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Radiopharmaceuticals for diagnosis in nuclear medicine: a short review

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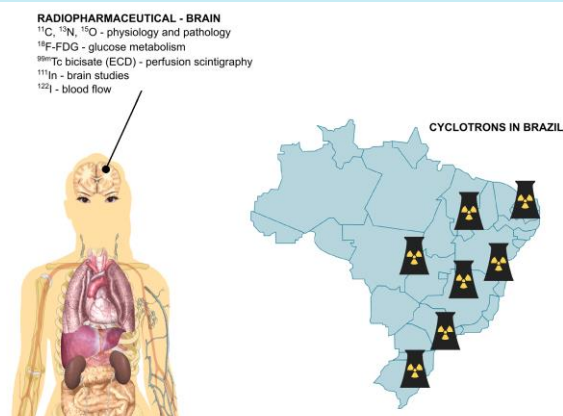
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ABSTRACT: Radiopharmaceuticals are radioactive compounds which have a bound radionuclide in their structure, whose purpose is directing the radionuclide to a location to be treated or to obtain images. Nuclear medicine is the medical specialty that employs radiopharmaceuticals, which has presented itself as a tremendously useful ally for medicine assisting in various diagnoses and treatments, especially for cancer. The general objective of this work is to identify the main radionuclides and metal complexes currently used as radiopharmaceuticals. The main metal complexes used as radiopharmaceuticals are compounds of technetium (^{99m}Tc) like sodium pertechnetate and methylenediphosphonate $\text{MDP-}^{99m}\text{Tc}$ and other compounds of indium (^{111}In), thallium (^{201}Tl), gallium (^{67}Ga , ^{68}Ga), iodine (^{123}I and ^{131}I), chromium (^{51}Cr), sulphur (^{35}S), phosphorus (^{32}P), fluorine (as fluorodeoxyglucose, ^{18}F -FDG and sodium fluorine, Na^{18}F), which are widely used in the nuclear medicine for diagnosis by imaging. They have been of great importance for the early diagnosis of numerous diseases, mainly cancer. Currently, technetium compounds are the majority of radiopharmaceuticals used in all countries. In Brazil, Institute of Energy and Nuclear Research (IPEN) is one of the most important distributors of radiopharmaceuticals, producing, importing and distributing them to clinics and hospitals over the country.



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1. Introduction

In nuclear medicine, radiopharmaceuticals are used in diagnostic imaging and radiotherapy, being of utmost importance for medicine in general to assist in diagnoses of organs and treatments of pathological conditions, especially cancer. In the imaging modality, radiopharmaceuticals are administered via oral, intravenous, or by inhalation



to enable visualization with their radioactive tracers of various organs, such as kidneys, lungs, thyroid and heart functions, bone metabolism and blood circulation. In therapeutic modality, aiming to treat cancer or over functioning thyroid gland, a high dose of radiation is delivered through specific radiopharmaceuticals targeting the diseased organ¹.

Radiopharmaceuticals generally consist of two components, a radioactive element (radionuclide), that permits external scan, linked to a non-radioactive element, a biologically active molecule, drug or cell (red and white blood cells labeled with a radionuclide, for example) that acts as a carrier or ligand, responsible for conducting the radionuclide to a specific organ².

Some characteristics are necessary for considering radiopharmaceuticals clinically useful for imaging: the decay of the radionuclide should be in specific ranges of energy emissions (511 keV for positron emission tomography – PET and 100-200 keV for gamma cameras) and in sufficient quantity for tomography detection; 2) it should not contain particulate radiation (beta emissions, for example), because it increases the radiation dose in patients; 3) the half-life should be for a few hours only; 4) the radionuclides should not be contaminated by other radionuclides of the same element nor even its stable radionuclides (carrier-free); 5) they should have specific activity, and the highest specific activity comes from carrier-free radionuclides; 6) the radiopharmaceutical should not have toxicity and does not manifest physiological effects; 7) the radiopharmaceutical should be available for instant usage and easy to compound; 8) the radiopharmaceutical should reach the target organ quickly and accurately, according to its intended application³.

Diagnostic radiopharmaceuticals have no pharmacological effects and their administration is not associated with relevant clinical side effects. Its clinical use, however, carries the inherent risk of exposure to radiation and possible contamination during radiopharmaceutical formulation, since most radiopharmaceuticals are administered intravenously³.

The most notable difference between normal medicines and radiopharmaceuticals is that the former has therapeutic effect while the latter does not. Besides that, radiopharmaceuticals have a short half-life, because of their rapid decay. For this reason, radiopharmaceuticals must be prepared immediately before their administration. The

preparation and use of radiopharmaceuticals with safety and expertise are therefore vital for operator and patient protection³.

Understanding the mechanism of interaction between the radioactive elements and the different molecules, drugs, cells and organs it is necessary for the development of more efficient imaging or therapeutic radiopharmaceuticals⁴.

2. Historical Bases of Nuclear Medicine and Radioactivity

Wilhelm Roentgen's work on X-ray studies has stimulated researchers such as Henri Poincaré whose studies are related to the hypothesis of X-ray emission and fluorescence. The first scientist to carry out the hypotheses proposed by Poincaré was Charles Henry, using zinc sulfide as an X-ray intensifier, concluding that in the presence of light, when the radiographs became sharper because of the substance⁵.

In 1896, Henri Becquerel used uranium salts on photographic plates, which resulted in marked radiographs without the presence of light. In 1905, Marie and Pierre Curie were the first to suggest radium for treatment of cancer. The Curies' work may be considered the beginning of modern nuclear medicine. In 1931, Ernest Lawrence built the first cyclotron, equipment that accelerated alpha particles, such as protons, deuterons, or helium ions, with the aim of penetrating the nucleus to produce stable and radioactive isotopes. A decade later, Lawrence's cyclotron had produced 223 radioactive isotopes, many of which are now of great value for medicinal uses and studies in the biological sciences⁶.

In 1930, Ernest Lawrence and Milton Livingstone, with their invention of the cyclotron, allowed the artificial production of new radioactive elements, but the quantities were very small. The medical use of radionuclides began during World War II with the Oak Ridge reactor in the United States, initiating the production of radionuclides in global scale. Hal Anger, in 1958, developed the image-scintillation chamber, which did not require the movement of the detector. It had a higher geometric resolution, and it was possible to obtain different projections of the same distribution of the radiopharmaceutical. However, computers were not yet capable of acquiring the information and transforming it into images. So, the information was sent to the cathode ray tube for it to be recorded on photographic plates or films. The modern

scintillation cameras used nowadays are the Anger camera type⁷.

Nuclear Medicine only had a diagnostic power when Paul Harper and his group introduced the ^{99m}Tc radionuclide as a marker. This radionuclide decays by isometric transition emitting photon with energy of 140 keV, gamma-type radiation and physical half-life of about 6 hours, which allows studies with reasonable intervals. In addition, it is obtained by the decay of the parent element ⁹⁹Mo, produced in ⁹⁹Mo/^{99m}Tc generators⁷.

The first radiopharmaceuticals were commercialized in 1950. ¹³¹Iodine was the first commercially available isotope, with Abbott Laboratories being the first company to produce radiopharmaceuticals for medical uses⁸.

The radioactive elements, thus classified, may have highly energetic unstable nuclides due to the excess of energy, which stabilizes by the emission of particles or electromagnetic radiation or charged particles during radioactive decay. In this context, there are three types of radiation: alpha, beta minus and gamma^{1,2}. Radiation propagates at a certain speed and contains energy with electric and magnetic charges that can be generated by natural sources or by artificial devices, such as a cyclotron. Ionizing radiation is generated from the energy emitted by an unstable nucleus in artificial form or by a cyclotron⁵.

3. Nuclear Medicine and Radiopharmaceuticals

Radiopharmaceuticals may be divided in two distinct groups: one that includes radionuclides with radioactive decay period (half life) less than 2 h, and other that includes radionuclides with half life higher than 2 h⁹.

Nuclear medicine cameras are proper for identifying radioactive particles. The type of radiation emitted defines the type of camera: SPECT cameras are used to detect nuclides that decay through direct emission of single gamma rays, and PET cameras are able to detect the pair of gamma rays emitted after a decay of positron¹⁰.

3.1 Nuclear medicine techniques

Diagnostic techniques in nuclear medicine use radioactive tracers that emit gamma radiation from within the body. The camera constructs an image from the points where the radiation is emitted. This image is magnified on a computer and it can be

observed on a monitor that indicates the anomalies¹¹.

The nuclear medicine techniques include Single Photon Emission Computerized Tomography (SPECT), Positron Emission Tomography (PET), and computed tomography-PET (PET-CT) (for better anatomical visualization), micro-PET (with ultra-high resolution) and microcomputerized axial tomography micro-CAT. These techniques are used to analyze biochemical dysfunctions as early signs of the disease, its mechanisms and association with disease states from cancer to cardiovascular diseases and mental disorders^{6,12}.

A SPECT exam is used primarily to visualize the blood flow through veins and arteries, and to perform pre-surgical evaluation of seizures. SPECT is also useful in the diagnosis of blood deprived areas of brain (ischemic), spinal stress fractures (spondylolysis) and tumors¹⁰.

The PET imaging detects the pair of gamma rays produced by the interaction between a positron and an electron in the tissues of the body. The electron and the positron neutralize each other producing two gamma rays in opposite directions. PET detects the electronic signal converting with scintillation crystals the energy released by gamma rays¹⁰.

^{99m}Technetium is the radionuclide that has the best characteristics to combine with gamma cameras and ¹⁸fluorine has the most desirable characteristics for PET³.

Although the SPECT and PET techniques capture images with high intensity, they have low spatial resolution because they are directed to the surface of the body they are accurately visualized. On the other hand, computerized tomography (CT) and magnetic resonance have greater spatial resolution, but with less sensitivity. To obtain such restrictions, the techniques are merged for images with excellent spatial resolution combined with high sensitivity¹⁰.

X-ray CT has a computational process that makes a three-dimensional image, resulting in images with much greater resolution and quantity of details of internal structures and organs of the body⁶. There are other non-nuclear techniques, which are not described in this review, but could be accessed in this reference¹⁰.

3.2. Radionuclides in medicine

Radionuclides have many applications in several areas that use nuclear technology. The use

of radiation and radionuclides in medicine is continuously increasing both for diagnosis and therapy worldwide.

In developed countries (1/4 of the world's population), one person in 50 is subject to nuclear medicine and the frequency of radionuclide therapy is about 10% of that number, according to the World Nuclear Association¹¹.

Radiation is used in nuclear medicine to obtain information about the organs of a person for treatment of a disease. In many cases, information is used for a quick diagnosis. Thyroid, bones, heart, liver, kidney and many other organs can be easily observed in the generated image and the anomalies of its functions are revealed. About 10,000 hospitals worldwide use radionuclides and about 90% of the procedures are for diagnosis. The radionuclide most used in diagnostics is ^{99m}Tc . It has been used in about 40 million exams per year, which means 80% of all exams in nuclear medicine worldwide¹¹.

Radionuclides are essential components of diagnostic exams. In combination with the equipment recording the images from the emitted gamma rays, the processes that occur in various parts of the body can be studied. For diagnosis, a dose of the radioactive material is given to the patient and the localization in the organ can be studied as a two-dimensional image or, using tomography, as a three-dimensional image. These gamma or positron tracers have short-lived isotopes and are linked to chemical compounds that allow specific physiological processes to be evaluated^{10,11}.

In the USA, more than 20 million medical applications per year are performed using radionuclides and in Europe about 10 million per

year¹¹. In Brazil, the Nuclear and Energy Research Institute (IPEN) reported that, in 2017, there were 360 diagnostic clinics and nuclear medicine hospitals, 70% in the South and Southeast regions of Brazil, 72 PETs installed, others to be licensed, 33 hospitals with rooms for therapy and approximately 1.8 million patients per year¹⁴.

3.3 Radiopharmaceuticals for diagnosis in human body

Medical doctors and chemists have identified a large number of chemicals that are absorbed by specific organs. Thyroid, for example, absorbs iodine while the brain absorbs glucose. Diagnostic radiopharmaceuticals can be used to monitor blood flow to the brain, liver, lung, heart, and kidney¹⁴.

Particulate radiation can be useful for destroying or weakening cancer cells (radiotherapy). The radionuclide that generates the radiation can be located in a certain organ in the same way used for diagnostics. In many cases, beta radiation causes the destruction of cancer cells. ^{177}Lu (Lutetium (^{177}Lu), for example, is prepared from ^{176}Yb (ytterbium (^{176}Yb)) which is irradiated to transform it into ^{177}Yb , which rapidly returns to ^{177}Lu . ^{90}Y (Yttrium (^{90}Y)) is used to treat cancer, especially non-Hodgkin's lymphoma and liver cancer. ^{131}I (Iodine (^{131}I)), ^{153}Sm (samarium (^{153}Sm)) and ^{32}P (phosphorus (^{32}P)) are also used in radiotherapy. ^{131}Cs (Cesium (^{131}Cs)), ^{103}Pd (palladium (^{103}Pd)) and ^{223}Ra (radium (^{223}Ra)) are used in special cases¹¹.

Figure 1 lists the radionuclides most commonly used for diagnosis and treatment of different organs of the human body.

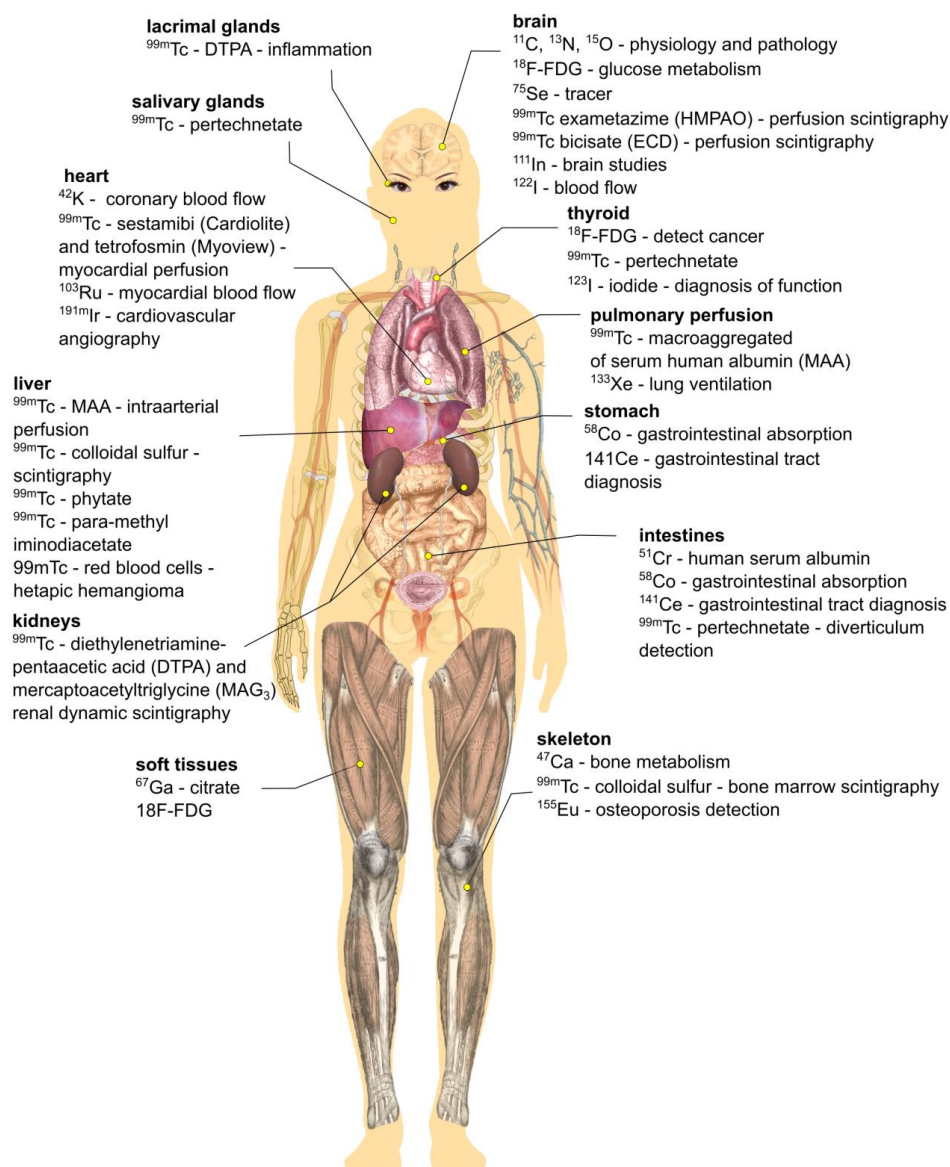


Figure 1. Different radiopharmaceuticals and target organs for imaging^{4,13,14}. Image released into the public domain, changed for the review purposes¹⁵.

4. Production of radionuclides

Radionuclides found in nature, such as uranium and radium, are heavy elements with high toxicity and long half-life (over 1,000 years), so they are not used clinically. Radionuclides used in nuclear medicine are artificially produced by neutron bombardment or nuclear fission⁴.

Many radionuclides are produced in nuclear reactors and cyclotrons. Generally, neutron-rich radioisotopes and those resulting from nuclear fission are produced in reactors (Table 1) and the neutron-poor radioisotopes are produced in cyclotrons (Table 2). There are about 30

radioisotopes produced by activation and 5 are reactor melt products. A list with 70 elements, their isotopes, half-lives, decay, main energy and applications can be found in the reference¹⁴.

Table 1. 30 selected radionuclides produced by nuclear fission¹⁴.

²¹³ bismuth	⁵⁹ iron	¹⁵³ samarium
¹³¹ caesium	²¹² lead	⁷⁵ selenium
¹³⁷ caesium	¹⁷⁷ lutetium	²⁴ sodium
⁵¹ chromium	⁹⁹ molybdenum	⁸⁹ strontium
⁶⁰ cobalt-60	¹⁰³ palladium	^{99m} technetium
¹⁶⁵ dysprosium	³² phosphorus	²²⁷ thorium
¹⁶⁹ erbium	⁴² potassium	¹³³ xenon
¹⁶⁶ holmium	²²³ radium	¹⁶⁹ ytterbium
¹³¹ iodine	¹⁸⁶ rhenium	¹⁷⁷ ytterbium
¹⁹² iridium	¹⁸⁸ rhenium	⁹⁰ yttrium

Table 2. 18 selected radionuclides produced by cyclotrons¹⁴.

²²⁵ actinium	⁶⁷ copper
²¹¹ astatine	⁶⁷ gallium
²¹³ bismuth	¹²⁷ xenon
¹¹ carbon	¹¹¹ indium
¹³ nitrogen	¹²³ iodine
¹⁵ oxygen	¹²⁴ iodine
¹⁸ fluorine	^{81m} krypton
⁵⁷ cobalt	⁸² rubidium
⁶⁴ copper	²⁰¹ thallium

In Brazil, the main producer of radiopharmaceuticals is IPEN, located in the city of São Paulo, state of São Paulo. IPEN is the only producer in the country of the ^{99m}technetium generator, which is used in 80% of the nuclear medicine procedures in Brazil. IPEN is also responsible for the production of 38 radiopharmaceuticals with distribution for all the Brazilian states¹³. According to data from the National Commission for Nuclear Energy (CNEN) Management Report for 2017, published in August 2018, about the radiopharmaceutical industry in Brazil, the main producers of radiopharmaceuticals are: Nuclear and Energy Research Institute (IPEN – São Paulo), Nuclear Technology Development Center (CDTN – Belo Horizonte), Northeast Regional Center for Nuclear Sciences (CRCN-NE – Recife), Nuclear Engineering Institute (IEN – Rio de Janeiro) operating nuclear reactors and particle accelerators, producing and commercializing supplies for the medical area. The Institute of Radiation Protection and Dosimetry (IRD – Rio de Janeiro) and the Laboratory of Poços de Caldas

(LAPOC – Poços de Caldas) are research laboratories that provide services to other laboratories, industries and companies and do not produce radiopharmaceuticals¹³.

The constitutional amendment 49 published in February 9, 2006 defines that production, commercialization and use of radionuclides with a half-life less than or equal to two hours are authorized and commercialization and use of radionuclides for research and medical, agricultural and industrial uses¹⁴.

Table 3 shows the radiopharmaceuticals produced in Brazil and places where they are manufactured.

Table 3. Radiopharmaceuticals produced in Brazil¹³.

Product	Place of production
sodium iodide (¹²³ I)	IEN
sodium iodide (¹³¹ I)	IPEN
gallium citrate (⁶⁷ Ga)	IPEN
thallium chloride (²⁰¹ Tl)	IPEN
sodium chromate (⁵¹ Cr)	IPEN
generator ⁹⁹ Mo – ^{99m} Tc	IPEN
sodium sulfate (³⁵ S)	IPEN
phosphoric acid (³² P)	IPEN
sodium phosphate (³² P)	IPEN
¹⁸ fluorodeoxyglucose (¹⁸ F-FDG)	IPEN, IEN, CDTN, CRCN-NE
EDTMP (¹⁵³ Sm)	IPEN
sodium fluoride (Na ¹⁸ F)	IPEN, CDTN
¹¹¹ indium (¹¹¹ In)	IPEN
dotatate (¹⁷⁷ Lu)	IPEN

In addition to these radiopharmaceuticals, CNEN supplies sealed sources (¹³³Ba, ¹³⁷Cs and ⁵⁷Co), ¹⁹²Ir and ¹²⁵I seeds, both used in oncological treatments, using brachytherapy procedures¹³.

Production of technetium in Brazil still depends on raw material from foreign origin (⁹⁹molybdenum), and on the costs of importation. However, within the next few years, the CNEN aims at implementing the Brazilian Multipurpose Reactor (RMB) in the city of Iperó, state of São Paulo. Also, the Federal Government plans to initiate RMB's usage in 2024, becoming independent and guaranteeing the nationalization of the ⁹⁹molybdenum radionuclide for the country's

demand^{16,17}. This reactor must produce *circa* 1,000 Ci of ^{99}Mo per week (Ci (*curie*) is a unit of radionuclide activity, defined as: $1\text{ Ci} = 3,7 \times 10^{10}$ disintegrations per second²⁰). As a comparison, in 2014, national demand was 450 Ci ^{99}Mo /week^{17,18};

the worldwide demand, in 2018, was 9 400 Ci ^{99}Mo /week¹⁹.

Figure 2 shows all cyclotrons installed and in operation in Brazil in 2019.

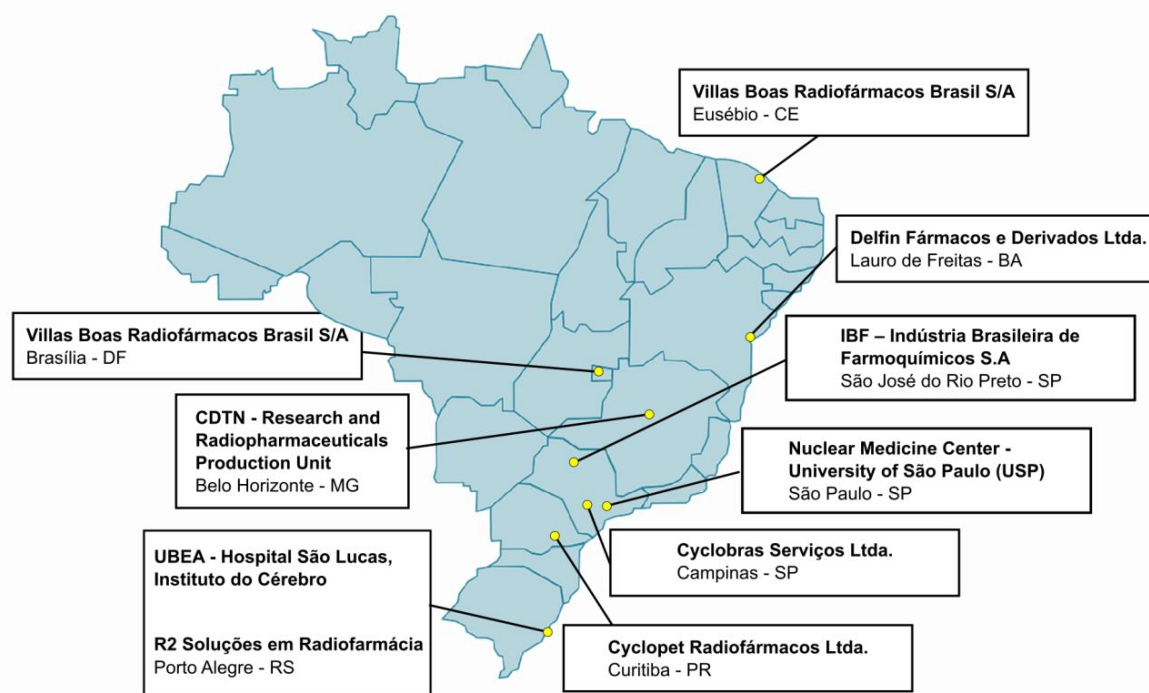


Figure 2. Cyclotron installations in Brazil²¹. Image released into the public domain, changed for the review purposes²².

The main difficulties for production of new radiopharmaceuticals in Brazil are the lack of a 70 MeV high energy cyclotron accelerator in the country and the adequacy of the facilities to follow the Brazilian National Sanitary Surveillance Agency (Anvisa) Resolution nº 63¹⁴.

5. Conclusions

Radionuclides have many applications in several areas which use nuclear energy. The importance and uses of radionuclides in medicine is continuously increasing for diagnosis and therapy worldwide. In 2018, about 10,000 hospitals used radionuclides and about 90% of the procedures were for diagnosis. In Brazil, the Institute of Energy and Nuclear Research (IPEN) reported that in 2017 there were more than 440 diagnostic clinics and nuclear medicine hospitals, 55% in the Southeast region of Brazil, 19% in Northeast and 15% in South region; 72 PETs installed, with about 1.8 million people supported.

There are about 40 radionuclides produced in nuclear reactors and about 20 radionuclides produced in cyclotrons.

$^{99\text{m}}\text{Tc}$ is the most used radionuclide for diagnosis, accounting for 67.3% of total CNEN revenue in 2017. Besides $^{99\text{m}}\text{Tc}$, ^{131}I (13.7%), ^{67}Ga (2.9%), ^{177}Lu Dotatate (2.9%) and ^{18}F -FDG (1.1%) were more frequently used in Brazil in 2017.

SPECT and PET are the two most used techniques in nuclear medicine during a large period, but nowadays other techniques with more accurate results are emerging, among them X-ray computed tomography e with three-dimension images.

6. Acknowledgements

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