Radiopharmaceuticals

6

"Primum non nocere"

–First do not harm—Hippocrates

6.1 Introduction

The use of specific radiotracers called radio pharmaceuticals for imaging organ function and disease states is a unique capability of nuclear medicine. Unlike other imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US), nuclear medicine procedures are able of mapping physiological or pathological activities and thereby giving more specific information about the organ function and dysfunction. The widespread utilization and growing demands for these techniques are directly attributable to the development and availability of a vast range of specific radiopharmaceuticals.

Radiopharmaceuticals are medicinal formulations containing radioisotopes that are safe for administration in humans, for diagnosis, or for therapy. The diagnosis radiopharmaceuticals usually have no pharmacologic effect because in most cases they are used in trace quantities; they should be sterile and pyrogenic-free. Although radiotracers were tried as a therapeutic medicine immediately after the discovery of radioactivity, the first significant applications came much later with the availability of cyclotrons for acceleration of particles to produce radioisotopes. Subsequently, nuclear reactors realized the ability to prepare larger quantities of radioisotopes. The most commonly used "reactor" to produce isotopes in medical applications is molybdenum-99 generator (for the production of technetium-99m).

The early use of cyclotron in radiopharmaceutical field was for the production of long-lived radioisotopes that can be used to prepare tracers for diagnosis imaging. For this, medium- to high-energy (20–70 MeV) cyclotrons with high beam currents were needed. With the advent of positron emission tomography (PET), there has been a surge in the production of low-energy cyclotrons (9–19 MeV) exclusively for the production of short-lived PET radionuclides such as fluorine-18 (F-18), carbon-11 (C-11), nitrogen-13 (N-13), and oxygen-15 (O-15). The majority of the cyclotrons worldwide are now used for the preparation of fluorine-18 for making radiolabeled glucose for medical imaging.

Currently there are over 100 radiopharmaceuticals developed using either reactor or cyclotron-produced radioisotopes which are used for the diagnosis of several common diseases and the therapy of a few selected diseases, including cancer.

Radiopharmaceuticals production involves handling of large quantities of radioactive substances and chemical processing.

The last decade has seen an increase in the use of PET in regular diagnosis imaging and a commensurate use of PET radiopharmaceuticals, particularly fluorine-18 in the form of fluorodeoxyglucose (18F-FDG). The associated 511 keV high-energy radiations need thicker shielding and more sophisticated handling devices. Regarding the short half-lives, the emphasis is also increasing on the validation process and strict adherence to

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Table 6.1 The ideal radiopharmaceutical

Radionuclide criteria	Radio pharmacokinetic criteria	Radiobiological criteria	Economic criteria
Gamma or X-ray emission detectable outside the body	Maximum ratio target organ/ surrounding tissues	In diagnostic tests, no corpuscular emission	Low cost
Optimal photonic energy (50–300 keV)	Optimal effective halftime ($T_{1/2}$); it must be eliminated from the body with a $T_{1/2}$ similar to the duration of the diagnostic test	Short halftime and effective halftime	Availability at hospital
Halftime ($T_{1/2}$) short, but sufficient till the end of the diagnostic test	The radionuclide should be chemically suitable for incorporating it into the pharmaceutical, without altering its biological behavior		Adequate equipment
Absence or as low as possible of alpha, beta particles, Auger electrons			Easy to prepare

approved procedures in handling all steps of the manufacture, rather than relying on the final quality control (QC) test results alone.

The specific features of the ideal radiopharmaceutical are summarized in Table 6.1. It must be emphasized, however, that there is no radiopharmaceutical that has all these properties. For the definition of this radiopharmaceutical, there are radionuclide criteria, radiopharmaceutical, radiobiological, and economical criteria.

Regarding the radiopharmaceuticals, the presence of radionuclide gives the level of radiotoxicity to the entire product. Radiotoxicity refers to radioactive materials that are toxic to living cells or tissues.

Radiotoxicity results from the:

- Type of radiation
- The radionuclide half-life
- The biological half-life in the tissues
- The dose absorbed in the organ

There are four groups of toxicity. The radiotoxicity of most commune radionuclides is presented as follows:

Group 1: Very High Radiotoxicity

Pb-210 Po-210 Ra-223 Ra-226 Ra-228 Ac-227 Th-230 Pa-231 Pu-238 Am-241 Am-243 Cm-242 Cm-243 Cm-244 Cm-245 Cm-246 Cf-249 Cf-250 Cf-252 Ra-226

Group 2: High Radiotoxicity

Na-22 Cl-36 Ca-45 Sc-46 Mn-54 Co-56 Co-60 Sr-89 Sr-90 Y-91 Zr-95 Ru-106 Ag-110m Cd-115m In-114m Sb-124 Sb-125 Te-127m Te-129m I-124 ***I-125*** I-126 ***I-131*** I-133 Cs-134 Cs-137 Ba-140 Ce-144 Eu-152 (13 y) Eu-154 Tb-160 Tm-170 Hf-181 Ta-182 Ir-192 Tl-204 Bi-207 Bi-210 At-211 Pb-212 Ra-224 Ac-228 Pa-230

Group 3: Moderate Radiotoxicity

Be-7 C-14 ***F-18*** Na-24 C1–38 Si-31 P-32 S-35 Ar-41 K-42 K-43 Ca-47 Sc-47 Sc-48 V-48 Cr-51 Mn-52 Mn-56 Fe-52 Fe-55 Fe-59 Co-57 Co-58 Ni-63 Ni-65 Cu-64 Zn-65 Zn-69m Ga-72 As-73 As-74 As-76 As-77 Se-75 Br-82 Kr-85m Kr-87 Rb-86 Sr-85 Sr-91 ***Y-90*** Y-92 Y-93 Zr-97 Nb-93m Nb-95 Mo-99 Tc-96 Tc-97m Tc-97 Tc-99 Ru-97 Ru-103 Ru-105 Rh-105 Pd-103 Pd-109 Ag-105 Ag-111 Cd-109 Cd-115 In-115m Sn-113 Sn 125 Sb-122 Te-125m Te-127 Te-129 Te-31m Te-132 I-130 I-132 I-134 I-135 Xe-135 Cs-131 Cs-136 Ba-31 La-140 Ce-141 Ce-143 Pr-142 Pr 143 Nd-147 Nd-149 Pm-147 Pm-149 Sm-151 Sm-153 Eu-152 Eu-155 Gd-153 Gd-159 Dy-165 Dy-166 Ho-166 Er-169 Er-171 Tm-171 Yb-175 ***Lu-177*** W-181 W-185 W-187 Re-183 Re-186 Re-188 Os-185 Os-191 Os-193 Ir-190 Ir-194 Pt-l91 Pt-193 Pt-197 Au-196 Au-198 Au-l99 Hg-197 Hg-197m Hg-203 Tl-200 Tl-201 Tl-202 Pb-203 Bi-206 Bi-212 Rn-220 Rn-222

Group 4: Low Radiotoxicity

H-3 O-15 Ar-37 Co-58m Ni-59 Zn-69 Ge-71 Kr-85 Sr-85m Rb-87 Y-9lm Zr-93 Nb-97 Tc-96m ***Tc-99m*** Rh-103m In-113m I-129 Xe-131m Xe-133 Cs-134m Cs-135 Sm-147 Re-187 Os-191m Pt-193m Pt-197m

Considering this fact, in nuclear endocrinology, there are not used radiopharmaceuticals with very high radiotoxicity; the iodine isotopes I-125 and I-131 belong to the group of high radiotoxicity (group 2), and this is important to keep in mind, in order to limit the unjustifiable indication of diagnostic tests. The most frequent used in diagnosis is Tc-99m, which is included in the group 4 of radiation toxicity, of low risk.

6.2 Radiopharmaceuticals in Endocrinology

In nuclear endocrinology, radiopharmaceuticals may be classified according to their purpose: diagnosis or therapy. Even if the compounds are multiple, the radionuclides which are linked to this substances are relatively limited, many of them laying on some physiological features and proprieties of the endocrine system (Table 6.2).

6.2.1 Fluorine-18 Fluorodeoxyglucose (18F-FDG)

Fluorine-18 is a positron-emitting radioisotope. The application of 18F-FDG was aimed for mapping glucose metabolism in tumors considered to be highly glucose consuming. The major use of 18F-FDG subsequently emerged in the detection, staging, and treatment response monitoring of various types of cancers. Currently, in PET studies, the use of 18F-FDG accounts for the majority of all images performed with radiopharmaceuticals. A number of other fluorine-18-labeled radiopharmaceuticals have been developed, and many more are under clinical investigations.

Table 6.2 The most common radiopharmaceuticals used in nuclear endocrinology

Radiopharmaceutical	Usage
F-18 fluorodeoxyglucose (18F-FDG)	Tracer for PET (thyroid, endocrine tumors)
F-18 choline (18-FCH)	Tracer for PET parathyroid
16α-(18F)Fluoro-17β-Estradiol (18F-FES)	Tracer for PET tumors expressing estrogen receptors
Gallium-67 citrate	Infection and inflammation
Gallium-68 DOTA (Ga-68 DOTA)	Neuroendocrine tumors
Iod-123 as sodium iodide (I-123 NaI)	Thyroid, adrenal glands
Iod-124 as sodium iodide (I-124 NaI)	Tracer for PET (thyroid, endocrine tumors)
Iod-125 as sodium iodide (I-125 NaI)	Thyroid
Iod-131 as sodium iodide (I-131 NaI)	Thyroid, adrenal glands
Iod-123 as metaiodobenzylguanidine (I-123 MIBG)	Thyroid, adrenal glands, neuroendocrine tumors
Iod-131 as metaiodobenzylguanidine (I-131 MIBG)	
Indium-111 pentetreotide (In-111 pentetreotide)	Endocrine tumors
Technetium-99m pertechnetate (Tc-99m Pt)	Thyroid
Technetium-99m sestamibi (Tc-99m MIBI)	Parathyroid
Technetium-99m tetrofosmin (Tc-99m tetrofosmin)	Parathyroid
Technetium-99m Tekrotyde	Neuroendocrine tumors
Technetium-99m dimercaptosuccinic acid (Tc-99m DMSA)	Thyroid
Thallium-201 chloride (Tl-201 chloride)	Thyroid
Other peptide receptor radiotracers (PRR)—(lutetium-177, yttrium-90, etc.)	Endocrine tumors

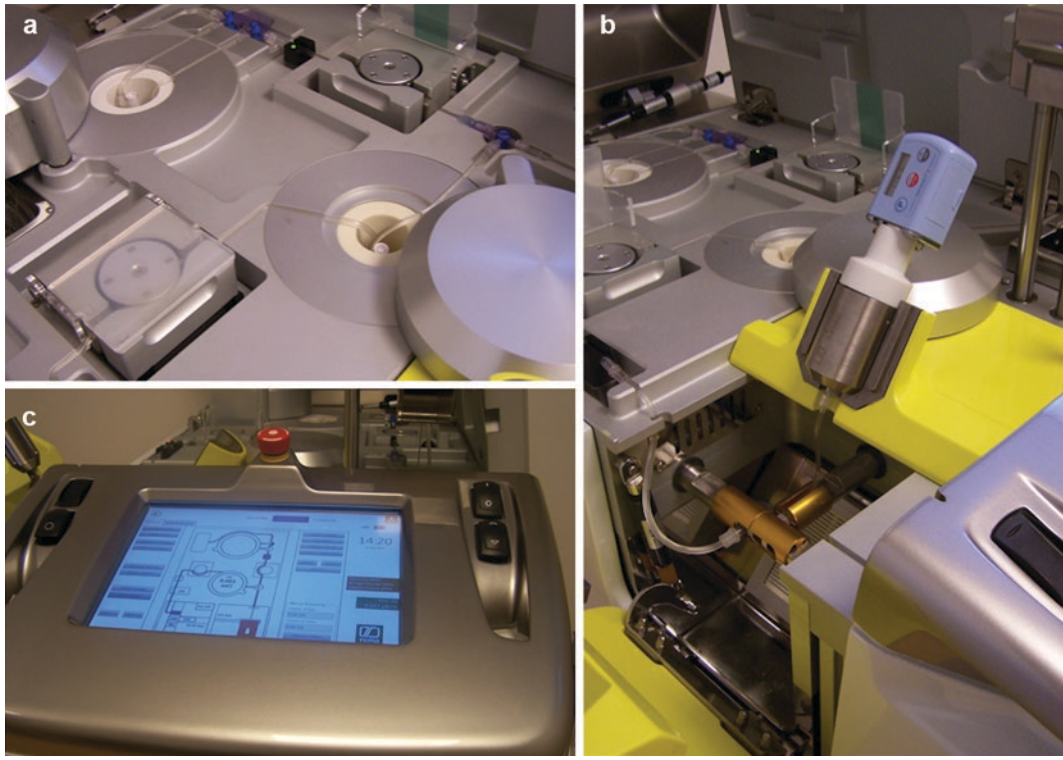

Fig. 6.1 The 18F-FDG calibrator used for loading and calibrating 18F-FDG for PET or PET/CT imaging, model *Karl 100 (Tema Sinergie)*: dispersing (**a**), loading in the syringe (**b**), and calibrating (**c**)

Increasing clinical demand for 18F-FDG has triggered technological advances in various fields such as accelerator technology, radiochemistry, automated processing modules, detector systems, and imaging software.

Dispensers and injectors perform the most critical steps in the radiopharmaceutical handling processes. In Fig. 6.1 the equipment for loading, dispensing, and calibrating the dose of F18-FDG ready for injection for PET/CT imaging is presented.

The use of 18F-FDG in endocrinology was not particularly interesting, until the experience brought the necessary knowledges, especially in endocrine cancers. Nevertheless PET studies are still indicated in well-defined clinical situations, due to some less invasive and more accessible methods that might be used in the frequent pathologies, such as those of the thyroid gland; regarding the diagnosis of the endocrine tumors, the role of PET/CT is clear and will be discussed in the following chapters of the book.

6.2.2 Fluorine-18 Fluorocholine (18F-FCH)

F18-Fluorocholine PET/CT appears to be a promising, effective imaging method for localization of hyperfunctioning parathyroid tissue. The performance of 18F-FCH PET/CT was superior to Tc-99m MIBI standard methods, particularly in patients with multiple lesions or hyperplasia. The tracer was first used in prostate cancer, where the mechanism consists in the following mechanism: FCH enters cell through choline transporters with accumulation in tumors in part due to malignancy-induced overexpression of choline kinase (CK) that catalyzes the phosphorylation of choline to form phosphorylcholine followed by generation of phosphatidylcholine in the tumor cell membrane.

The lack of availability and the costs are limiting seriously the use of this tracer in parathyroid pathology, being necessary larger studies to conclude on the superiority of the method, over the standard MIBI imaging.

6.2.3 Radiopharmaceuticals with Gallium-68 and Gallium-67

Gallium-67 is produced by bombardment of Zn-68 in a cyclotron. Ga-67 decays by electron capture to Zn-67, with a half-life of about 78 h. There are three gamma emissions at 93, 185, and 300 keV. Following intravenous injection, gallium distributes widely in the body. It binds to circulating proteins, fact that leads to long persistency in the plasma. Gallium has a wide normal distribution throughout the soft tissues, mainly in the liver, spleen, bone, bone marrow, and bowel. There is a rapid uptake in the zones with high rate of inflammation, due mainly to the increased capillary permeability occurring in these processes.

Somatostatin receptors are expressed by many neuroendocrine and non-neuroendocrine cells of the body, so different organs may be imaged by somatostatin receptor scintigraphy, including the liver, spleen, pituitary gland, thyroid, kidneys, adrenal glands, salivary glands, stomach wall, and bowel.

Ga-67 citrate was considered the master radiopharmaceutical for tumor imaging and detection of inflammatory sites. Its role is highly affected after the introduction of PET tracers.

Gallium-68 (halftime is 68 min) is available from the Ge-68/Ga-68 generator. In terms of radiochemistry, labeling with metallic nuclides is based on chelating systems which are coupled to biomolecules or which have interesting biological properties themselves. A new tracer is Ga-68 DOTA (Ga-68-labeled 1,4,7,10-tetraazacyclododecane-*N*, *N′*,*N″*,*N‴*-tetraacetic acid). Ga-68 DOTA-conjugated peptides (DOTA-TOC, DOTA-NOC, DOTA-TATE) are rapidly cleared from the blood. Arterial activity elimination is bi-exponential, and no radioactive metabolites are detected within 4 h in serum and urine. Excretion is almost entirely through the kidneys.

Just recently the Ge-68/Ga-68 generators and the DOTA-conjugated peptide obtained a marketing authorization, until now, and they have to be prepared taking into account national regulations and good radiopharmaceutical practices (GRPP) as outlined in specific European Association of Nuclear Medicine (EANM) guidelines. PET with Ga-68-DOTA-conjugated peptides has brought dramatic improvement in spatial resolution and is being used more and more often in specialized centers. All of them can bind to some of the somatostatin receptors, and they also present different affinity profile for other somatostatin receptor subtypes. In particular, PET clearly offers higher resolution and improved pharmacokinetics as compared to somatostatin receptor scintigraphy, with promising results for the detection of somatostatin receptor expressing tumors, and provides prognostic information and selection for targeted specific treatments.

6.2.4 Radiopharmaceuticals with Radioiodine

6.2.4.1 Radioiodine I-123 Sodium Iodide (I-123 NaI)

The isotope iodine-123 (I-123) with a half-life of 13.22 h is used as a tracer, in order to evaluate the anatomic and physiologic function of the thyroid. It decays by electron capture to tellurium-123 and emits gamma radiation with predominant energies of 159 and 127 keV. This is the most suitable isotope of the iodine for the diagnosis study of thyroid diseases. The half-life of approximately 13.2 h is ideal for the 24-h iodine uptake test and also diagnostic scanning imaging of the thyroid tissue.

The energy of the photons, 159 keV, is ideal for the NaI (sodium iodide) crystal detector of current gamma cameras. It has a much higher photon flux than I-131. It gives approximately 20 times the counting rate of I-131 for the same administered dose. The radiation burden to the thyroid is far less (1%) comparing to I-131 mainly because of the absence of beta radiation compound. This is the reason why this isotope is reserved only for diagnosis, not being suitable for treatment.

Moreover, scanning a thyroid remnant or metastasis from differentiated thyroid carcinoma with I-123 does not cause "stunning" of the tissue (with loss of uptake) because of the low radiation burden of this isotope.

Iodine-123 is supplied as sodium iodide (NaI), sometimes in basic solution in which it has been dissolved as the free element. This is administered to a patient in capsule form, by intravenous injection, or (less common due to the risk of spilling) as a drinkable solution. Quantitative measurements of the thyroid can be performed to calculate the iodine uptake (absorption).

6.2.4.2 Radioiodine I-124 Sodium Iodide (I-124 NaI)

I-124 is a proton-rich isotope of iodine with a half-life of 4.18 days. Its modes of decay are 74.4% electron capture and 25.6% positron emission. I-124 decays to Te-124 and may be obtained by nuclear reactions in the cyclotron.

This radiopharmaceutical can be used to obtain a direct image of the thyroid using positron emission tomography (PET) or labeled to a pharmaceutical to form a positron-emitting radiopharmaceutical, which is injected into the body and imaged by PET scan.

In the recent years, the use of the radiopharmaceutical increased mainly in thyroid cancer dosimetry studies on PET/CT.

6.2.4.3 Radioiodine I-125 Sodium Iodide (I-125 NaI)

Radioiodine I-125 is a radioisotope of iodine, which has a half-life of 59.4 days and is used in biochemistry, in some radioimmunoassay tests, in nuclear endocrinology imaging, in radiotherapy for prostate, and in brain tumor treatments.

I-125 decays by electron capture while excited to tellurium-125. The relatively long half-life and the low-energy photon emissions are the main criteria, which determine I-125 to be suitable in the radioimmunoassay tests and brachytherapy, less for imaging. I-123 is preferably used, due to its shorter half-life and better penetration. The emission gamma rays are at 35.5 keV.

6.2.4.4 Radioiodine I-131 Sodium Iodide (I-131 NaI)

This iodine isotope is the most used radiopharmaceutical in nuclear endocrinology therapies. It is the "parent" of radionuclide therapies, and until now, there is no other specific treatment in differentiated thyroid carcinomas with better results than I-131.

I-131 has 78 neutrons and 53 protons with the atomic mass (A) of 131. Most I-131 production comes from nuclear neutron irradiation of natural tellurium target, Te-130. Its half-life is of 8.02 days.

Radioiodine I-131 decays with beta and gamma emissions. This is the major propriety of I-131, which makes it useful both in imaging and in therapy.

The I-131 decay is in two steps:

1. Firstly, the I-131 decay leads to unstable xenon and beta particles with energies of 606, 248, and 807 keV. In this decay occurs also an antineutrino (Eq. 6.1):

$$^{131}_{53}\mathrm{I} \Rightarrow ^{131}_{54}\mathrm{Xe}^{*} + e^{-} + \nu \tag{6.1}$$

   e^{-} is the beta minus particle.
   ν is the antineutrino.
   $^{131}_{54}\mathrm{Xe}^{*}$ is the unstable xenon.
   Due to their high energy, the beta particles penetrate the tissues of 0.6–2 mm, fact that is suitable in therapy.
2. Secondly, the unstable Xe^{*} passes rapidly in stable Xe with gamma rays emission. Almost 90% of the gamma energy is of 364 keV, the rest being of 723 keV (Eq. 6.2).

$$^{131}_{54}\mathrm{Xe}^{*} \Rightarrow ^{131}_{54}\mathrm{Xe} + \gamma \tag{6.2}$$

These features make I-131 proper for diagnosis, due to the gamma energy able to be detected by the gamma cameras. For nuclear endocrinologists, it is important to remember that this level of energy imposes the use of collimators for medium energy, different from those used for Tc-99m. If the number of cameras is limited, the change of collimator is time consuming and needs a careful organization of both patients and examinations.

Fig. 6.2 The I-131 shielded container (**a**) and the capsule (**b**) ready to be used by patient for radioiodine therapy

One must keep in mind that the presence of beta particles limits the use of I-131 in diagnostic procedures, other than those recommended in the follow-up of thyroid carcinomas.

The beta particles produce the irradiation and destroy thyroid tissue, fact that justifies its use in treatment of some thyroid diseases.

It is important to underline that the penetration of beta particles of 0.6–2 mm in the narrowing tissues is the basis for using this radionuclide in the treatment of some situations of medullar thyroid carcinomas. In this particular thyroid cancer, the tumor occurs from C cells of the thyroid, which do not trap radioiodine. This penetration propriety justifies the irradiation of C cells from the surrounding follicular cells, which are iodine selective.

The pharmacological presentation is of I-131 sodium iodide. This sodium iodide I-131 may be a solution, as it has an activity strictly calibrated per volume unit, or gelatine capsules. The capsules have precise calibrated doses of I-131, ready to use according to the endocrinologist's prescription of dosage (Fig. 6.2)

6.2.4.5 Radioiodine I-123 Metaiodobenzylguanidine (I-123 MIBG)

I-123 metaiodobenzylguanidine (I-123 MIBG), or iobenguane, is a combination of an iodinated benzyl and a guanidine group labeled with I-123, especially developed for the diagnosis of tumors of neuroendocrine origin. MIBG enters neuroendocrine cells by an active uptake mechanism via the epinephrine transporter and is deposited in the neurosecretory granules, resulting in a specific concentration in contrast to the cells of the surrounding tissues.

MIBG scintigraphy is used to image tumors of neuroendocrine origin, particularly those of neuroectodermal origin (pheochromocytomas, paragangliomas, and neuroblastomas), and other neuroendocrine tumors (e.g., carcinoids, medullary thyroid carcinoma).

The 159 keV gamma energy of I-123 is more suitable for imaging (especially when using SPECT) than the 360 keV photons of I-131; with the latter, results are usually available within 24 h, whereas with I-131, MIBG-delayed images may be required for optimal target to background ratios.

I-123-labeled agent is to be considered the radiopharmaceutical of choice as it has a more favorable dosimetry and provides better image quality allowing an accurate anatomical localization by the use of SPECT/CT hybrid systems. Nonetheless, I-131 MIBG is widely used for most routine applications mainly in adult patients because of its rapid availability and the possibility of obtaining delayed scans.

The effective dose is of 0.013 mSv/MBq for adults, from an I-123 MIBG scanning.

The radioactive MIBG preparation is usually a ready-for-use licensed radiopharmaceutical, which is sold by specialized companies. The compound is radioiodinated by isotope exchange and distributed to nuclear medicine centers, where no additional preparation is required.

6.2.4.6 Radioiodine I-131 Metaiodobenzylguanidine (I-131 MIBG)

I-131 metaiodobenzylguanidine (I-131 MIBG) is a combination of an iodinated benzyl and a guanidine group labeled with I-131, both developed for the diagnosis and treatment of tumors mainly derived from adrenal medulla. Because of its energy of 364 keV and the presence of beta

particles, this radiotracer is not one of the best radiopharmaceuticals for the diagnosis of these neuroendocrine tumors; the injuries to other surrounding tissues may occur due to beta particles penetration. In opposition, this particularity is the major feature that makes the I-131 MIBG the selective targeted treatment for the tumors of neuroendocrine origin.

Even if there are some disadvantages, like the high burden rate and the delay in obtaining the final results of the examination, this radiotracer is still very popular among the endocrinology centers mainly because of its large availability (half-life much longer than I-123) and more accessible price.

Regarding the I-131 MIBG for treatment, the indications are laying on the particular beta emission, which is able to destroy tumor tissues with the features of neuroendocrine tumors.

For I-123 and I-131, it is important to underline, both for diagnostic and therapy, the mandatory indication of blocking the thyroid, before any of these procedures is done, in order to protect the gland from the injuries caused by iodine trapping. The blocking starts 1 day before the procedure and continues 2–4 days afterward. As a special precaution in both cases, there are many drugs that may interfere with the uptake or with the vesicular storage of the tracers, fact that requires a special attention when preparing the patient for examination.

I-131 MIBG is also indicated in the evaluation of the response to treatment by analyzing the uptake of the radiopharmaceutical in the tumor.

The effective dose calculated for an adult in an I-131 MIBG procedure is of 0.14 mSv/MBq, which is ten times higher per MBq than in the case of I-123 MIBG.

6.2.5 Indium-111 Pentetreotide (In-111 Pentetreotide)

Indium In-111 pentetreotide is a diagnostic radiopharmaceutical with indication in the diagnosis of the neuroendocrine tumors.

Indium In-111 pentetreotide is an agent for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors.

The product is represented by two components:

1. The vial, which contains a lyophilized mixture ofpentetreotide[*N*-(diethylenetriamine-*N*,*N*,*N*′,*N*″-tetraacetic acid-*N*″-acetyl)-D-phenylalanyl-L-hemicystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-hemicystyl-L-threoninol cyclic (2→7) disulfide] (also known as octreotide DTPA), and other unspecific compounds. Prior to lyophilization, sodium hydroxide, or hydrochloric acid, may have been added for pH adjustment. The vial contents are sterile and non-pyrogenic. No bacteriostatic preservative is present.
2. A 10 mL vial of indium In-111 chloride sterile solution, which contains 1.1 mL of 111 MBq/mL (3.0 mCi/mL) indium In-111 chloride in 0.02 N HCl at the time of calibration. The vial contents are sterile and non-pyrogenic. No bacteriostatic preservative is present. Indium In-111 pentetreotide is prepared by combining the two kit components.

The indium In-111 pentetreotide solution is suitable for intravenous administration as it is, or it may be diluted to a maximum volume of 3.0 mL with 0.9% sodium chloride injection. The labeling yield of indium In-111 pentetreotide should be determined before administration to the patient by chromatography.

Indium In-111 decays by electron capture to cadmium-111 (stable) and has a physical half-life of 2.805 days (67.32 h). The biological half-life is of 6 h.

Pentetreotide is a form of octreotide, which is a long-acting analogue of the human hormone somatostatin. Indium In-111 pentetreotide binds to somatostatin receptors on the cell surfaces throughout the body. Within an hour from the injection, most of the dose of indium In-111 pentetreotide distributes from plasma to extravascular body tissues and concentrates in tumors containing a high density of somatostatin receptors. After background clearance, visualization of somatostatin receptor-rich tissue is achieved. In addition to somatostatin receptor-rich tumors,

other organs are normally visualized, such as pituitary gland, thyroid gland, liver, spleen, and urinary bladder and also the bowel. Excretion is made almost exclusively via the kidneys.

Indium In-111 pentetreotide binds to cell surface receptors for somatostatin; the hormonal in vitro effect is one-tenth from the effect of the octreotide.

The recommended intravenous dose for planar imaging is of 111 MBq (3.0 mCi) of indium In-111 pentetreotide. The recommended intravenous dose for SPECT imaging is of 222 MBq (6.0 mCi) of indium In-111 pentetreotide.

The effective dose of In-111 pentetreotide in adults is of 13.03 mSv/111 MBq, dose used for one scan.

A better sensitivity and resolution is by using the SPECT/CT, mainly in the neuroendocrine tumor of the gastrointestinal tract.

The use of In-111 octreotide has the same basic principles as the therapeutic agents of somatostatin analogues, with the systemic action and special indication in the therapy of neuroendocrine tumors with somatostatin expression, so the imaging test might be a selection tool for the responder patients.

6.2.6 Radiopharmaceuticals with Techentium-99m

Technetium-99m (Tc-99m) is the radioisotope most widely used in nuclear medicine diagnosis. It is estimated that over 80% of the nearly 25 million nuclear medicine diagnostic studies carried out annually are done with this single isotope. This percentage share is expected to remain in the foreseeable future, notwithstanding the introduction of new diagnostic radiopharmaceuticals containing other radionuclides. The availability of the short-lived technetium-99m (a half-life of 6 h), as the daughter product of the long-lived molybdenum-99 (a half-life of 66 h), is one of the major factors, which have promoted the universal use of this radioisotope. The parent radionuclide molybdenum-99 (Mo-99) can be prepared in abundant quantities by the fission of uranium-235 in a nuclear reactor with a fission yield of about 6%.

There are only a limited number of industrial companies and national centers producing molybdenum-99 from fission products, but together they have the adequate capacity to meet the world's demands for molybdenum-99.

The generator is an automated, highly shielded system, allowing easy elution of a sterile and pyrogen-free Tc-99m sodium pertechnetate solution. This solution is eluted from an alumina chromatography column.

The device consists of the following parts (Fig. 6.3):

- Chromatography column which contains alumina, which absorbs molybdate ions but releases pertechnetate ions when eluted with saline solution.
- Inlet needle connected to the top of the column.
- Sterilization filter with hydrophobic spot; one of its ends is linked to the lower part of the column while the other one to an outlet needle.
- Lead shielding (minimum thickness, 41 mm; maximum thickness, 70 mm).
- The outer cylindrical cover is in plastic (diameter, 130 mm; maximum height, 278 mm).

The complete system weighs about 16 kg. Each generator is shipped ready to use and does not need to be assembled by the user. The generator of technetium is conceived to elute the whole available activity into 5 mL. It is possible, however, to elute larger volumes (10 or 15 mL) to obtain a different radioactive concentration. The elute must be used within 6 h from the elution. The Tc-99m pertechnetate (Tc-99m Pt) solution eluted from the generator is a clear, colorless, isotonic, sterile, and pyrogen-free solution with a pH ranging from 4.5 to 7.5, meeting the requirements of European and US Pharmacopoeias. The available generators have different activities, varying from 2.5 GBq (67.5 mCi) Mo-99, corresponding to 2.2 GBq (59.0 mCi) Tc-99m at calibration, up to 25.0 GBq (675.0 mCi) Mo 99m, corresponding to 21.9 GBq (591.0 mCi) Tc-99m at calibration. Recently, the available activities became much higher, going up to 175 GBq.

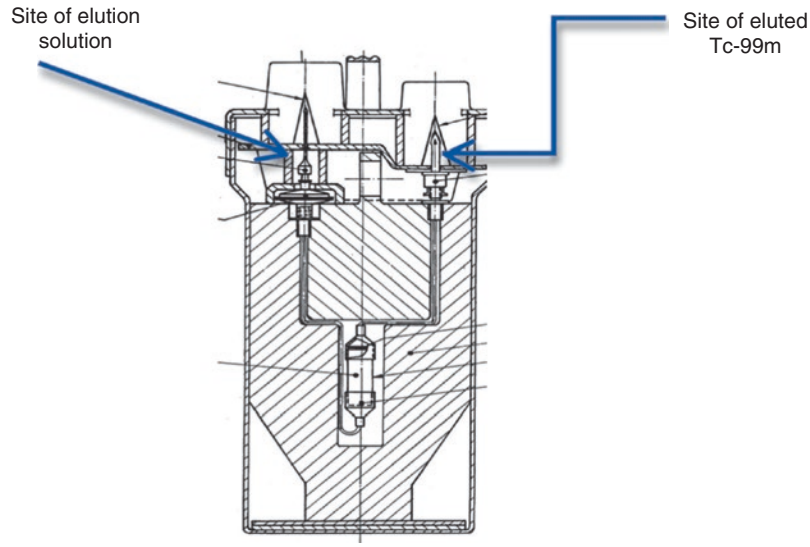

Fig. 6.3 The scheme of the Tc-99m generator

Intermediate doses are also available. Until now, no adverse reactions have been observed. Injectable Tc-99m sodium pertechnetate solution should not be administered to pregnant or breast-feeding women.

The generator of Tc-99m is delivered in the medical unit at the begging of each week or twice a month in a ready-to-use form. A total amount of activity is calculated for each type of generator, and it represents the life of the generator; in fact, these data establish how many days we are able to benefit from that generator, how many patients, and what kind of examinations may be proceeded until the decay will lead to a total consumption of the radiotracer. Usually, the process of preparation of radiolabeled compounds with Tc-99m is repeated every morning, starting with the elution of the generator. Figures 6.4, 6.5, and 6.6 show a brief presentation of this process. Figure 6.4 presents the vials (c, d, e, f), some of them specially designed for radioactive materials, made of materials such as lead (b) or tungsten (a). There is a series of special shielding, made on tungsten, for syringes of different sizes and types (g), which confers high protection during their manipulation.

Figure 6.5 presents the materials ready to be used under the sterile laminar flow hood. The next image (Fig. 6.6) presents the generator with the vials, one of sterile saline solution and the other shielded with the eluted technetium.

Figure 6.7 presents the next steps where the eluted Tc-99m is calibrated. The transfer takes place in a sterile area, and the measurement of the activity is performed with an instrument called calibrator (Figs. 6.8 and 6.9). This instrument must be adjusted according to the type of radionuclide that we intend to measure (attention to the energy!).

The early technetium radiopharmaceuticals were developed by taking advantage of the physiological properties, such as adsorption, distribution, metabolism, and excretion of various technetium-99m complexes, and were used for imaging the thyroid, the liver, the bone, the kidneys, etc.

Technetium-99m radiopharmaceuticals are often formulated from the so-called "cold" kits (they do not contain radioactivity). When treated with a sodium pertechnetate solution eluted from a technetium-99m generator, the final product used for patient injection is directly formed. Cold kits are prepared in such a manner as to have stability, ranging from several months to a few years, and may be transported at room temperature and then stored in a refrigerator to ensure stability. Large-scale preparation of cold kits requires special techniques and facilities, and it is

Fig. 6.4 Elution kit for Tc-99m generator

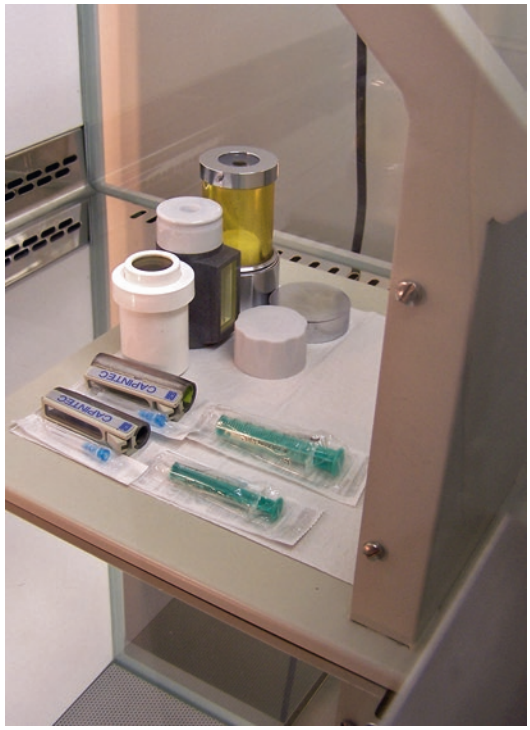

Fig. 6.5 Shielding for elution and injection preparation under sterile laminar flow

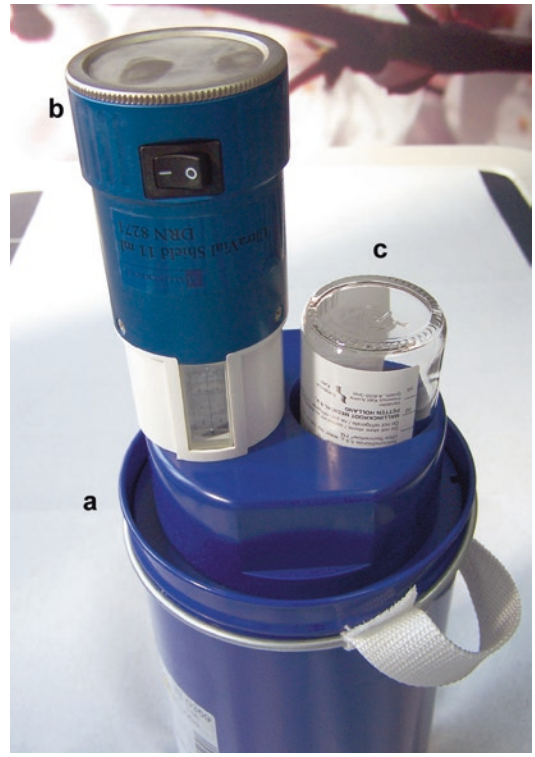

Fig. 6.6 The generator with eluted Tc-99m Pt ready to use

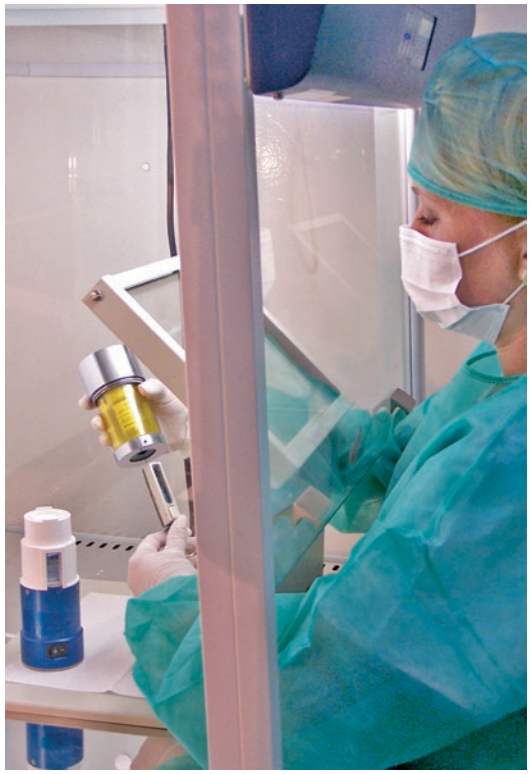

Fig. 6.7 The dose of Tc-99m Pt, ready for calibration

Fig. 6.8 Calibration of the dose

Fig. 6.9 The calibrator, adjusted for the use of Tc-99m

mostly performed by industrial companies and in national laboratories.

The investigations used for the development of cancer imaging agents mostly use peptides and antibodies as carrier molecules to target tumor sites. Radiopharmaceuticals can provide useful information about the function and molecular biology of the tumor, by measuring several of its causal factors. In the future, the specific roles of technetium-99m radiopharmaceuticals for imaging in oncology may include, for example, the lymphatic system, the development of new blood vessels, and monitoring gene therapy.

The most frequently used substances to be labeled with Tc-99m in nuclear endocrinology are presented in the next sections.

As a particular situation, the pure eluted technetium-99m is a ready-to-use radiopharmaceutical, so-called technetium-99m pertechnetate.

6.2.6.1 Technetium-99m Pertechnetate (Tc-99m Pt)

This is the simplest, cheapest, and easiest to prepare radiotracer in nuclear endocrinology, mainly used in thyroid imaging. This product, having the symbol Tc-99m Pt, is injected IV in order to evaluate the function, by thyroid uptake, and the structure of the thyroid, by scan (scintigraphy).

The pertechnetate of Tc-99m is actually the brut product from the generator being the pure eluate obtained without any labeling compounds. After the elution of the generator, the pertechnetate is just calibrated, and it is ready to be injected for scanning.

This Tc-99m Pt represents the most common radiotracer, used worldwide for thyroid scanning; all other radiopharmaceuticals based on Tc-99m use the Tc-99m Pt for labeling.

In thyroid imaging, the fundament of this procedure is to have an image of the thyroid gland obtained in direct relation with the blood flow and not with the main thyroid process of organification of iodine.

6.2.6.2 Technetium-99m MIBI (Tc-99m MIBI or Sestamibi)

This radiopharmaceutical is the most important tracer in parathyroid gland imaging. Initially being a product with indication in myocardial perfusion and breast imaging, its proprieties imposed the procedure of MIBI scan, as the imagistic "gold standard" in the diagnostic of primary hyperparathyroidism.

Composition of the kit:

- 2-Methoxyisobutylisonitrile (MIBI) copper (I) tetrafluoroborate
- Stannous chloride
- L-Cysteine hydrochloride monohydrate
- Sodium citrate dihydrate
- Mannitol

Tc-99m MIBI is administered intravenously after labeling the kit with a sterile, oxidant-free solution of eluate from a radionuclide generator of technetium. The radioactivity of a given dose should always be adjusted taking into account its usefulness in diagnosis.

Tc-99m MIBI is a lipophilic cation complex, which is accumulated in the cardiac muscle in proportion to the blood flow. Although the mechanism of uptake is not known, studies on cellular fractionation show that 84% of it is within the cytoplasm. The diffusion to the intracellular compartment occurs easily and in proportion to the blood flow. The process of washing the complex out from the cardiac muscle is slow. The effective half-life in the cardiac muscle is similar to the physical half-life of technetium-99m. The complex is redistributed in a small extent.

Tc-99m MIBI is accumulated within the cells through active transport and passive diffusion, a process facilitated by the lipophilic nature of tracer, and by the negative transmembrane potential found in metabolically hyperactive cells in hyperparathyroidism. As increased numbers of mitochondria have been found in hyperactive parathyroid cells, intramitochondrial sequestration may be an additional mechanism of Tc-99m MIBI tissue binding. This may account for slower Tc-99m MIBI washout from hyperactive parathyroid compared to normal thyroid and parathyroid tissues.

Tc-99m MIBI radiopharmaceutical may be used within 6 h since the end of the labeling procedure.

The safety regulations regarding work in the conditions of ionizing radiation exposure should be strictly respected during the preparation and administration of a radiopharmaceutical.

The labeling procedure consists of:

- The vial with lyophilisate is placed in a lead protective container.
- With a syringe (piercing the rubber stopper), introduce Tc-99m Pt with the desired activity supplemented with physiological saline solution into a vial containing lyophilised MIBI.
- Without withdrawing the needle, remove the volume of gas equal to the volume of solution introduced with the same syringe, in order to counteract the pressure.
- Shake the vial until the contents are fully dissolved (about 1 min).
- Take the vial out of the lead container, place it in a hot boiling water bath (the water should

be boiling during the procedure of labeling), and boil for 10–12 min. While boiling, do not allow contact between boiling water and an aluminum cap.
- Take the vial out of the boiling water bath; put it into a lead container and leave to cool down to room temperature (about 15 min).
- The resulted solution is a ready-to-use solution for injections.

The determination of radiochemical purity should be performed with ascending thin-layer chromatography. The sum of contaminations of unbound Tc-99m Pt and a reduced form of Tc-99m should not be higher than 5% of the total activity.

Tc-99m MIBI is also used in the evaluation of thyroid nodules. It was a method considered to be able to bring new data in relation to define the differential diagnosis between a benign and a malignant thyroid nodule. In a dual phase study (early and late scans), the behavior of a nodule, with respect to MIBI, was reported by some authors as being at least as sensitive as the genetic results from a fine needle aspiration biopsy.

6.2.6.3 Technetium-99m Tetrofosmin (Tc-99m Tetrofosmin)

Some centers use Tc-99m tetrofosmin to perform parathyroid scanning. Studies have shown that myocardial uptake of Tc-99m tetrofosmin is linearly related to coronary blood flow, confirming the effectiveness of the complex as a myocardial perfusion imaging agent. Additional studies concluded that Tc-99m tetrofosmin is taken up/retained by the mitochondria of parathyroid cells. This mechanism is dependent on the mitochondrial membrane potential in a manner similar to that of other lipophilic technetium cationic complexes.

In a critical manner, the use of sestamibi or tetrofosmin in the scanning of parathyroid is a subject that will not be discussed in this section, but it is important to underline that both tracers and methods were used in this endocrine pathology, and until nowadays, the clinical studies continue to establish the superiority of one of the tracer.

Each vial contains a pre-dispensed, sterile, non-pyrogenic, lyophilized mixture of tetrofosmin [6,9-bis(2-ethoxyethyl)-3,12-dioxa-6,9-diphosphatetradecane] and other excipients. The lyophilized powder is sealed under a nitrogen atmosphere with a rubber closure. The product contains no antimicrobial preservative. When technetium Tc-99m pertechnetate is added to tetrofosmin in the presence of stannous reductants, a lipophilic, cationic technetium Tc-99m complex is formed, the Tc-99m tetrofosmin. This complex is the active ingredient in the reconstituted drug product, on whose biodistribution and pharmacokinetic properties the indications for use depend. This product does not need boiling for labeling.

6.2.6.4 Technetium-99m (V) DMSA (Tc-99m (V) DMSA)

Dimercaptosuccinic acid (DMSA) pentavalent is used for the evaluation of the medullary thyroid carcinoma. Clinical trials showed improvement of patient management in this disease, succeeding to localize the recurrence in the presence of an increased serum level of calcitonin.

Technetium-99m (V) DMSA is prepared using the DMSA kit, but it requires the addition of a second component (bicarbonate buffer, 4.4%, pH 9.0) for adjusting the pH to 8–9 prior to labeling.

- The freeze-dried kit using 1.0 mL of bicarbonate buffer at pH 9.0 is well mixed.
- Add 2 mL of Tc-99m Pt solution containing a maximum of 3 mCi (1.11 MBq) of activity.
- Stir for 1 min and allow standing for 20 min. The Tc-99m (V) DMSA labeled in this manner should be stable for over 4 h after labeling.

Radiochemical purity is determined by ascending chromatography.

6.2.6.5 Technetium-99m Tektrotyde (Tc-99m Tektrotyde)

Tc-99m Tektrotyd (HYNIC-[D-Phe1,Tyr3-octreotide]·TFA) is a radiopharmaceutical indicated for diagnostics of pathological lesions in which somatostatin receptors are overexpressed (particularly subtypes 2 and 3, 5): gastro-entero-

pancreatic neuroendocrine tumors (GEP-NET); pituitary adenomas; tumors originating in a sympathetic system; pheochromocytoma, paraganglioma, neuroblastoma, and ganglioneurinoma; and medullary thyroid carcinoma. It is also used in other tumors which may overexpress somatostatin receptors, beyond endocrinology area: breast cancer, melanoma, lymphomas, prostate cancer, non-small lung carcinoma, sarcoma, renal cell carcinoma, astrocytoma, meningioma, and ovarian cancer.

6.2.7 Thallium-201 Chloride (Tl-201 Chloride)

Thallium-201 has the atomic mass (*A*) of 201 and the proton number (*Z*) 81.

Tl-201 decays to mercury Hg-201 by electron capture with a half-life of 3.0408 days. The X-ray energies are 69 and 83 keV, and the γ-ray energies are 135, 166, and 167 keV.

Thallium-201 chloride is an isotonic sterile solution for IV administration, with a pH ranging from 4.0 to 7.0.

The main cardiac diagnostic indications are myocardial scintigraphy in the evaluation of coronary perfusion and cellular viability in ischemic heart disease, cardiomyopathies, myocarditis, myocardial contusion, and secondary lesions.

In endocrinology, it is used for parathyroid scintigraphy, but not as a standard investigation, and also in some special cases of thyroid tumors and metastases, like the differentiated thyroid tumors that are not iodine sensitive anymore.

The development of sophisticated molecular carriers and the availability of radionuclides in high purity and adequate specific activity are contributing toward the successful application of radionuclide therapy.

6.2.8 Radiopharmaceuticals for Targeted Radionuclide Therapy

Selective molecule-binding radionuclide therapy involves the use of radiopharmaceuticals to selectively radiation releases to a disease site, as this would potentially deliver the absorbed radiation dose more selectively to cancerous tissues.

Advances in tumor biology, recombinant antibody technology, solid-phase peptide synthesis, and radiopharmaceutical chemistry molecular vectors are being developed for targeted therapy. When labeled with therapeutic radionuclides, peptide molecules have the potential to destroy receptor-expressing tumors, an approach referred to as peptide receptor radionuclide therapy (PRRT).

Yttrium-90 and Lutetium-177 are frequently used as radionuclides in such PRRT studies.

Lutetium-177 (halftime is 6.71 days) is a radionuclide that has both beta particle emissions for therapeutic use and gamma emissions (113 and 208 keV) for imaging purposes. It has a short radius of penetration, which makes it suitable for the radioimmunotherapy of small and soft tumors. Both Y-90 and Lu-177-DOTA analogues were developed for targeted radiotherapy of neuroendocrine tumors.

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