In hepatocytes these compounds are rendered water-soluble by conjugation with glucuronic acid and are then excreted into the bile through the hepatocyte bile ducts, ending up ultimately into the intestine.

About 8–17% of the injected activity of ^{99m}Tc-mebrofenin remains in the circulation 30 min after injection. Approximately 1–9% of the administered activity is excreted in the urine over the first 2 h after injection. In fasting individuals, the maximum liver uptake occurs by 10 min postinjection and peak gallbladder activity by 30–60 min after injection. Only a minor fraction of the injected activity is eliminated in the urine (<5%), because of their binding to plasma proteins and low water solubility. In cases where the gallbladder is visualized but no activity has entered the bowel, additional pharmacologic intervention, with cholecystokinin, is required. In cases where the gallbladder is not visualized within 1 h of administration of ^{99m}Tc-mebrofenin,

morphine administration may be helpful to cause contraction of the sphincter of Oddi, resulting in filling of the gallbladder (in the absence of cholecystitis).

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-IDA derivatives are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.016 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Gallbladder wall 0.11 mGy/MBq
  - Colonic wall 0.072 mGy/MBq
  - Small intestine wall 0.043 mGy/MBq

Key Learning Points

- ^{99m}Tc-labeled iminodiacetic acid derivatives (^{99m}Tc-IDA) are analogs of lidocaine consisting of lipophilic anions with very low affinity for plasma proteins.
- They are used for hepatobiliary functional imaging, as they are extracted by hepatocytes and then excreted into the bile.

2.3.14 ^{99m}Tc-Sulesomab

The murine monoclonal antibody IMMU-MN3 was originally raised with the aim of targeting the tumor-associated carcinoembryonic antigen (CEA)—to be used as a radiolabeled agent for immunoscintigraphy and possibly radioimmunotherapy of CEA-expressing tumors. Although the results of CEA-targeting studies were disappointing, it turned out that the antibody efficiently bound an antigen abundantly expressed on the cell membrane of granulocytes, the so-called nonspecific cross-reacting antigen NCA90. The use of ^{99m}Tc-sulesomab (a mixture of Fab′-SH (Fab_2), heavy and light chains, and other fragments of the IMMU-MN3 antibody) for imaging sites of infection/inflammation is based on this property.

The main indication for scintigraphy with ^{99m}Tc-sulesomab is for the identification and localization of infection, particularly osteomyelitis of appendicular bones (e.g., osteomyelitis complicating diabetic foot ulcers). In certain clinical conditions, it constitutes therefore a valid alternative to scintigraphy with radiolabeled autologous leukocytes, which is burdened with some limitations, e.g., requirement for a quite large blood sample (from patients who are frequently critically ill) and potential hazard of infection for the nuclear medicine personnel handling leukocytes from high-risk patients.

The choice of fragments rather than whole intact immunoglobulins is based on the notion that these preparations are less immunogenic (thus reducing the risk of raising human anti-murine antibodies—HAMA) and that Fab fragments of antibodies have much faster clearance kinetics than the intact IgG molecules. Furthermore, the free thiol groups present in the Fab′ fragment following chemical reduction allow direct radiolabeling with ^{99m}Tc. Following i.v. injection, concentration of ^{99m}Tc-sulesomab in the blood at 1 h postinjection is 34% of the initial level, declining to 17% at 4 h and 7% at 24 h. The route of excretion is predominantly renal, 41% of the radiolabel being excreted in the urine over the first 24 h after administration.

Imaging with ^{99m}Tc-sulesomab should be acquired 1–8 h postinjection, without relevant differences in the detection rate of osteomyelitis between the 1–2 h time point and the 5–8 h time point. Although planar imaging is performed first in all views necessary to adequately visualize the affected area(s), SPECT/CT imaging is crucial for distinguishing pure osteomyelitis from infection of soft tissues only.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-sulesomab are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.0077 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Kidneys 0.0449 mGy/MBq
  - Urinary bladder wall 0.0221 mGy/MBq
  - Spleen 0.0115 mGy/MBq

Key Learning Point

- ^{99m}Tc-Sulesomab is a murine monoclonal antibody used for the identification and localization of infection.

2.3.15 ^{99m}Tc-EDDA/HYNIC-[Tyr^3]-Octreotide (TOC) and Other Somatostatin Analogs

^{99m}Tc-EDDA/HYNIC-octreotide is a somatostatin (SST) analog labeled with ^{99m}Tc. SST is a 14-amino acid peptide produced endogenously mainly in the central nervous system. Physiologic functions of SST include inhibition of secretion of various hormones, such as insulin and glucagon. Receptors for somatostatin are overexpressed in most of neuroendocrine tumors, and receptor activation inhibits function cell growth, therefore also tumor growth. For this reason, SST analogs are used in oncology as antitumor drugs in patients with some neuroendocrine tumors. Five different types of receptors for SST have been identified, named SSTR1-5 (type 2 being divided into subtypes 2a and 2b). Native SST has a very short biological half-life (3 min), which limits its use both as an oncological thera-

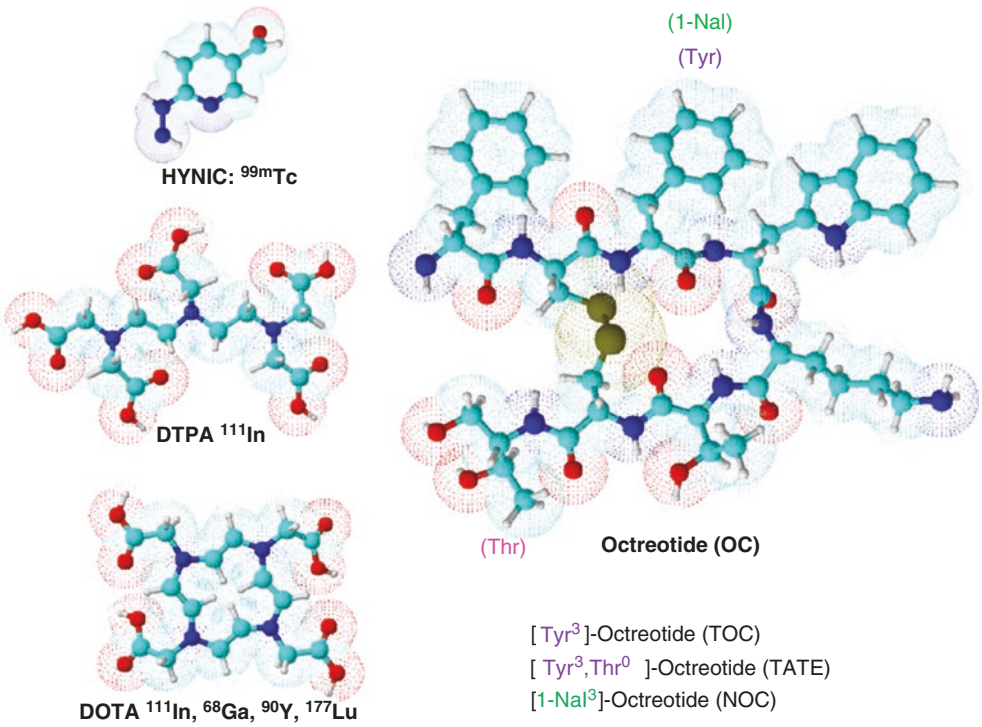

Fig. 2.15 Tridimensional structure of the somatostatin analogs of major interest in nuclear medicine and of the chelating agents used for labeling with different radionuclides (HYNIC, DTPA, DOTA). Color codes: *red* = O; *white* = H; *light blue* = C; *blue* = N; olive green = S

peutic drug as such and, upon radiolabeling, as a radiopharmaceutical for either diagnostic or therapeutic application.

Several SST analogs have therefore been developed, with longer biological half-life and physiological biodistribution and biological activity similar to native SST (Fig. 2.15), as follows:

- Octreotide (OT), with medium/high affinity for SSTR2 and medium affinity for SSTR3 and SSTR5. It is employed for imaging in conventional nuclear medicine, labeled with ^{111}I through the DTPA chelator (^{111}In-DTPA-octreotide or ^{111}In-pentetreotide).
- [Tyr^3]-Octreotide (TOC), with high affinity for SSTR2, medium/high affinity for SSTR5, and low affinity for SSTR3. It is employed for imaging in conventional nuclear medicine, labeled with ^{99m}Tc through the HYNIC/EDDA chelator (^{99m}Tc-EDDA/HYNIC-octreotide). Through the DOTA[1] chelator, it can be labeled with ^{68}Ga for PET imaging (^{68}Ga-DOTA-TOC) or with ^{90}Y for therapy (^{90}Y-DOTA-TOC).
- [Tyr^3,Thr^0]-Octreotide (TATE), with very high affinity for SSTR2 (six- to ninefold greater than TOC), medium affinity for SSTR5, but no affinity for SSTR3. Through the DOTA chelator, it can be labeled with ^{177}Lu for therapy (^{177}Lu-DOTA-TATE).
- [1,NaI^3]-Octreotide (NOC), with high affinity for SSTR2 and SSTR5 and medium/high affinity for SSTR3. Through the DOTA chelator, it can be labeled with ^{68}Ga for PET imaging (^{68}Ga-DOTA-NOC).

[1]DOTA = tetraazacyclododecane-1,4,7,10-tetraacetic acid

Mainly because of the favorable physical properties and wide availability of ^{99m}Tc, ^{99m}Tc-EDDA/HYNIC-octreotide offers several advantages over ^{111}In-pentetreotide, such as ready availability (because of the possibility to label the lyophilized kit "on demand" when needed), possibility to administer higher amounts of activity (because of the more favorable dosimetry parameters), faster imaging (completed within 4–6 h versus up to 24 h), better image quality and detection capability (with higher target/nontarget ratios because of more favorable counting statistics), and overall better cost-effectiveness.

After intravenous administration, ^{99m}Tc-EDDA/HYNIC-TOC is rapidly cleared from the blood, although with some residual binding to blood cells (<5% of injected activity throughout several hour postinjection). As early as 10 min postinjection, accumulation of ^{99m}Tc-EDDA/HYNIC-TOC is detected in the main sites of physiologic uptake/excretion (i.e., the liver, spleen, and kidneys), as well as in the tumor lesions expressing SST receptors.

Maximal tumor/background ratios are observed at 4 h after injection, cancer lesions remaining still detectable at 24 h. Minor excretion through the gastrointestinal tract is observed in delayed images. ^{99m}Tc-EDDA/HYNIC-TOC is excreted mainly by the renal route, with only a small fraction undergoing hepatobiliary clearance.

The main radiation dosimetry estimates to patients following intravenous administration of ^{99m}Tc-EDDA/HYNIC-TOC are reported here below, normalized to unit of administered activity:

- Effective dose 0.005 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Spleen 0.037 mGy/MBq
  - Kidney 0.02 mGy/MBq
  - Urinary bladder wall 0.012 mGy/MBq

There are also other ^{99m}Tc-labeled SST analogs, such as ^{99m}Tc-HYNIC-octreotide, ^{99m}Tc-vapreotide, ^{99m}Tc-depreotide, and ^{99m}Tc-demotate. ^{99m}Tc-HYNIC-Octreotate differs from ^{99m}Tc-HYNIC-octreotide for the presence of the more hydrophilic tyrosine in the third position and of the terminal threonine causing higher receptor affinity and better internalization properties.

^{99m}Tc-Depreotide had been approved for discriminating malignant from benign solitary pulmonary nodules. This synthetic 10-amino acid peptide (which can be easily labeled with ^{99m}Tc due to the presence of a particular amino acid sequence) was originally developed as a potent SST analog exhibiting good affinity for SSTR2, SSTR3, and SSTR5. After initial studies aimed at targeting neuroendocrine tumors, strong binding of ^{99m}Tc-depreotide to SST receptors expressed in both small cell and non-small cell lung cancer was observed. However, this radiopharmaceutical is no longer available commercially, because of the growing use of [^{18}F]FDG PET for characterizing solitary pulmonary nodules (and lung cancers in general).

Key Learning Points

- Receptors for somatostatin are overexpressed in the majority of neuroendocrine tumors, and their activation inhibits function cell growth.
- These targets are used in oncology for cancer treatment, with the purpose of inhibiting tumor growth.
- Several exogenous somatostatin analogs have been developed, labeled with different radionuclides for both therapeutic and imaging purposes; ^{99m}Tc-EDDA/HYNIC-octreotide is the most commonly used radiopharmaceutical labeled with ^{99m}Tc to image neuroendocrine tumors.

2.4 Radiopharmaceuticals Labeled with Indium-111

2.4.1 ^{111}In-DTPA-Octreotide (^{111}In-Pentetreotide)

The 8-amino acid ^{111}In-pentetreotide is an analog of the active part of SST (Fig. 2.15), linked to a chelating group constituted by DTPA that makes radiolabeling with ^{111}In possible (although such binding is not as stable as the binding of metallic radionuclides with the DOTA chelator). This cyclotron-produced radionuclide has a quite long physical half-life (2.8 days) and emits γ-rays with energy peaks of 171 keV (90%) and 245 keV (94%), with additional X-ray emission of 23–26 keV. Due to these energy emission levels, scintigraphy with ^{111}In-labeled agents is generally performed with gamma cameras equipped with medium-energy collimators.

Scintigraphy with ^{111}In-pentetreotide (that has medium/high affinity for SSTR2 and medium affinity for SSTR3 and SSTR5) is primarily employed to investigate patients with neuroendocrine tumors expressing SST receptors (especially gastroenteropancreatic and carcinoid tumors) for the purposes of staging, restaging, and evaluation of response to treatments. Increased expression of SST receptors occurs also in tumors originating from the neural crest, such as paragangliomas, neuroblastomas, pheochromocytomas, and medullary thyroid carcinomas. Furthermore, varying degrees of SST receptor expression are also observed in non-neuroendocrine tumors, such as breast cancer and some lymphomas (both Hodgkin's and non-Hodgkin's lymphomas). Finally, increased SST receptor expression occurs even in non-neoplastic disorders, especially in subacute and chronic inflammation (mainly of the granulomatous type, as in sarcoidosis).

Following i.v. injection, ^{111}In-pentetreotide is rapidly cleared from the plasma; only one third of the injected activity remains in the blood pool at 10 min after administration. Plasma levels continue to decline steadily, so that by 20 h postinjection, about 1% of the activity is found in the blood pool.

^{111}In-Pentetreotide is mainly excreted by the kidneys, 50% of injected activity being recovered in the urine within 6 h and up to 85–90% at 24 h after administration. A smaller fraction of radiopharmaceutical is excreted through the hepatobiliary system, corresponding to about 2% of the injected activity after 3 days. Scintigraphy shows physiologic uptake in the spleen (about 2.5% of injected activity at 24 h), liver (2%), and kidneys. In most patients, the thyroid, pituitary, and intestine are also visualized during scintigraphy with ^{111}In-pentetreotide. The standard injected activity into an adult patient is 110–220 MBq.

Key Learning Points

- ^{111}In-Pentetreotide is a somatostatin analog that avidly binds to somatostatin receptors on cell membranes, generally overexpressed in neuroendocrine tumors.
- It is the most commonly ^{111}In-labeled radiopharmaceutical used in conventional nuclear medicine and is employed to investigate patients with neuroendocrine tumors, especially gastroenteropancreatic and carcinoid tumors.

The main radiation dosimetry estimates to patients following intravenous administration of ^{111}In-pentetreotide are reported here below, normalized to unit of administered activity:

- Effective dose 0.054 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Spleen 0.57 mGy/MBq
  - Kidney 0.41 mGy/MBq
  - Urinary bladder wall 0.2 mGy/MBq

2.4.2 ^{111}In-DTPA

The primary use of ^{111}In-DTPA is for intrathecal radiopharmaceutical administration for cisternoscintigraphy, determining CSF shunt patency, and assessing the dynamics of the cerebrospinal fluid (CSF). Tracers administered through this route undergo partial absorption in the subarachnoid space, some of the CSF flowing to the basal cisterns within 2–4 h and then progressing to the Sylvian cisterns, to the interhemispheric cisterns, and over the cerebral convexities. In normal individuals, the radiopharmaceutical ascends to the parasagittal region within 24 h, clearing partially or completely from the basal cisterns and Sylvian regions.

Due to reabsorption and passage of ^{111}In-DTPA into the systemic circulation, about 65% of the administered activity is excreted in the urine within 24 h after intrathecal injection, increasing to 85% at 72 h. The recommended activity of ^{111}In-DTPA to be injected intrathecally for radionuclide cisternography is 18.5 MBq in a standard adult individual with 70-kg body weight.

The main radiation dosimetry estimates to patients following intrathecal administration of ^{111}In-DTPA are reported here below, normalized to unit of administered activity according to the route of injection—lumbar or cisternal:

- Effective dose 0.14 mSv/MBq (lumbar) and 0.12 mSv/MBq (cisternal)
- Tissues/organs with the highest values of absorbed dose:
  - Spinal cord 0.95 mGy/MBq (lumbar) and 0.57 mGy/MBq (cisternal)
  - Red marrow 0.24 mGy/MBq (lumbar) and 0.14 mGy/MBq (cisternal)
  - Urinary bladder wall 0.20 mGy/MBq (lumbar) and 0.18 mGy/MBq (cisternal)

Key Learning Points

- ^{111}In-DTPA is a small chelated compound with negative electrical charge.
- Radiolabeling with ^{111}In permits to perform cisternoscintigraphy after intrathecal administration, with delayed imaging—even up to 72 h post-administration.

2.5 Radioiodinated Imaging Agents

The radioisotopes of iodine used for conventional gamma camera imaging are ^{123}I (for diagnosis) and ^{131}I (mostly for therapy), whereas ^{124}I is used for PET imaging. In addition to its use in the simple chemical form of iodide anion for imaging the thyroid parenchyma and follicular cell-derived thyroid cancers, radioiodine can replace some functional groups in larger molecules, such as the $–CH_3^-$ group (whose radius is similar to the atomic radius of iodine) or the hydroxylic group $–OH^-$ through a process of nucleophilic/electrophilic substitution. Both the $–CH_3^-$ group and the $–OH^-$ radical are abundant in amino acids (typically in tyrosine) that are widely present and frequently exposed to the surface of macromolecules present in biological systems—being therefore available for a substitution reaction with (radio)iodine.

^{131}I is historically one of the first radionuclides made available for medical applications and still remains a milestone for therapeutic applications, due to its emission of β-particles. Because of its concomitant γ-emission, ^{131}I (which has an 8-day physical half-life) is also still used for some specific diagnostic applications, typically in the chemical form of sodium iodide for imaging patients with differentiated thyroid cancer. Because of the main γ-emission with a relatively high energy (364 keV), image acquisition with ^{131}I-labeled radiopharmaceuticals requires the use of gamma cameras equipped with medium-high-energy collimators, which results in suboptimal image quality. Moreover, the β-particle emission associated with its decay results in a relatively high radiation burden to patients.

^{123}I does not suffer from these drawbacks, since it has a much shorter physical half-life (13.2 h) than ^{131}I and does not emit β^- particles, thus resulting in a more favorable radiation burden to patients. Moreover, the energy of its γ-emission (159 keV) is optimal for gamma camera imaging and allows for the use of high-resolution collimators.

2.5.1 ^{123}I/^{131}I-Sodium Iodide

^{123}I-Iodide and ^{131}I-iodide share exactly the same pharmacokinetic and uptake characteristics. As mentioned above, the use of ^{123}I-iodide is to be preferred over ^{131}I-iodide for diagnostic imaging (especially in children) because of its lower radiation burden to patient and better image quality; the only practical drawback is the much higher cost of ^{123}I-iodide, associated also with a more complex distribution logistics.

Nevertheless, there are some specific diagnostic applications where ^{131}I-iodide is still largely employed in the clinical practice. In particular, this radiopharmaceutical is used for measuring radioiodine uptake prior to radiometabolic therapy of hyperthyroid patients and for whole-body scintigraphy (^{131}I-WBS) in patients with differentiated thyroid cancer. For these two applications, the administered activities are very

different: only a trace amount of radioactivity (0.37–1.85 MBq) to measure thyroid uptake but up to 185 MBq for ^{131}I-WBS in thyroid cancer patients. In both cases, the radiopharmaceutical is generally administered orally as a capsule, while in pediatric patients or in patients with swallowing problems a liquid formulation is also available, for either oral or intravenous administration.

After administration, ^{123}I- and ^{131}I-iodide have a pattern of distribution and metabolism exactly as the native ^{127}I-iodide present in the circulation and in interstitial fluid. In particular, iodine is actively transported into the thyroid cells by the Na^+/I^- symporter (NIS) against a concentration gradient, intracellular concentration being 20- to 40-fold higher than extracellular concentration. Once inside the thyroid cells, iodine is oxidized by the thyroid-specific enzyme peroxidase; this reaction starts the organification process that leads to incorporation of iodine into tyrosine, an amino acid contained in the thyroglobulin molecules produced by the endoplasmic reticulum and Golgi apparatus. Molecules of monoiodotyrosine (MIT) and diiodotyrosine (DIT) are thus formed. These two chemical species are then combined to produce the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Thyroid hormones stored in the follicle-filling colloid are finally secreted into the circulation. The fundamental steps of this complex metabolic pathway (i.e., NIS expression/activity and secretion of thyroid hormones by pinocytosis) are stimulated by TSH.

In addition to the thyroid, iodine is also concentrated by the salivary glands, sweat glands, stomach, mammary glands, and placenta.

^{123}I-Iodide is generally used for thyroid scintigraphy in patients with benign thyroid disease, both for diagnostic imaging and for measuring radioiodine uptake. ^{123}I-Iodide is in principle to be preferred over ^{131}I-iodide for whole-body dosimetric purposes in patients with thyroid malignancies and also to avoid the thyroid stunning effect prior to high-dose therapy with ^{131}I-iodide. The concept of thyroid stunning relies on the hypothesis which implies that the radiation effects from the relatively low activity of the diagnostic β-emitter ^{131}I-iodide activities may impair the ability of the remnant thyroid tissue or metastases to concentrate iodine, thus jeopardizing the therapeutic outcomes.

^{123}I-Iodide is generally administered orally, although an i.v. formulation is also available. The standard activity administered for thyroid scintigraphy in a 70-kg adult individual varies from 2 MBq (for measuring radioiodine uptake) to 111 MBq (for thyroid scintigraphy). Higher ^{123}I activities are required for whole-body scans (40–200 MBq) and even higher for SPECT acquisitions, images being acquired 24 h after administration.

The main radiation dosimetry estimates to patients following intravenous administration of ^{123}I-iodide are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.15 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Thyroid 2.7 mGy/MBq
  - Urinary bladder wall 0.077 mGy/MBq
  - Gastric wall 0.064 mGy/MBq

The main radiation dosimetry estimates to patients following oral administration of ^{123}I-iodide are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.15 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Thyroid 2.5 mGy/MBq
  - Gastric wall 0.12 mGy/MBq
  - Urinary bladder wall 0.066 mGy/MBq

Key Learning Points

- The radioisotopes of iodine used for conventional gamma camera imaging are ^{123}I and ^{131}I.
- The use of the simple chemical form of iodide anion intends for imaging the thyroid parenchyma and follicular cell-derived thyroid cancers.
- Through a process of nucleophilic/electrophilic substitution, ^{123}I and ^{131}I can be used to label further molecules with biological targets.

2.5.2 ^{123}I-Ortho-Iodo-Hippuric Acid (^{123}I-Hippuran)

^{123}I-Hippuran (or ^{123}I-OIH) is an anionic structural analog of para-aminohippurate, a natural substance that is normally excreted in the urine by both tubular secretion (80%) and glomerular filtration (20%). Despite a relatively high binding to plasma proteins (approximately 60% of circulating activity), ^{123}I-hippuran (Fig. 2.16) has a high extraction fraction (about 85% at each passage through the kidneys), because of

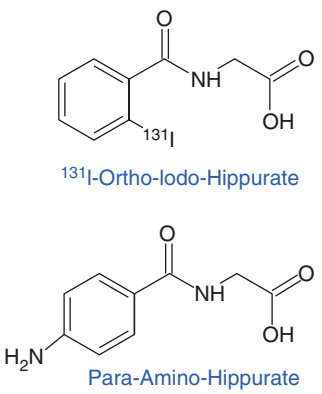

Fig. 2.16 Chemical structure of para-aminohippurate (bottom) and of its radioiodinated analog labeled with ^{131}I

an active secretion process that results in progressively rising concentrations along the proximal renal tubules. Similarly as described for ^{99m}Tc-MAG3, active trans-tubular transport of ^{123}I-hippuran is mediated by transmembrane exchangers located in the basolateral membrane of tubular cells, only indirectly coupled with Na^+/K^+ ATPase.

After i.v. injection, ^{123}I-hippuran is rapidly cleared from the blood and enters different extracellular compartments. In addition to the predominant renal excretion (about 70% of injected activity within 30 min postinjection), there is also a minor fraction of hepatobiliary excretion.

The radiopharmaceutical is supplied as a sterile, pyrogen-free solution ready for administration, which is performed by rapid i.v. bolus injection. Although ^{123}I-hippuran has optimal characteristics for imaging associated with a low radiation burden to patients (but is burdened by high cost and complex distribution logistics), the less expensive ^{131}I-hippuran is also available, as also is ^{125}I-hippuran; the latter tracer is used for measurements of renal function based only on blood sampling and in vitro counting with a well-type γ-counter—without gamma camera imaging.

Quantitative analysis of the data acquired during dynamic renal scintigraphy with radiolabeled hippuran allows calculation of the "effective" renal plasma flow (ERPF), an overall parameter of renal function that can be associated with measurement of GFR in order to calculate the renal filtration fraction.

The main radiation dosimetry estimates to patients following intravenous administration of ^{123}I-hippuran are reported here below, normalized to unit of administered activity [12]:

- Effective dose 0.015 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Urinary bladder wall 0.2 mGy/MBq
  - Uterus 0.017 mGy/MBq
  - Lower large bowel 0.0075 mGy/MBq

The main radiation dosimetry estimates to patients following intravenous administration of ^{131}I-Hippuran are reported here below [12], normalized to unit of administered activity:

- Effective dose 0.066 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Urinary bladder wall 0.96 mGy/MBq
  - Uterus 0.035 mGy/MBq
  - Kidney 0.03 mGy/MBq

Key Learning Points

- ^{123}I-hippuran is an anionic structural analog of para-aminohippurate, a natural substance that is normally excreted in the urine by both tubular secretion and glomerular filtration.
- It is used for dynamic renal scintigraphy and "effective" renal plasma flow (ERPF) calculation.

2.5.3 Radioiodinated Meta-Iodo-Benzyl-Guanidine (MIBG)

In the MIBG molecule (also known as iobenguane), the benzyl group of bretylium is combined with the guanidine group of guanethidine. Both bretylium and guanethidine are potent neuron-blocking agents that act selectively on adrenergic nerves [13]. A combination of the benzyl portion of bretylium with the guanidine group of guanethidine results in the production of a variety of substituted aralkyl-guanidines with even greater anti-adrenergic potency [14]. MIBG is one of these derivatives that can be radioiodinated for imaging both the adrenal medulla and distribution of adrenergic innervation in the myocardium [15].

As a structural analog of catecholamines, MIBG is taken up by chromaffin cells via the same metabolic pathway of noradrenaline, through a sodium- and ATPase-dependent active process. Once in the cytoplasm, MIBG is actively stored in cytoplasmic secretion granules based on the vesicular monoamine transporter (VMAT1 and VMAT2). Thus, it physiologically accumulates in the neuronal secretory vesicles located in sympathetic system ganglia, in the medulla of adrenal glands, and in all other human tissues with high adrenergic innervation—such as myocardiocytes. The secretory vesicles release their contents by a process of exocytosis stimulated by membrane depolarization linked to calcium flow.

MIBG can be labeled with either ^{123}I (for diagnostic use only) or ^{131}I (for both diagnostic and therapeutic use). ^{123}I-MIBG is to be considered the diagnostic radiopharmaceutical of choice, especially for use in children, because of its more favorable radiation dosimetry and better image quality being also suitable for hybrid SPECT/CT imaging. On the other hand, ^{131}I-MIBG is used for therapy.

MIBG scintigraphy is indicated to image tumors of neuroendocrine origin, particularly those of neuroectodermal nature, such as pheochromocytomas, paragangliomas, and neuroblastomas. Nevertheless, other neuroendocrine tumors (e.g., carcinoids, medullary thyroid carcinomas) can also be visualized (Fig. 2.17). It is an important diagnostic tool for staging, for evaluating response to treatment, and in patients who are candidate to ^{131}I-MIBG therapy.

In addition, MIBG scintigraphy can be employed to investigate disorders of sympathetic innervation, for example, in ischemic and nonischemic cardiomyopathy, as well as in patients with movement disorders (to distinguish idiopathic Parkinson's disease from multisystem atrophy) and for functional studies of the adrenal medulla.

Following i.v. injection, about 50% of the administered activity is excreted in the urine within the first 24 h, 70–90% of the activity being cumulatively excreted within 48 h. Since >95% of injected activity is excreted through the kidneys, the bladder and the excretory urinary tract can be visualized on the scan; about 3% of MIBG activity is eliminated via the gastrointestinal tract. The normal adrenal glands are visualized in 15% of the cases at 48–72 h after injection.

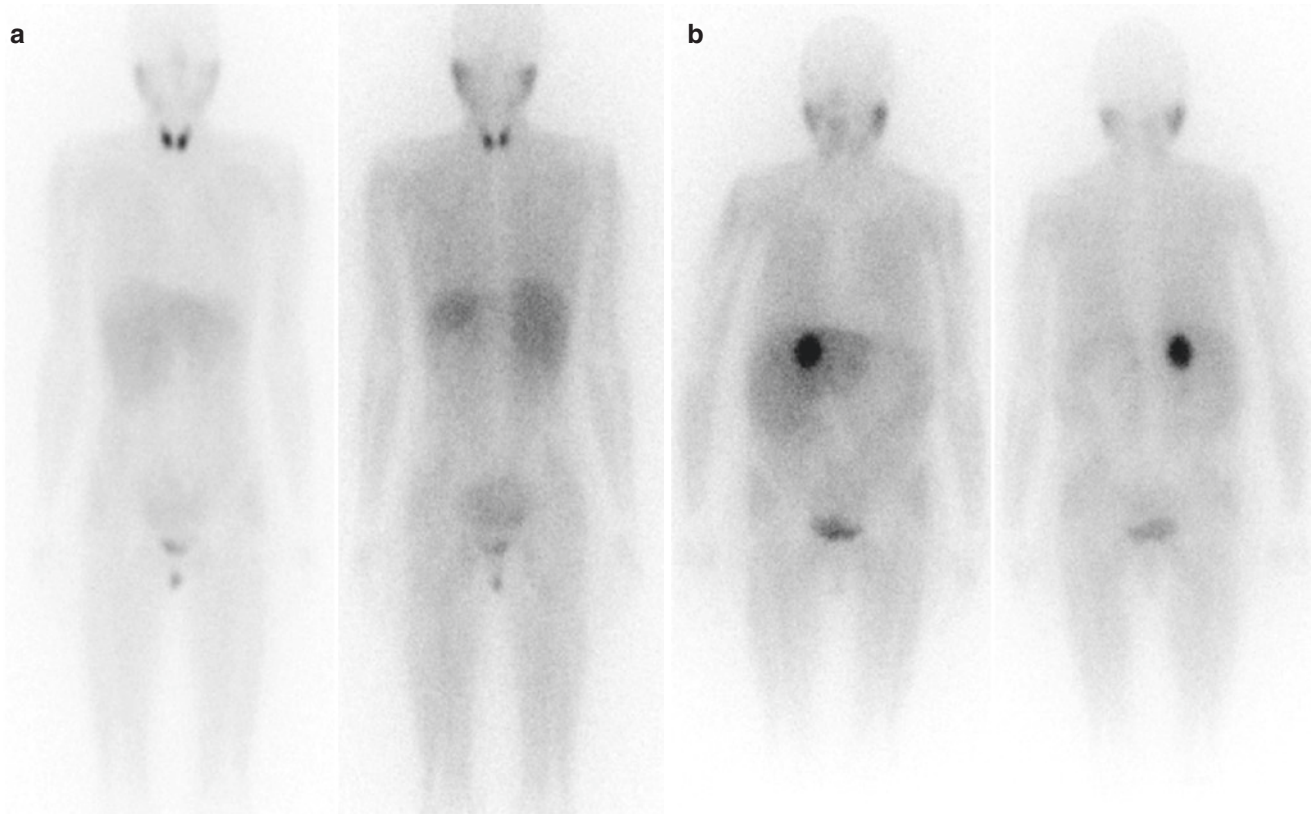

Fig. 2.17 Examples of planar whole-body imaging with ^{123}I-MIBG (anterior view on the left, posterior view on the right). (**a**) Pattern of normal physiologic distribution, without abnormal areas with focally increased tracer uptake (no thyroid-blocking protocol was employed). (**b**) Abnormally increased focal uptake in the right adrenal gland in a patient with suspected pheochromocytoma (optimal blocking of thyroidal uptake of radioiodide released during metabolic degradation of ^{123}I-MIBG)

MIBG does not bind to the postsynaptic adrenergic receptors and is not degraded by the enzymes normally degrading catecholamines, monoamine oxidase (MAO), and catecholamine-*O*-methyl transferase (COMT). Background activity visible in scans acquired early postinjection is related to early binding to circulating platelets and to nonspecific accumulation of the radiopharmaceutical (mainly by passive diffusion) in tissues such as the liver, spleen, lungs, salivary glands, thyroid gland, nasal mucosa, colon, skeletal muscles, and uterus. Since there is no physiological MIBG uptake in the bone, any focal or diffuse uptake in the bones are to be considered as skeletal metastasis and/or pathological involvement of the bone marrow.

Due to a certain "mass" effect of radiolabeled MIBG (especially for low-specific activity ^{131}I-MIBG), administration may induce the release into circulation of catecholamines previously stored in neurosecretory granules, with ensuing possible pharmacologic effects such as tachycardia and an arterial hypertensive crisis in patients with pheochromocytoma. Slow i.v. infusion of the radiopharmaceutical (over 1–5 min for a diagnostic procedure) is therefore recommended.

Moreover, since many drugs can interfere with MIBG uptake, the patient's medication list should be reviewed and interfering drugs discontinued before MIBG administration (see also Chap. 46 of this book "Current practical guidelines for the most common nuclear medicine procedures"). Furthermore, radioiodide released during degradation of the radiopharmaceutical can accumulate in the gastrointestinal tract as well as in the thyroid. Therefore, a thyroid-blocking protocol is recommended, especially in children, by administering supersaturated potassium iodide solution or Lugol's solution starting 24–48 h before radiopharmaceutical administration and continuing for at least 3 days, according to protocols published in international guidelines.

The main radiation dosimetry estimates to patients following intravenous administration of ^{123}I-MIBG are reported here below, normalized to unit of administered activity [12]:

- Effective dose 0.018 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Liver 0.071 mGy/MBq
  - Urinary bladder wall 0.07 mGy/MBq
  - Spleen 0.02 mGy/MBq

The main radiation dosimetry estimates to patients following intravenous administration of ^{131}I-MIBG are reported here below, normalized to unit of administered activity [12]:

- Effective dose 0.2 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Liver 0.83 mGy/MBq
  - Urinary bladder wall 0.59 mGy/MBq
  - Spleen 0.49 mGy/MBq

Key Learning Points

- Radioiodinated MIBG (or iobenguane) is a structural analog of catecholamines.
- MIBG can be labeled with either ^{123}I (for diagnostic use only) or ^{131}I (for both diagnostic and therapeutic uses) for imaging the adrenal medulla and tumors of neuroectodermal nature, such as pheochromocytomas, paragangliomas, and neuroblastomas.
- ^{123}I-MIBG is also commonly used to investigate the distribution of adrenergic innervation in the myocardium, in patients with ischemic cardiomyopathy, as well as in patients with movement disorders.

2.5.4 ^{123}I-N-ω-FluoroPropyl-2βCarbomethoxy-3β-(4-Iodophenyl)-nor-Tropane (^{123}I-FP-CIT)

This radiopharmaceutical (also known as ^{123}I-ioflupane) is a radioiodinated cocaine analog in which the external bond between the aromatic ring and the group tropane is replaced with a direct C=C bond (Fig. 2.18).

As an antagonist of the dopamine transporter (DAT), ^{123}I-FP-CIT binds with high affinity and selectivity to dopamine receptors in the presynaptic endings of dopaminergic neurons in the *substantia nigra* whose ending axons connect with the postsynaptic neurons in the *putamen* and caudate (*striatum* nucleus) using dopamine as the neurotransmitter. Dopamine is produced in the presynaptic nerve endings and stored into vesicles by the vesicular monoamine transporter 2 (VMAT-2, an integral membrane protein that transports neurotransmitters such as dopamine from the cytosol into vesicles). Upon excitation, dopamine is released from these vesicles into the synapse and binds to the predominantly postsynaptic dopamine receptors. On the presynaptic side, the DAT system removes dopamine out of the synaptic cleft and back into the nigrostriatal axon endings for either storage or degradation.

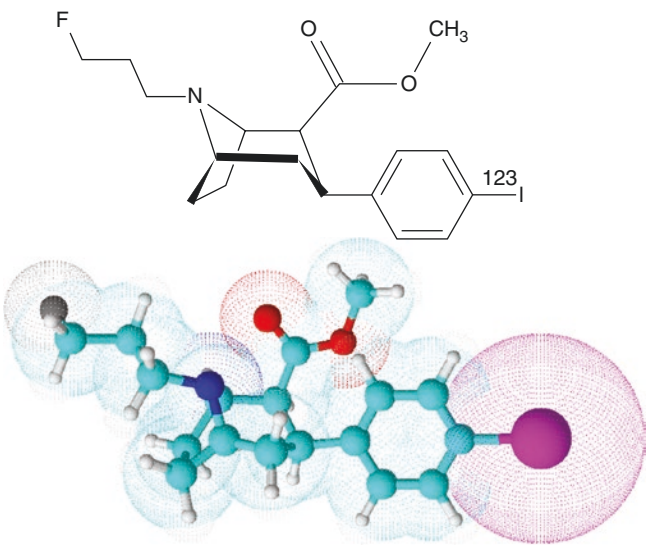

Fig. 2.18 Chemical and tridimensional structure of ^{123}I-FP-CIT. Color codes: *magenta* = ^{123}I; *red* = O; *white* = H; *light blue* = C; *blue* = N; *gray* = F

^{123}I-FP-CIT scintigraphy is performed to evaluate integrity of the dopaminergic nigrostriatal pathway. The main clinical indication of brain scintigraphy with ^{123}I-FP-CIT is for the identification of patients with essential tremor (or some other conditions such as drug-induced Parkinsonism and psychogenic Parkinsonism) versus those with presynaptic Parkinsonian syndromes (including idiopathic Parkinson's disease and atypical Parkinsonisms such as multistage atrophy, progressive supranuclear palsy, or cortico-basal degeneration). In patients with presynaptic Parkinsonism, scintigraphy neuronal degeneration in the substantia nigra causes reduced uptake of ^{123}I-FP-CIT in the putamen and caudate, whereas tracer uptake is normal in essential tremor and in the other forms of Parkinsonism.

An additional indication for scintigraphy with ^{123}I-FP-CIT is in the differential diagnosis between dementia with Lewy bodies (where tracer uptake is reduced because of nigrostriatal degeneration) and Alzheimer's disease (where integrity of the nigrostriatal system is preserved).

The standard injected activity of ^{123}I-FP-CIT is 111–185 MBq, and SPECT acquisition is performed within 3–6 h after administration. Due to the release of ^{123}I-iodide during tracer catabolism, a thyroid-blocking protocol is recommended, by administering supersaturated potassium iodide solution or Lugol's solution.

Uptake of ^{123}I-FP-CIT in the brain is very rapid: about 7% of the injected activity is retained in the cerebral tissue as early as 10 min after i.v. administration (30% of this amount being taken up in the striatum). At 5 h postinjection, the brain-retained activity has already decreased to 3%. Blood clearance of ^{123}I-FP-CIT is rapid, so that 5 min after injection, only 5% of the radiopharmaceutical is still present in circulating blood. Excretion occurs predominantly through the kidneys (>60% at 48 h), while approximately 15% of the injected activity is excreted through the gastrointestinal tract.

Although very rarely, some side effects have been reported, such as headache, tingling, dizziness, increased appetite, and pain at the intravenous injection site.

Since uptake of ^{123}I-FP-CIT is receptor-mediated, attention must be paid to possible interference by other medications/drugs involved in the dopaminergic system that may alter the specific tracer binding; if possible, such medications should be discontinued for at least five half-lives. The main substances that may interfere with the results of the scan with ^{123}I-FP-CIT are amphetamines, benzatropine, bupropion, cocaine, and sertraline.

The main radiation dosimetry estimates to patients following intravenous administration of ^{123}I-FP-CIT are reported here below, normalized to unit of administered activity:

- Effective dose 0.025 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Liver 0.085 mGy/MBq
  - Colonic wall 0.059 mGy/MBq
  - Spleen and gallbladder wall 0.044 mGy/MBq

Key Learning Points

- ^{123}I-FP-CIT (or ioflupane) is a radioiodinated cocaine analog able to bind with high affinity and selectivity to dopamine transporter (DAT) in the presynaptic endings of basal ganglia.
- It is commonly used for brain SPECT when investigating patients with movement disorders and/or neurodegenerative diseases.

2.5.5 ^{123}I-Iodobenzamide (^{123}I-IBZM)

^{123}I-IBZM (also known as ^{123}I-iolopride; see Fig. 2.19) targets the D2 postsynaptic receptors in the *striatum* nucleus (*putamen* and caudate).

The main clinical indication for the use of this radiopharmaceutical is for the differential diagnosis between idiopathic Parkinson's disease (with generally preserved—or even upregulated D2 postsynaptic receptor activity) and other Parkinsonisms (with degeneration of the D2 postsynaptic structures). Additional indications include the evaluation of D2 receptor blockade by neuroleptics, suspected Wilson's disease and Huntington's disease, and pituitary adenoma (the presence of D2 receptors may have implications for the therapeutic strategy).

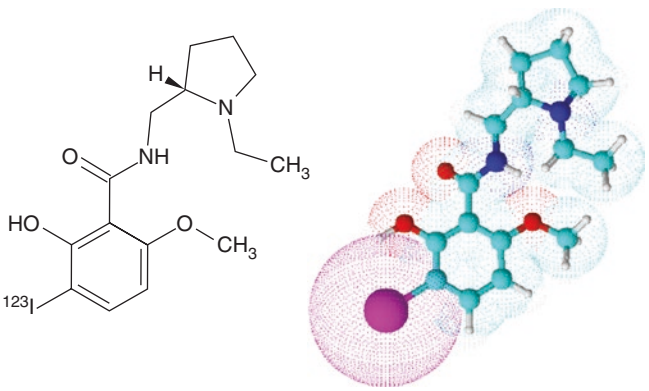

Fig. 2.19 Chemical and tridimensional structure of ^{123}I-IBZM. Color codes: *magenta* = ^{123}I; *red* = O; *white* = H; *light blue* = C; *blue* = N

Furthermore, scintigraphy with ^{123}I-IBZM has also been performed in patients with extra central nervous system conditions, i.e., to image melanoma lesions. The exact mechanism thereby ^{123}I-IBZM is taken up by melanoma cells is not clear yet. In addition to the increased arterial flow typical of tumor neoangiogenesis, ^{123}I-IBZM might bind to D2 receptors expressed on the melanoma cell membrane, and/or it might interact specifically with some intracellular structures, such as melanin and its precursors.

Following i.v. injection, about 75% of ^{123}I-IBZM circulating in the blood is bound to plasma proteins; only about 3–4% of the injected activity crosses the blood-brain barrier due to its lipophilic characteristics, neutral charge, and small size. The majority of circulating ^{123}I-IBZM is in fact quickly converted into two hydrophilic metabolites that are therefore no longer able to diffuse through the blood-brain barrier. The fraction of ^{123}I-IBZM entering the brain is taken up by the postsynaptic D2 receptors present in the *striatum* dopaminergic system. Optimal target/background ratio is reached about 40 min after injection, plateauing up to over 3 h.

The radiopharmaceutical undergoes predominant urinary excretion (about 40% at 24 h and 60% at 48 h after administration). As with other ^{123}I-labeled radiopharmaceuticals, adequate patient's preparation is recommended to prevent thyroid uptake of radioiodide released during the metabolic degradation of the tracer.

The main radiation dosimetry estimates to patients following intravenous administration of ^{123}I-IBZM are reported here below, normalized to unit of administered activity [12]:

- Effective dose 0.034 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Thyroid 0.16 mGy/MBq
  - Urinary bladder wall 0.07 mGy/MBq
  - Lower large bowel wall 0.064 mGy/MBq

Key Learning Points

- ^{123}I-IBZM (or iolopride) targets the D2 postsynaptic receptors of the basal ganglia.
- It is used for brain SPECT when investigating patients with movement disorders.

2.6 ^{201}Tl-Chloride

The monovalent cation Tl^+ has biochemical characteristics similar to those of the K^+ ion. Following i.v. injection, ^{201}Tl is rapidly cleared from the blood because of diffuse uptake into cells of all organs and tissues, with a pattern of distribution that is largely determined by the magnitude of regional blood flow. Therefore, in excitable cells (typically neurons and muscle cells), ^{201}Tl undergoes the continuous transmembrane flux that physiologically occurs along an electropotential gradient during depolarization (passive transport) and subsequent repolarization (an energy-dependent process linked to the Na^+/K^+ pump). These sustained transmembrane exchanges explain the high intracellular concentration of Tl^+ ions, mimicking the distribution of the K^+ ions.

Because of the typical high accumulation in myocardial cells (that physiologically undergo continual, sequential depolarization, and repolarization), ^{201}Tl has been used to investigate myocardial perfusion; in fact, myocardial uptake increases proportionally with perfusion, and prolonged retention depends on the integrity of cell membrane, hence on myocardiocyte viability. Since ^{201}Tl is not trapped in myocytes or in other tissues, redistribution in rest condition of ^{201}Tl occurs over several hour following administration at the peak of a stress test. This redistribution process renders the $^{201}Tl^+$ ion available for possible myocardial accumulation at rest in regions that were ischemic when ^{201}Tl was injected at peak stress, thus allowing redistribution images to be acquired that are fairly independent of perfusion and mainly reflect viability.

Besides its uptake in myocardial tissue, the $^{201}Tl^+$ ions tend to accumulate in all metabolically active cells, including cancer cells. ^{201}Tl-Chloride has therefore been used for tumor imaging as an indicator of cell viability, particularly for discriminating viable tumor tissue from fibrous scar tissue after surgery and/or radiation therapy (especially in patients with brain gliomas) and also for parathyroid scintigraphy (where this agent has however been completely replaced with ^{99m}Tc-sestamibi).

Following i.v. administration, about 85% of $^{201}Tl^+$ ions are cleared from the blood during a single circulation, so that about 2 min after administration <5% of the injected activity is still circulating. About 5% of the injected activity localizes in the myocardium in proportion to regional perfusion and viability. The tracer has a biological half-life of approximately 10 days in the body.

^{201}Tl is a cyclotron-produced radionuclide that decays by electron capture with a relatively long physical half-life (73.1 h) and emission of γ-photons of 135 and 167 keV (12% abundance) and X-rays of energy 67–82 keV (88% abundance, which is the emission on which gamma camera imaging is based). Because of these physical characteristics, the quality of gamma camera imaging with ^{201}Tl is suboptimal due to the low energy of the X-ray emission that implies significant scatter and attenuation by soft tissues. Furthermore, there is a relatively high radiation burden to patients, which limits the amount of activity that can be administered, therefore also counting statistics, which leads to low signal-to-noise ratios—especially in obese patients.

The main radiation dosimetry estimates to patients following intravenous administration of ^{201}Tl-chloride are reported here below, normalized to unit of administered activity [12]:

- Effective dose 0.14 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Kidneys 0.48 mGy/MBq
  - Bone surface 0.38 mGy/MBq
  - Large bowel wall 0.25 mGy/MBq

Key Learning Points

- The monovalent cation $^{201}Tl^+$ of ^{201}Tl-chloride has biochemical characteristics similar to those of the K^+ ion.
- In addition to its main use for myocardial perfusion scintigraphy, ^{201}Tl-chloride has been used for tumor imaging as an indicator of cell viability, especially in patients with brain tumors, and also for parathyroid scintigraphy.

2.7 ^{67}Ga-Citrate

The cyclotron-produced radionuclide ^{67}Ga (a metal element) is obtained by proton irradiation of enriched zinc. It has a physical half-life of 3.26 days and decays by electron capture to stable zinc (^{67}Zn) emitting γ-rays with multiple energy peaks, principally 93 keV (39%), 185 keV (21%), 300 keV (17%), and 394 keV (7%).

Following i.v. injection of ^{67}Ga-citrate, $^{67}Ga^{2+}$ ions form at physiological pH; the metabolic pathways in the body of these metallic ions are similar to those of the Fe^{2+} ions. About 90% of injected activity binds to plasma proteins, especially transferrin, with ensuing slow blood clearance. During the first 24 h, up to 25% of the injected activity is excreted through the kidneys, while at later time points, the main excretion route becomes the bowel. By 48 h postinjection, about 75% of the injected activity remains in the body and is equally distributed among the liver, bone and bone marrow, and soft tissues. Less intense physiologic uptake is usually observed in the nasopharynx, lacrimal glands, thymus, breasts, and spleen.

Although not yet fully clarified, most of this process is due to intracellular accumulation mediated by the transferrin receptors. The main mechanism of accumulation in tumor and inflammation sites appears to be linked to the complex formed by $^{67}Ga^{2+}$ with transferrin, for which membrane receptors are present ubiquitously but are overexpressed especially on membranes of cells undergoing active proliferation and metabolic activation, such as tumor and inflammatory cells.

An additional mechanism of ^{67}Ga accumulation is mediated by its binding to lactoferrin, generally located in the extracellular inflammatory spaces. Thus, ^{67}Ga reaching inflammation sites bound to transferrin may migrate to lactoferrin, which in turn binds to specific receptors present on macrophages' surface. Enhanced expression of lactoferrin receptors has been shown also in lymphoma cells, a factor that seems to contribute for 10–25% of total uptake to ^{67}Ga accumulation in lymphomas.

Following its introduction into the clinical practice in the late 1960s [16], ^{67}Ga-citrate has had a well-defined role both in benign conditions (localization of infection/inflammation sites, characterization of chronic granulomatous diseases such as sarcoidosis) and in neoplastic conditions (especially lymphomas and sarcoma, for staging, prognosis, and evaluation of residual disease after treatment). However, the traditional applications of scintigraphy with ^{67}Ga-citrate have currently been replaced with [^{18}F]FDG PET wherever a PET scanner is available.

Images should be ideally acquired 48 h after i.v. administration, when a satisfactory tumor-to-background ratio is reached; sometimes images are also recorded at 72 and 96 h to determine if subtle regions of activity become more prominent above background activity. SPECT or SPECT/CT imaging may enhance reliability of the scan, although the γ-emission energies of this radionuclide are suboptimal for imaging and the high radiation burden limits the maximum activity that can safely be administered to patients.

The standard activity administered to an adult individual is 150–220 MBq but up to 330 MBq in large-sized patients.

The main radiation dosimetry estimates to patients following intravenous administration of ^{67}Ga-citrate are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.1 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Bone surface 0.63 mGy/MBq
  - Red bone marrow 0.21 mGy/MBq
  - Large bowel wall 0.16 mGy/MBq

Key Learning Points

- ^{67}Ga-Citrate is a historical radiopharmaceutical with a quite complex mechanism of accumulation that has had a role both in benign conditions (characterization and localization of infection/inflammation and chronic granulomatous diseases such as sarcoidosis) and in neoplastic conditions (especially lymphomas and sarcoma).
- Currently, the traditional applications of scintigraphy with ^{67}Ga-citrate have mainly been replaced with [^{18}F]FDG PET imaging.

2.8 Lung Ventilation Radiopharmaceuticals

Lung ventilation scintigraphy is indicated to assess regional distribution of ventilation in different clinical conditions, ranging from acute pulmonary embolism to chronic obstructive pulmonary disease. The radiopharmaceuticals that have been used or are currently used for lung ventilation scintigraphy can be divided into two classes:

- Radioaerosols, i.e., a two-phase system consisting of particles that may be liquid, solid, or a combination suspended in gas, mapping distribution of the ventilated lung volume (usually with static imaging at equilibrium)
- Radioactive gases that allow dynamic single-breath imaging either at equilibrium or during the washout phase

Special nebulizers are employed to produce radioaerosols using ^{99m}Tc-DTPA, ^{99m}Tc-Technegas, or ^{99m}Tc-nanocolloidal albumin as the suspended phase.

2.8.1 ^{99m}Tc-DTPA Aerosol

This radiopharmaceutical is the most common agent employed to produce radiolabeled liquid aerosols, using a nebulizer to produce particles (ideal size 0.1–0.2 μm, maximum diameter <2 μm) capable of being readily inhaled. Air or oxygen is forced through the nebulizer at 30–50 psi to produce aerosol droplets that are then inhaled by the patient through a mouthpiece. Exhaled air from the patient is trapped in the filter attached to the aerosol unit, thus preventing any contamination of the surrounding area with radioactive materials. About 10% of the activity is deposited in the lungs of a subject with normal respiratory function, while the

remainder remains airborne and is exhaled. The pattern of deposition of the radioactive droplets within the lung depends on their size, shape, density, and electrical charge. The larger particles tend to settle in the central area, while the smaller particles deposit in the peripheral areas.

The biological half-life in the lung is 55–108 min in healthy individuals and 15–33 min in healthy smokers. Clearance of radioactivity deposited in the alveolar region occurs by transepithelial diffusion; ^{99m}Tc-DTPA enters then the general circulation and is excreted by urinary clearance.

Even though the activity of ^{99m}Tc-DTPA dispensed in the nebulizer is approximately 900–1300 MBq, the activity actually reaching the lungs is generally <100 MBq. This amount is much lower than the activity of ^{99m}Tc-MAA normally injected i.v. for a lung perfusion scan; therefore, when planning a ventilation/perfusion scan in patients with suspected acute pulmonary embolism, the ^{99m}Tc-DTPA ventilation scan (with multi-view planar imaging or with SPECT) should be performed first.

The main radiation dosimetry estimates to patients following administration of ^{99m}Tc-DTPA as a radioaerosol are reported here below, normalized to unit of administered activity [12]:

- Effective dose 0.1 mSv/MBq
- Tissue/organ with the highest value of absorbed dose:
  - Urinary bladder wall 0.047 mGy/MBq

2.8.2 ^{99m}Tc-Technegas

The aerosol ^{99m}Tc-technegas, mostly used in Europe, consists of ^{99m}Tc-labeled solid graphite particles (diameter 0.005–0.2 μm) generated at high temperature [17]. These "ultrafine" particles tend to grow by aggregation; thus, ^{99m}Tc-technegas should be used within 10 min from generation.

The patient (who is sitting with his/her back lying against the gamma camera collimator) inhales the radioaerosol through closed, single-use circuit breathing tubes, until a counting rate of 2000 counts/s is attained. Inhaled ^{99m}Tc-technegas particles adhere to the walls of the alveoli and are slowly cleared by reabsorption.

The images obtained with ^{99m}Tc-technegas have superior quality than those obtained with ^{99m}Tc-DPTA aerosol or ^{133}Xe (see further below); moreover, its use has minimized the problem of particle clumping in patients with chronic obstructive pulmonary disease, which is instead observed when using ^{99m}Tc-DTPA aerosol. The administered activity to the lung is 20–30 MBq.

The main radiation dosimetry estimates to patients following administration of ^{99m}Tc-technegas as a radioaerosol are reported here below, normalized to unit of administered activity [3]:

- Effective dose 0.015 mSv/MBq
- Tissue/organ with the highest value of absorbed dose:
  - Lung parenchyma 0.011 mGy/MBq

2.8.3 Xenon-133

Xenon-133 (^{133}Xe) is a noble (i.e., chemically inert), liposoluble radioactive gas, which is historically the first agent that was used for lung ventilation studies [18]. Because of its lipophilicity, this gas diffuses rapidly also through the blood-brain barrier and has therefore been used in the past to measure in a quantitative manner rCBF (expressed as milliliter/minute per unit mass) and also myocardial blood flow (following intracoronary artery injection).

^{133}Xe has a physical half-life of 5.3 days and decays through emission of γ-rays, associated however with some β^- emission. The energy of its γ-emission photopeak (81 keV) is lower than that of ^{99m}Tc (140 keV); therefore, when performing a ventilation/perfusion scan in patients with suspected acute pulmonary embolism, lung perfusion scintigraphy with ^{99m}Tc-MAA is acquired after the ^{133}Xe ventilation study.

Upon inhalation in an airtight closed system, ^{133}Xe diffuses through the alveolar wall and enters the pulmonary venous circulation via the capillaries to reach peripheral organs/tissues through arterial circulation. When it returns to the lung via venous blood, ^{133}Xe is exhaled after a single pass, with a very short biological half-life (30 s).

^{133}Xe single deep-breath inspiration, equilibrium, and washout images are acquired using a standard gamma camera. The standard activity administered for a lung ventilation study is 200–750 MBq.

For radiation safety and in order to avoid dispersion of the radioactive gas in the environment, the room where the scan is performed must be equipped with a special closed system for inhaling ^{133}Xe, and the air conditioning system must include an activated charcoal filter for trapping any radioactive gas before release of the filtered air in the environment.

The main radiation dosimetry estimates to patients following inhalation of ^{133}Xe are reported here below, normalized to unit of administered activity:

- Effective dose 0.00071 mSv/MBq
- Tissue/organ with the highest value of absorbed dose:
  - Lung parenchyma 0.0041 mGy/MBq

Key Learning Points

- Radiopharmaceuticals for lung ventilation scintigraphy are administered by inhalation.
- Radioaerosols such as ^{99m}Tc-DTPA, ^{99m}Tc-technegas, or ^{99m}Tc-nanocolloidal albumin are produced by special nebulizers allowing inhalation of the suspended phase containing the radioactive particles.
- The radioactive gas historically employed for lung ventilation is ^{133}Xe.

2.9 Other Radiopharmaceuticals

Over the years, many other radiopharmaceuticals have been developed in addition to those described in the previous sections. Some of these radiopharmaceuticals are no longer employed in the clinical practice, mostly because they have been replaced with others, e.g., with more specific binding or with more favorable radiation exposure characteristics, or are not commercially available in Europe and/or the USA. Other single-photon-emitting radiopharmaceuticals have not yet proceeded through all phases of clinical trial, also because most of the attention is currently devoted to the development of PET radiopharmaceuticals.

Among radiopharmaceuticals for nuclear cardiology, mention should be made of tracers developed for assessing myocardial perfusion (such as ^{99m}Tc-teboroxime) or myocardial metabolism (^{123}I-labeled fatty acids, used predominantly in Japan), radiopharmaceuticals localizing in acute myocardial infarction (such as ^{99m}Tc-pyrophosphate, ^{111}In-antimyosin antibodies, ^{99m}Tc-glucarate, ^{99m}Tc-HYNIC-annexin-V), and radiopharmaceuticals with preferential accumulation in hypoxic tissues (used also in the cerebral or tumor areas).

Radiolabeled analogs of amphetamine diffusing through the blood-brain barrier (e.g., ^{123}I-IMP and ^{123}I-HIPDM) have been used for assessing rCBF, while ^{123}I-iomazenil displays high affinity for central-type benzodiazepine receptors—constituting therefore a useful marker of neuronal viability.

^{131}I-6-iodomethyl-norcholesterol and ^{75}Se-norcholesterol are radiolabeled analogs of cholesterol that have been used for scintigraphy of the adrenal cortex. Because of this property, indications to their use included evaluation of patients with hypercortisolemia (Cushing's disease), hyperaldosteronism, and hyperandrogenism and in the case of adrenal incidentaloma (to evaluate the nature of the lesion), as well as identification of any ectopic adrenal tissue or adrenal residual tissue after surgery. However, both tracers (especially ^{75}Se-norcholesterol) suffer from important limitations in terms of both emission energy and, above all, radiodosimetric burden to the patient.

The radiolabeled monoclonal antibody Fab′ fragment ^{99m}Tc-arcitumomab is directed against the carcinoembryonic antigen (CEA), typically overexpressed by colorectal cancer cells (but also other tumors, both of the gastrointestinal tract and of various organs and/or tissues). This radiopharmaceutical is no more employed in the clinical practice, as it has been replaced with [^{18}F]FDG for PET/CT imaging with clearly superior diagnostic performance. The main indication for ^{99m}Tc-arcitumomab scintigraphy was restaging of colorectal cancer patients carcinoma with rising serum CEA levels posttreatment.

^{99m}Tc-Apcitide has been proposed to visualize recent venous thrombosis. It binds to the GP IIb/IIIa receptors on activated platelets that are responsible for aggregation and formation of thrombi; its main indication was therefore for the detection of acute deep vein thrombosis in lower extremities.

^{99m}Tc-Glucoeptonate has been used for static renal scintigraphy, while ^{51}Cr-EDTA and ^{125}I-iothalamate can still be used for measuring the glomerular filtration rate through techniques based on in vitro measurements (i.e., using only blood sampling, without scintigraphic imaging).

Finally, several novel peptide-based radiopharmaceuticals are being evaluated for the visualization and characterization of neuroendocrine tumors. In addition to ^{99m}Tc-depreotide, new radiolabeled SST analogs with more favorable characteristics than ^{111}In-pentetreotide or ^{99m}Tc-EDDA/HYNIC-TOC are under investigation. Besides ligands for the SST receptors, other receptor/ligand systems are also under intensive investigations, such as those based on, e.g., bombesin, bioactive fragments of cholecystokinin, and vascular-active intestinal peptide.

2.9.1 Perspectives in Molecular Imaging Based on Single-Photon-Emitting Radiopharmaceuticals

Advancing knowledge in the pathophysiology of tissues/organs opens new opportunities for the development of novel radiopharmaceuticals, most of which are not approved yet for commercial use. Intensive search is ongoing especially for tumor-targeting agents with better specificity and sensitivity. The features that tumor cells exhibit regarding expression of intra- and extracellular molecules are often different from those exhibited by normal, nonmalignant transformed cells. These attributes constitute the basis for developing new imaging targets for diagnostic applications as well as for developing new anticancer drugs and for assessing tumor response to treatment. The successful choice of a target molecule potentially leads to the development not only of a molecular imaging probe but also of a therapeutic agent capable to inhibit the disease process, an approach that is now defined as "theragnostics."

Tumor cells often display altered energy metabolism, as reflected, for example, in increased glucose uptake and shifted balances in metabolic products. Thus, at the preclinical level, a variety of single-photon-emitting tracers are under evaluation for use as markers for (neo)angiogenesis, apoptosis, hypoxia, acidosis, metabolic activity, and proteolytic activity.

Angiogenesis represents an interesting molecular target not only for imaging but also for targeted forms of therapy. It consists of formation of new vessels as an essential process in the growth of solid tumors. Examples for target anti-angiogenic therapies currently used in the clinical practice are cilengitide (that inhibits integrin receptors

$\alpha_v\beta_3$ and $\alpha_v\beta_5$) and bevacizumab, an antibody targeting the vascular endothelial growth factor (VEGF). Different potential molecular targets to monitor angiogenesis are potentially available for imaging purposes. The most suitable candidates for the development of new radiotracers are currently represented by integrin antagonists, extracellular matrix protein inhibitors, or matrix metalloproteinase, as well as by ligands binding to tyrosine kinases or growth factor receptors.

Integrins are heterodimeric membrane receptors constituted by α- and β-subunits that mediate the interactions between cells and the extracellular matrix and soluble molecules (such as growth factors). So far 18 different α-subunits and 8 different β-subunits have been identified, corresponding to 24 different integrin receptors. Integrin $\alpha_v\beta_3$ is being intensively investigated in oncology, because it is highly expressed on the cell surface of activated endothelial cells in newly formed blood vessels. In the preclinical setting, a large variety of imaging strategies have been successfully employed for imaging integrin expression. All the tracers that are used for imaging of integrin expression are based on the tripeptide sequence arginine-glycine-aspartic acid (or RGD, in the single letter code). RGD binds to the integrin containing the α_v subunit, a physiologic integrin-binding ligand that is abundant in proteins of the extracellular matrix. Accordingly, a variety of radiolabeled RGD-based peptides have been developed for noninvasive imaging of integrin $\alpha_v\beta_3$ expression with either single-photon imaging or, in most of the cases, PET. ^{99m}Tc-labeled RGD peptides have been the subject of few investigations, some of these peptides having proceeded to the stage of clinical investigation, such as ^{99m}Tc-aP2, ^{99m}Tc-NC100692 (also known as ^{99m}Tc-maraciclatide), ^{99m}Tc-3PRGD2, ^{99m}Tc-RGD-BBN, and ^{99m}Tc-labeled RGD dimeric peptides with PEG4 and Gly3.

Among the extracellular matrix proteins, the polymorphic matrix protein fibronectin belongs to the family of universal cell adhesion molecules involved in vascular proliferation and widely expressed in neoplastic tissues. Fibronectin is the target of the experimental tracer ^{99m}Tc-AP39.

Also matrix metalloproteinases are potential targets for molecular imaging. They are involved in the degradation of the basement membrane and of the extracellular matrix, thus facilitating the migration of endothelial cells and formation of new vessels, both processes being typically enhanced in malignant tissues. Overexpression of matrix metalloproteinases correlates with tumor aggressiveness and metastatic potential; in this regard, hydroxamate-based tracers labeled with ^{111}In, ^{99m}Tc, or ^{123}I display promising binding properties.

The epidermal growth factor receptor (EGFR) is involved in the regulation of cell growth, as well as in the differentiation and survival of cells. It is overexpressed in several human malignancies and is often associated with an aggressive tumor phenotype and poor prognosis. "Cold" (i.e., non-radiolabeled) monoclonal antibodies against this receptor have been developed for therapeutic purposes, including cetuximab and trastuzumab; other small molecules (such as gefitinib and erlotinib) that act as tyrosine kinase inhibitors (TKIs) target the receptor catalytic domain of EGFR. Several single-photon-emitting radiopharmaceuticals have been developed for preclinical trials, including ^{99m}Tc-cetuximab or ^{111}In-DTPA-pertuzumab.

Apoptosis is a process of regulated (or programmed) cell death that, in its classic form, does not cause inflammation. Upon a variety of molecular signals that activate apoptosis, the lipid composition of the outer and inner leaflets of the plasma membrane is altered, so that some molecules such as phosphatidylserine and phosphatidylethanolamine (that are normally retained on the intracellular side of the cell membrane) are exposed on the outer side of the cell membrane. The most promising single-photon-emitting radiopharmaceuticals currently under investigation that target phosphatidylserine and phosphatidylethanolamine are represented by radiolabeled annexin-V (^{99m}Tc-HYNIC-annexin-V) and by duramycin (^{99m}Tc-duramycin).

Key Learning Points

- Over the years, many other radiopharmaceuticals have been developed in addition to those described in the previous sections.
- Some of these radiopharmaceuticals are no longer employed in the clinical practice mostly because they have been replaced with others with more specific binding or with more favorable radiation exposure characteristics.
- On the other hand, the current efficacy of the molecular targeting of new several anticancer drugs has increased interest on the development of novel radiopharmaceuticals not only for diagnostic applications but also for therapeutic purpose. This approach is now defined as "theragnostics."

References

1. Lassmann MS, Treves T, For the EANM/SNMMI Paediatric Dosage Harmonization Working Group. Paediatric radiopharmaceutical administration: harmonization of the 2007 EANM paediatric dosage card (version 1.5.2008) and the 2010 North American consensus guidelines. Eur J Nucl Med Mol Imaging. 2014;41:1636. Accessible at: http://www.eanm.org/publications/dosage-card/.
2. Williams JG. Pertechnetate and the stomach. A continuing controversy. J Nucl Med. 1983;24:63–6.

3. ICRP. Radiation dose to patients from radiopharmaceuticals: a compendium of current information related to frequently used substances. ICRP publication 128. Ann ICRP. 2015;44(2S):7.
4. Eckelman W, Richards P. Instant ^{99m}Tc-DTPA. J Nucl Med. 1970;11:761.
5. Fritzberg AR, Kasina S, Eshima D, Johnson DL. Synthesis and biological evaluation of technetium-99m MAG3 as a hippuran replacement. J Nucl Med. 1986;27:111–6.
6. Alazraki N, Aarsvold JN, Audisio RA, Glass E, Grant SF, Kunikowska J, et al. The EANM and SNMMI practice guideline for lymphoscintigraphy and sentinel node localization in breast cancer. Eur J Nucl Med Mol Imaging. 2014;41:1259–60.
7. Fazzi P, Borsò E, Albertelli R, Mariani G, Giuntini C. Comparative performance of two inhaler systems to assess distribution of convective ventilation by ^{99m}Tc-labeled aerosol scintigraphy in patients with airway obstruction. Q J Nucl Med Mol Imaging. 2009;53:428–36.
8. Abrams MJ, Davison A, Jones AG, et al. Synthesis and characterization of hexakis (alkylisocyanide) and hexakis (arylisocyanide complexes of Technetium (I)). Inorg Chem. 1983;22:2798.
9. Coakley AJ, Kettle AG, Wells CP, O'Doherty MJ, Collins RE. ^{99m}Tc-Sestamibi – a new agent for parathyroid imaging. Nucl Med Commun. 1989;10:791–4.
10. Khalkhali I, Mena I, Jouanne E, et al. Prone scintimammography in patients with suspicion of carcinoma of the breast. J Am Coll Surg. 1994;178:49–7.
11. Kelly JD, Forster AM, Higley B, et al. Technetium-99m-tetrofosmin as a new radiopharmaceutical for myocardial perfusion imaging. J Nucl Med. 1993;34:222.
12. ICRP. Radiation dose to patients from radiopharmaceuticals. ICRP publication 53. Ann ICRP. 1988;18(1-4):149.
13. Nickers NM, Collier B. Drugs inhibiting adrenergic nerves and structures innervated by them. In: Goodman LS, Gilman A, editors. The pharmacological basis of therapeutics. 5th ed. New York, NY: Macmillan Publishing Co; 1975. p. 553–64.
14. Short JH, Darby TD. Sympathetic nervous system blocking agents. III. Derivatives of benzylguanidine. J Med Chem. 1967;10:833–40.
15. Wieland DM, Wu J, Brown LE, Mangner TJ, Swanson DP, Beierwaltes WH. Radiolabeled adrenergic neuron-blocking agents: adrenomedullary imaging with[^{131}I]Iodobenzylguanidine. J Nucl Med. 1980;21:349–53.
16. Edwards CL, Hayes RL. Tumor scanning with ^{67}Ga citrate. J Nucl Med. 1969;10:103–5.
17. Kropp J, Buhr W, Bockisch A, Grünwald F, Ruhlmann J, Hotze A, Biersack HJ. Inhalation scintigraphy of the lung using the new ultrafine aerosol Technegas. Nuklearmedizin. 1989;28:46.
18. Knipping HW, Bolt W, Venrath H, Valentin H, Ludes H, Endler P. A new method of heart and lung function testing, the regional functional analysis in the lung and heart clinic by the radioactive noble gas xenon 133 (isotope thoracography). Dtsch Med Wochenschr. 1955;80:1146–7.

Suggested Readings

Ell PJ, Gambhir SS, editors. Nuclear medicine in clinical diagnosis and treatment. 3rd ed. New York, NY: Churchill Livingston; 2004.
Herbert JC, Eckelman WC, Neumann RD, editors. Nuclear medicine – diagnosis and therapy. New York, NY: Thieme Medical Publishers; 1996.
IAEA. Good practice for introducing radiopharmaceuticals for clinical use. Vienna: International Atomic Energy Agency (IAEA; 2015.
IAEA. Operational guidance on hospital radiopharmacy. Vienna: International Atomic Energy Agency (IAEA); 2008.
IAEA. Radiopharmaceuticals for sentinel lymph node detection: status and trends. Vienna: International Atomic Energy Agency (IAEA); 2015.
IAEA. Technetium-99m radiopharmaceuticals: status and trends. Vienna: International Atomic Energy Agency (IAEA); 2010.
Kowalsky RJ, Falen SW, editors. Radiopharmaceuticals in nuclear pharmacy and nuclear medicine. 3rd ed. Washington, DC: American Pharmacists Association; 2011.
Owunwanne A, Patel M, Sadek S, editors. The handbook of radiopharmaceuticals. New York, NY: Springer; 1995.
Schwochau K, editor. Technetium: chemistry and radiopharmaceuticals. Hoboken, NJ: Wiley; 2000.
Subramanian G, Rhodes BA, Cooper JF, Sodd VJ. Radiopharmaceuticals. New York, NY: Society of Nuclear Medicine; 1975.
Theobald T, editor. Sampson's textbook of radiopharmacy. 4th ed. London: Pharmaceutical Press; 2010.
Vallabhajosula S. Molecular imaging – radiopharmaceuticals for PET and SPECT. Berlin: Springer; 2009.
Welch MJ, Redvanly CS, editors. Handbook of radiopharmaceuticals: radiochemistry and applications. Hoboken, NJ: Wiley; 2003.