Nuclear Medicine in Endocrine Disorders

Diagnosis and Therapy

George Barberio Coura-Filho
Mayara Torres Silva de Oliveira
Ana Luiza Morais de Campos

Springer

Nuclear Medicine in Endocrine Disorders

George Barberio Coura-Filho
Mayara Torres Silva de Oliveira
Ana Luiza Morais de Campos

Nuclear Medicine in Endocrine Disorders

Diagnosis and Therapy

Springer

George Barberio Coura-Filho
Nuclear Medicine Physician and Researcher
São Paulo State Cancer Institute–University of São Paulo Medical School (HCFMUSP)
São Paulo, São Paulo, Brazil

Ana Luiza Morais de Campos
DIMEN Medicina Nuclear
São Paulo, São Paulo, Brazil

Mayara Torres Silva de Oliveira
DIMEN Medicina Nuclear
São Paulo, São Paulo, Brazil

ISBN 978-3-031-13223-0 ISBN 978-3-031-13224-7 (eBook)
https://doi.org/10.1007/978-3-031-13224-7

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

This book is dedicated to my family that has been of constant support and a safe haven, as well as to all my teachers and colleagues that share a passion for the Nuclear Medicine and Endocrinology fields.

George Barberio Coura-Filho

To my father, who introduced Nuclear Medicine into my life and inspires me every day.

To my mother, who gave me strength to write this book and taught me everything about life.

With all my love,

Ana Luiza Morais de Campos

I dedicate this book to my parents, who gave me the opportunity to be who I am and to study medicine. To my beloved husband who always supported me. To my teachers and coworkers who always inspire me.

With love,

Mayara Torres Silva de Oliveira

Preface

Nuclear Medicine is a medical specialty that has an important role in the management of endocrine disorders, but frequently is not completely addressed at medical schools. Many non-Nuclear Medicine physicians are eager to better understand how it can be used to help differentiate between illnesses, how it can improve clinical decisions, or how it can be used in the treatment of benign and malignant endocrine diseases.

This book is meant to be an accessory tool to medical doctors better understand Nuclear Medicine and its role in endocrinology. It takes the mission of clarifying how basic nuclear medicine works, why patient preparation is necessary, and how it is performed before procedures and also in which clinical settings benefits of nuclear medicine are mostly obtained.

It is also a book that helps those initiating or already working in the Nuclear Medicine field to improve knowledge in its endocrine use. And hopefully this book will help directly or indirectly many patients that are always at the center of our concerns.

São Paulo, São Paulo, Brazil — George Barberio Coura-Filho
São Paulo, São Paulo, Brazil — Mayara Torres Silva de Oliveira
São Paulo, São Paulo, Brazil — Ana Luiza Morais de Campos

Contents

Part I
Basics and Principles of Nuclear Medicine

Chapter 1
Basic Principles of Radiopharmaceuticals

1.1 Introduction

Radiopharmaceuticals are the pharmaceuticals that incorporate a radionuclide. Most radiopharmaceuticals are a combination of a radioactive nuclide or radionuclide, and a biologically active molecule or drug that acts as a carrier and determines localization and biodistribution [1, 2]. From a regulatory point of view, the term radiopharmaceutical represents any radiolabeled molecule intended for human use [3].

For a few radiotracers, the radioactive atoms themselves confer the desired localization properties. Both naturally occurring and synthetic molecules can potentially be radiolabeled [1, 2].

An unstable atom that undergoes radioactive decay to achieve stability is called radionuclide. Radionuclides try to become stable by emitting electromagnetic radiation (gamma or X-rays) or charged particles during radioactive decay [4]. The radiation these atoms emit can be used in medical imaging and therapy [1].

Although many naturally occurring radioactive nuclides exists, those that are commonly administered to patients in nuclear medicine are artificially produced. Naturally occurring radionuclides are heavy and toxic elements with long half-lives and usually no clinical role in diagnostic or treatments in nuclear medicine. Most radionuclides used in nuclear medicine are produced by particle accelerators, nuclear reactors, or radionuclide generators [1, 5].

Radiopharmaceuticals retract physiology, biochemistry, or pathology in the body without causing any physiological effect. They are referred to as radiotracers because they are administered in sub-pharmacological doses that "traces" a particular physiological or pathological body process [1]. One of the most important characteristics of a tracer is the ability to study the components of a homeostatic system without disturbing their function [3].

G. B. Coura-Filho et al., *Nuclear Medicine in Endocrine Disorders*,
https://doi.org/10.1007/978-3-031-13224-7_1

They can be divided into two subgroups: diagnostics and therapeutics [2]. Diagnostic radiopharmaceuticals often include gamma-ray or positron-emitting radionuclides and therapeutic radiopharmaceuticals contain usually an alpha particle or beta particle [2].

If a gamma-ray-emitting pharmaceutical is used, the imaging modality used is the single-photon emission computed tomography (SPECT), whereas, in the case of positron emitting, the imaging modality is the positron emission tomography (PET) [2].

Imaging modalities are usually divided into anatomical and molecular imaging techniques. In contrast to computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound, the nuclear medicine molecular imaging modalities (PET and SPECT) can identify changes due to diseases at molecular and cellular levels before tissue structural changes become visible. They rely on the injection of radiotracers at nanomolar blood concentrations [6].

The emitted radiation may also be detected intraoperatively using a small detector (Gamma-probe), for example, for sentinel node identification or localization of occult lesions [4]. Alternatively, the radiation emitted by the radionuclide can be quantified ex vivo in body fluids [4].

In general, radiopharmaceuticals are administered intravenously and will distribute over the body and concentrate in the target tissue/cells. The concentration of the radiopharmaceutical in surrounding tissue will be in equilibrium with the plasma concentration that will decrease due to clearance of the radiopharmaceutical from plasma by excretory organs such as liver and kidneys [4].

A small number of radiopharmaceuticals are administered via other routes such as inhaled (lung ventilation study), oral (for example thyroid study), intra-arterial (trans arterial radioembolization), and peritumoral injection (sentinel node visualization) [4].

Adverse reactions to radiopharmaceuticals are extremely rare and when they occur, they are usually mild and rarely fatal [1].

Although technetium-99 m radiopharmaceuticals in combination with planar scintigraphy or SPECT represent the majority of diagnostic radiopharmaceuticals, research toward new PET radiopharmaceuticals is by far more prominent nowadays. Besides this, a spectacular growth of radiopharmaceuticals for targeted radionuclide therapy is expected in the near future [4].

1.2 Cyclotron-Produced Radionuclides

Cyclotrons and other charged-particle accelerators produce radionuclides by bombarding stable nuclei with high-energy charged particles. Charged particles must be accelerated to high kinetic energies to overcome and penetrate the repulsive coulomb barrier of the target atoms' nuclei [5].

1.3 Nuclear Reactor-Produced Radionuclides

Nuclear reactors are another major source of clinically used radionuclides. Neutrons, being uncharged, have an advantage in that they can penetrate the nucleus without being accelerated to high energies. There are two principal methods by which radionuclides are produced in a reactor: nuclear fission and neutron activation [5].

1.4 Radionuclide Generators

The radionuclide generators are production systems based on the principle of decay from a long half-life primary radionuclide (parent) to a shorter half-life secondary radionuclide (daughter). Examples are given in Table 1.1 [7].

The great advantage of this system, when compared to the production of radionuclides in reactors or cyclotrons, is that the system is generally small, allows easy transport, and has a period of use from weeks to years. However, the parent radionuclide must be produced in a reactor or cyclotron [7].

1.5 Ideal Diagnostic Radiopharmaceuticals

Nowadays there are 116 chemical elements and more than 3000 nuclides and radionuclides from these elements. To the nuclear medicine routine, there are a few of them available, because they should have an adequate decay form, radiation energy, and physical half-life [7].

An ideal diagnostic radiopharmaceutical should have a low radiation dose, maximum concentration in the tissue of interest while minimizing the uptake of nontarget tissues—to better detect and evaluate lesions—safety, convenience, and cost-effectiveness [5]. Furthermore, the effective half-life must be long enough for the application for which the radiopharmaceutical is intended [1].

Radionuclides should have a chemical form, pH, concentration, and other characteristics that facilitate rapid complexing with the pharmaceutical under normal laboratory conditions. The compounded radiopharmaceutical should be stable, with a shelf life compatible with clinical use, and should be readily available from several manufacturers to minimize cost [5].

Table 1.1 Examples of generator systems used in Nuclear Medicine

Father	Father half-life	Daughter	Daughter half-life
Mo-99	66 h	Tc-99 m	6 h
Rb-81	4.5 h	Kr-81 m	13 s
Ge-68	270 days	Ga-68	68 min
Sr-82	25 days	Rb-82	1.3 min

1.6 Diagnosis: SPECT Radionuclides

SPECT is based on the detection of single photon emission upon decay of a radionuclide by rotating detectors, providing a 3D image representing the distribution of the radionuclide in the body [4]. The predominant radioisotope used in SPECT imaging is the metastable form of technetium (99mTc, T1/2 = 6 h). This isotope can be easily generated via a molybdenum-technetium generator [4].

1.7 Diagnosis: PET Radionuclides

PET is based on detection of two 511 keV photons that are emitted in opposite directions upon annihilation of a positronium, that results from combination of an electron and a positron, the latter being emitted from a neutron deficient nucleus [4]. The most used radionuclide in PET is the 18F-Fluordeoxyglucose.

1.8 Therapeutic Radiopharmaceuticals

At higher radiation activities radiopharmaceuticals exert cytotoxic effects [6]. A variety of radiopharmaceuticals have been introduced to treat malignant and inflammatory lesions in nuclear medicine. To destroy the diseased tissues, radionuclides with high linear energy transfer (LET) such as beta, alpha, Auger, or low energy conversion electron emitters are needed [8].

The goal of radiopharmaceutical therapy is to deliver a sufficient dose to the target organ, tissue, or cell while limiting the dose to nontarget tissue [8]. The "theranostics" concept has the potential to enlarge treatment options, by combining therapeutic agents with a corresponding diagnostic marker [6].

1.9 Factors Affecting the Biodistribution of Radiopharmaceuticals

Important factors affecting radiopharmaceuticals biodistribution can be described in the 5 major categories:

- Factors associated with radiopharmaceutical preparation and formulation.
- Factors caused by radiopharmaceutical administration techniques and procedures.
- Factors caused by pathophysiological and biochemical changes.
- Factors caused by medical procedures.
- Factors associated with drug therapy or drug interaction [3].

1.10 Quality Control

Radiopharmaceuticals, both for diagnosis and treatment, are products administered mainly intravenously and, therefore, must have guaranteed chemical and radiochemical quality, in addition to the sterility of the product. The pharmaceutical and radiopharmaceutical industries are highly regulated and supervised, so that the products are unlikely to fail the specifications of quality controls when they reach consumers [7].

The purity and quality of a radiopharmaceutical preparation has a pronounced effect on the "in vivo" radiopharmaceutical behavior, the subsequent scan interpretation, and the diagnostic accuracy of the imaging procedure [5].

In centers, where there is manipulation of radiopharmaceuticals, several and rigorous quality control tests must be carried out before the product is used by the patient [7]. These tests generally are divided into two different categories:

- The physicochemical tests are essential to determine the chemistry, purity, and the integrity of a formulation.
- The biological tests establish the sterility and apyrogenicity of the radiopharmaceutical [5].

References

1. Ziessman HA, O'Malley JP, Thrall JH, Fahey FH. Nuclear medicine. 4th ed. Philadelphia, PA: Elsevier/Saunders; 2014, 452 p. (Requisites).
2. Molavipordanjani S, Tolmachev V, Hosseinimehr SJ. Basic and practical concepts of radiopharmaceutical purification methods. Drug Discov Today. 2019;24(1):315–24.
3. Vallabhajosula S, Killeen RP, Osborne JR. Altered biodistribution of radiopharmaceuticals: role of radiochemical/pharmaceutical purity, physiological, and pharmacologic factors. Semin Nucl Med. 2019;40(4):220–41.
4. Vermeulen K, Vandamme M, Bormans G, Cleeren F. Design and challenges of radiopharmaceuticals. Semin Nucl Med. 2019;49(5):339–56.
5. Bushberg JT, organizador. The essential physics of medical imaging. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012, 1030 p.
6. Sarko D, Eisenhut M, Haberkorn U, Mier W. Bifunctional chelators in the design and application of radiopharmaceuticals for oncological diseases. Curr Med Chem. 2012;19(17):2667–88.
7. Hironaka FH, Ono CR, Buchpiguel CA, Sapienza MT, Lima MS. Medicina Nuclear Princípios e Aplicações. 2nd ed. Rio de Janeiro: Atheneu; 2017.
8. Ercan MT, Caglar M. Therapeutic radiopharmaceuticals. Curr Pharm Des. 2000;6(11):1085–121.

Chapter 2
Basic Principles of Scintigraphy and SPECT (Single-Photon Emission Computed Tomography)

2.1 Introduction

Nuclear imaging assesses how organs function (being the main advantage of this imaging modality) after administering a radiopharmaceutical by intravenous, intra-arterial, or subdermal injection, which may be introduced through the gastrointestinal tract or through the breathing (gas or aerosol). Other radiologic tests assess mainly anatomy. The ionizing radiation, which accompanies the decay of the administered radioactivity, can be detected, measured, and imaged with instruments such as gamma cameras. The radiation activity administered to a patient in need of scintigraphy is safe (except for pregnancy). It permits diagnosis and treatment planning for the system of the body being evaluated [1, 2].

Generic nuclear medicine images are acquired in an equipment called gamma camera in planar or single photon emission computed tomography (SPECT) acquisitions, consisting of several components like: a detection system, a form of collimation to select γ rays, electronics, and a computing system. By this complex system, it is possible to determine the in vivo distribution of the radiotracer and the patient's physiology can be inferred, providing diagnostic information [2, 3].

2.2 Main Modalities of Scintigraphic Acquisitions

Several types of planar gamma camera imagings are routinely performed: static, dynamic, whole-body, and SPECT.

1. *Static or planar acquisition:* a detector in a fixed position relative to the patient, planar imaging of a stable distribution of activity is observed, image acquisition shows a distribution which does not vary significantly over a few minutes. Ex: examination of thyroid.

G. B. Coura-Filho et al., *Nuclear Medicine in Endocrine Disorders*,
https://doi.org/10.1007/978-3-031-13224-7_2

2. *Dynamic imaging*: involves the acquisition of a temporally varying distribution of activity as a series of planar images (or frames). Several frame sets (or segments) of different frame duration are used in a single study. Usually used in distributions that vary significantly over a few minutes.
3. *Whole body scans*: the detectors move simultaneously and scan the patient's body from top to bottom. It is similar to static imaging, with either the detector(s) slowly translated over the stationary patient, but permits to observe the distribution of a radiopharmaceutical throughout the entire body in a single image. Scan speeds are 5–10 cm/min.
4. *SPECT*: SPECT imaging includes acquisition of multiple projection images from different angles around the subject of interest. Detectors rotate around the patient to obtain a digital representation of a 3D radioactive distribution of the body [1, 4].

2.3 Gamma Camera Systems

The gamma camera is the traditional equipment for nuclear medicine imaging and is a stationary device used for imaging the distribution of radioactivity. It consists of a number of components contributing to its ability to produce an accurate imaging of the distribution of radioactivity [5]. Its systems are comprised of four basic elements (Fig. 2.1):

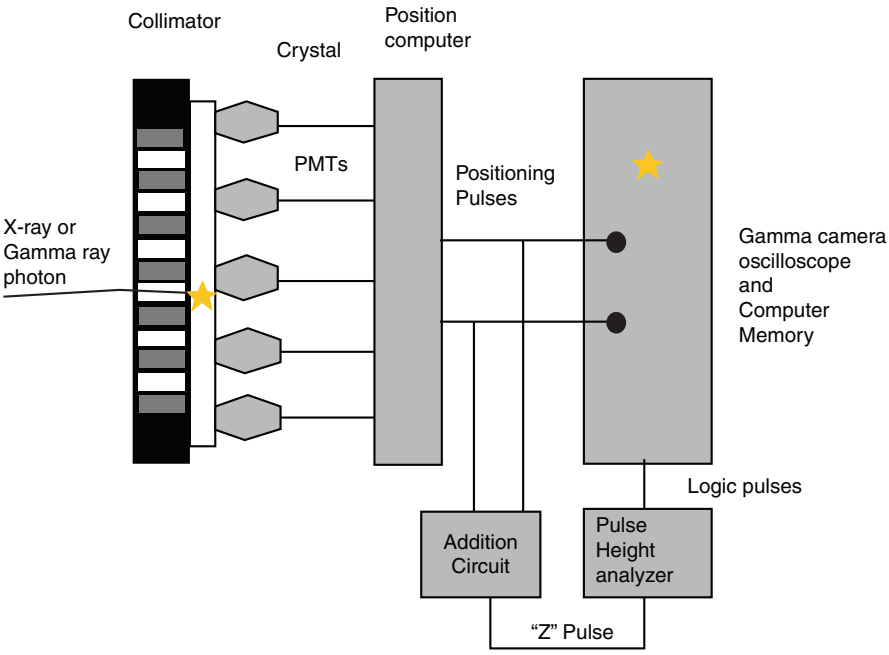

Fig. 2.1 Schematics of a scintillation gamma camera

1. The collimator, which defines the lines of response (LORs).
2. The radiation detector, which counts incident γ photons: the principle of radiation detection is based on the interaction of these radiations with the matter. The γ rays emitted by the radionuclide (administered into the patient) are detected when they interact and deposit energy in the crystal(s) of the imaging system. There are two main types of detectors: crystals that emit light that can be converted to an electrical signal when the γ ray interacts ("scintillators") and semiconductors, crystals that generate an electrical signal directly when the γ ray deposits energy in the crystal.
3. The computer system, which uses data from the detector to create 2-D histogram images of the number of counted photons: when a γ ray interacts in a scintillation crystal, it deposits some or all of its energy, this energy is re-emitted in the form of light. Scintillation crystals are coupled to photomultiplier tubes (PMTs), located behind the scintillator, their role is to convert light energy emitted by the crystal to an electrical signal that can be exploited in electronic circuits.

   The measured locations of the interaction of the γ rays must be converted to a 2-D or 3-D map through image reconstruction, to create an image of the distribution of radiotracer. For 2-D planar imaging, this can be displaying the number of events at each detector position. For SPECT imaging, where measurements are made from many views around the subject, the data must be combined through a reconstruction algorithm.
4. The gantry system, which supports and moves the gamma camera and patient.

   The camera can detect γ rays emitted by a radiotracer distributed in the patient's body. The lead collimator placed in front of the scintillation counter selects the direction of the γ rays entering the device and allows an image of the biodistribution of the tracer to be made [1, 3].

2.4 Gamma Camera SPECT Systems

SPECT (single-photon emission computerized tomography) is the equivalent in scintigraphy to what computed tomography (CT) is in radiology, and it is associated with hardware requirements that are beyond those needed for planar imaging. The gantry rotation is about the long axis of the patient. During rotation of the gantry, the patient bed typically does not move and many frames of planar images are acquired at equally distributed angles, covering arcs of up to 360°, for the reconstruction of tomographic images through the sum of all images (Fig. 2.2) [1, 3].

In SPECT imaging the camera head rotates around the object stepwise or continuously. At each step the camera collects events predetermined in time and rotates to the next step. Normally 64 or 128 angles are used for data collection. The data obtained at each angle provide a planar count distribution of the object [5].

SPECT typically provides very little anatomical information, but it can be improved, relating radionuclide uptake to high-resolution anatomic imaging when combined with computed tomography (SPECT-CT [3].

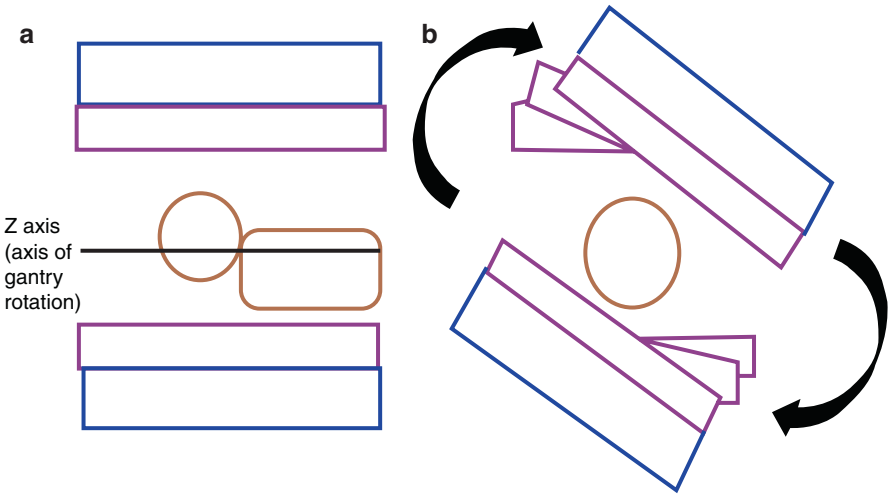

Fig. 2.2 A cross-section of a dual head gamma camera capable of acquiring two views simultaneously (dual head gamma camera) with opposing heads (**a**). A transverse slice showing multiple detector positions to illustrate multiple angular view after rotation of the gamma camera heads along the patient axis (**b**)

SPECT-CT is a hybrid machine in which functional and anatomical images are acquired simultaneously. It plays an important role in diagnosis, treatment, and follow-up [1] [6].

The primary signals from the radiation detectors are generally small and need to be amplified, for this, a preamplifier is needed prior to the main amplification process if the signals from the detector are very small. Preamplifiers are usually mounted immediately next to or as part of the output stage of the detector to minimize the noise produced prior to full amplification. The most important properties of an amplifier are gain, bandwidth, linearity, dynamic range, slew rate, rise time, ringing, overshoot, stability, and noise [3].

Once an amplified signal has been produced, it is then used to generate analog and digital information about the detected event. The analog information is generated by sending the pulse from the amplifier into a single or multichannel pulse height analyzer [3].

A study of diagnostic ^{131}I SPECT/CT in 123 patients found sensitivity of planar and SPECT/CT for the detection of iodine avid disease were both 62%, although SPECT/CT had significantly higher specificity than the planar imaging (94% vs 74%), which is the major gain of its use [6].

2.5 Main Forms of Radiation Used in Nuclear Imaging in Endocrinology

Radiations emitted as a result of radioactive decay, such as X, γ, and β rays, are ionizing radiations. X and γ rays are far more penetrating than β rays. Diagnostic X and γ rays interact with matter by the photoelectric effect or by Compton scatter. In the photoelectric effect, an X- or γ-ray's energy is completely transferred to an orbital electron in an atom of the stopping medium, ejecting the electron from the atom as a so-called photoelectron; the X or γ ray disappears in the process [4].

Gamma radiation is an electromagnetic radiation of high energy and is produced by subatomic particle interactions. Electromagnetic radiation is often considered to be made up of a stream of wave-like particle bundles (photons) which move at the speed of light and whose interaction properties are governed mainly by their associated wavelength [3].

Beta radiation are particles with the same mass of electrons but emitted from the unstable nucleus of the atom as a consequence of β radionuclide decay. A β decay process can occur whenever there is a relative excess of neutrons (β–) or protons (β+). One of the excess neutrons is converted into a proton, with the subsequent excess energy being released and shared between an emitted electron and an antineutrino. Many radionuclides exhibit β decay and, in all cases, the emitted particle follows a spectrum of possible energies rather than being emitted with a fixed, discrete energy. In general, the average β energy is around one-third of the maximum energy [3]. These particles are not suitable for imaging purposes but instead play an important role in nuclear medicine therapies as discussed later.

For radionuclides which emit both β particles and γ photons, it is usually the particulate radiation which delivers the greatest fraction of the radiation dose to the organ which has taken up the activity. For example, about 90% of the dose delivered to the thyroid gland by ^{131}I arises from the β component, but the γ emissions contribute more significantly to the overall whole body dose [3].

^{131}I has a main γ emission of 364 keV and a half-life (8 days) suitable for thyroid cancer imaging, and its particle emission allows radionuclide therapy of thyroid cancer metastases. Iodine-123 (^{123}I) can be used for diagnostic imaging. ^{123}I has the advantages of a lower 159 keV gamma emission better suited for modern gamma cameras, providing higher quality imaging. The uses of ^{123}I are higher costs for the isotope and shorter half-life (13 h) precluding multiday imaging [6].

References

1. Kharfi F. Principles and applications of nuclear medical imaging: a survey on recent developments. In: Kharfi F, editor. Imaging and radioanalytical techniques in interdisciplinary research - fundamentals and cutting edge applications [Internet]. InTech; 2013 [cited 2021 Jan 4]. http://www.intechopen.com/books/imaging-and-radioanalytical-techniques-in-interdisciplinary-research-fundamentals-and-cutting-edge-applications/principles-and-applications-of-nuclear-medical-imaging-a-survey-on-recent-developments.
2. Ziessman HA, O'Malley JP, Thrall JH, Fahey FH. Nuclear medicine. 4th ed. Philadelphia, PA: Elsevier/Saunders; 2014, 452 p (Requisites).
3. Bailey DL, American Association of Physicists in Medicine, editors. Nuclear medicine physics: a handbook for teachers and students. Vienna: International Atomic Energy Agency; 2014, 736 p (STI/PUB).
4. Zanzonico P. Principles of nuclear medicine imaging: planar, SPECT, PET, multi-modality, and autoradiography systems. Radiat Res. 2012;177(4):349–64.
5. Brownell A-L, Nikkinen P, Liewendahl K. The development of nuclear medicine imaging. Scand J Clin Lab Invest. 1990;50(sup201):119–25.
6. Wong KK, Fig LM, Youssef E, Ferretti A, Rubello D, Gross MD. Endocrine scintigraphy with hybrid SPECT/CT. Endocr Rev. 2014;35(5):717–46.

Chapter 3
Basic Principles of Positron Emission Tomography

3.1 Positron Emission Tomography (PET)

PET medical imaging normally includes short-lived positron-emitting isotopes, such as cyclotron-produced ^{11}C, ^{13}N, ^{15}O, and ^{18}F as well as generator-produced isotopes like ^{68}Ga and ^{82}Rb. The isotopes are usually produced by proton irradiation of natural or enriched targets [1].

Positron emission, also known as beta plus decay, is an isobaric decay process where a proton inside a radionuclide nucleus is converted into a neutron while releasing a positron and a neutrino [1].

Positron emission tomography (PET) is based on detecting the coincidence of two radiations of 511 keV that originate from a positron-electron annihilation [2]. After annihilation, the two 511 keV photons are emitted in opposite directions, at an angle of 180° [3]. In solids and liquids, positrons travel only very short distances before annihilation [4].

Positrons originate from radioactive elements and are annihilated in patient's tissues producing two photons that are emitted in opposite directions. The two photons are detected at a certain time interval—the "coincidence timing window"—by two electronically connected detectors. The 511 keV photons are converted to light photons in the scintillating crystal and electrical pulse formation occurs [2].

In PET equipment, two 511 keV annihilation photons are detected in coincidence by two detectors in opposition along a straight line, called line of response line (LOR) or coincidence line (Fig. 3.1) [1, 2].

Pulse height analysis follows the same characteristics as the conventional gamma scintillation camera. The detectors are mounted in a multi-ring arrangement to have the region of interest in the field of view (FOV) composed of the rings. In the full-body image, several fields of view are used to complete the entire study [2].

Annihilation coincidence detection leads to at least plus 100 times the sensitivity of PET compared to conventional nuclear medicine imaging and explains the higher

G. B. Coura-Filho et al., *Nuclear Medicine in Endocrine Disorders*,
https://doi.org/10.1007/978-3-031-13224-7_3

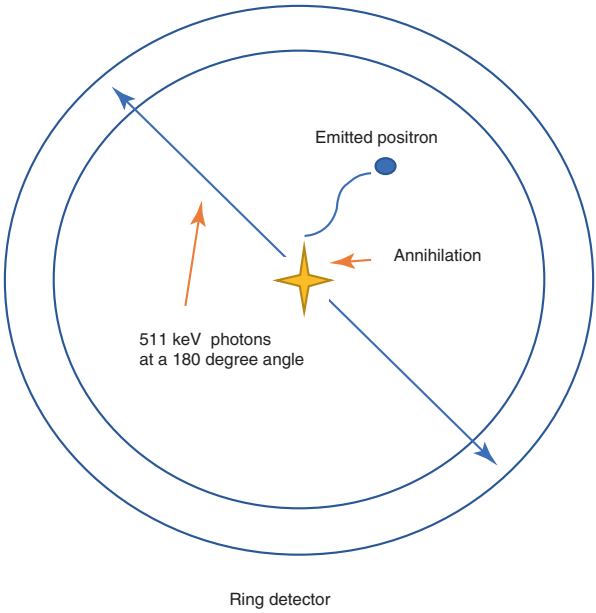

Fig. 3.1 PET detector ring. After emission, positrons travel a short distance in tissue before the annihilation event. The 511 keV photons are emitted at an angle of 180°

image quality [3]. Among the main advantages when compared to conventional imaging there are electronic collimation, higher detection efficiency, and better spatial resolution [2].

Nowadays, almost all PET systems are coupled to x-ray computed tomography (CT) systems, with a single patient bed passing through both systems, and are referred to as "PET/CT" systems [4].

PET has established wide clinical acceptance, particularly in oncology. It has become a key tool for the management of patients with a variety of malignancies as well as infections and inflammation [5].

PET offers an extensive gamma of radiopharmaceuticals to image different aspects of physiology and tumor biology. Currently, the most used PET tracer is an analog of glucose, the ^{18}F-FDG [6].

In clinical practice, nuclear medicine physicians interpret the images and distinguish tumors from physiological uptake, inflammation, or artifacts based on their experience [5].

3.2 Coincidence Timing Window

If the detection of the two 511 keV annihilation photons occurs in the center of the detector ring, the event must be recognized by two detectors at the same time [2]. Thus, the direction of photons can be determined without the use of absorptive

collimation. This process is referred to as annihilation coincidence detection and is the main feature of PET imaging [3].

However, annihilation can occur at any point in the FOV of the equipment and a photon can reach one detector at different times from another photon. Therefore, a time window must be several nanoseconds to consider events farther away from the center of the FOV, in addition to the time required for the electrical signal to travel through cables and electronic circuits [2].

3.3 Image Acquisition

PET systems are most used in a whole-body scanning mode. This usually means obtaining sequential segmental views of the body by moving the scanning table to acquire multiple contiguous views. There is a need to overlap the views to get uniform statistics counting, because in multiple detector ring systems, the detector rings at the edge of the FOV have less sensitivity than those in the middle. A whole-body scan in a dedicated PET scanner usually extends from the base of the brain to the mid-thighs using a two- or three-dimensional acquisition [3].

In a complete ring system, data is acquired 360° simultaneously, whereas in partial ring systems, the rings are moved around the patient so the acquisition takes place around the entire ring (360°) [2]. There are three steps in acquiring the PET exam:

1. Location of the detector pair in the ring is determined for each coincidence event.
2. Pulses are analyzed to verify if they are within the energy window set to 511 keV.
3. The coincidence circuit analyzes the data from the associated detectors and, if there is a coincidence, the position of the LOR is determined in polar coordinates and is stored in the computer's memory [2].

Unlike in the conventional gamma scintigraphy image—where individual events are recorded in an XY matrix—the coincidence events in the PET image are directly stored in the form of a sinogram [2]. PET data can be stored as sinograms (2D) or projections (3D) [3].

The radiopharmaceutical is administered to the patient, who waits for a period prior to image acquisition. This uptake period is for the radiopharmaceutical to reach peak accumulation in the organs of interest, and in some cases for the tracer to wash out from surrounding organs [5].

3.4 Events Detection

Coincident events detected by a pair of detectors are events that include true coincidence events, scattering coincidence, and random coincidence [3] [7].

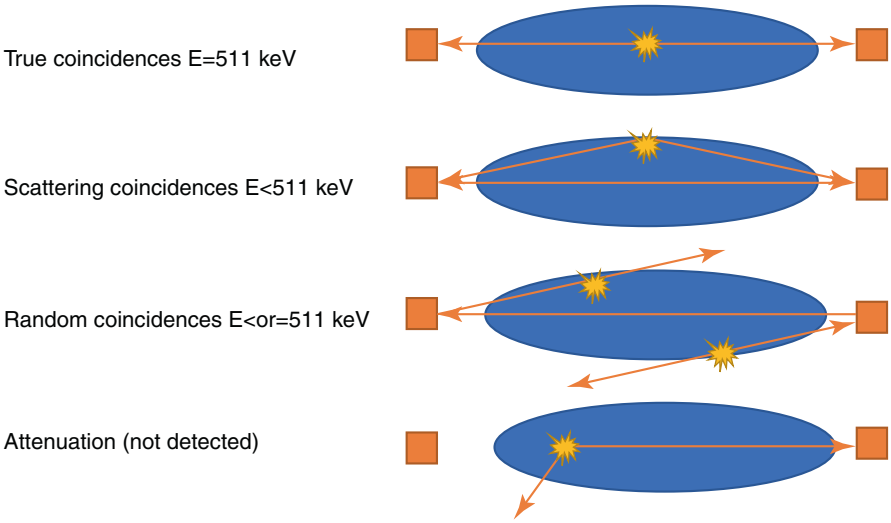

Fig. 3.2 Types of detected and not detected annihilation coincidences

A true coincidence is the nearly simultaneous interaction with the detectors of one annihilation. A scatter coincidence is a true coincidence because both interactions result from single positron annihilation. A random coincidence occurs when emissions from different annihilations interact nearly simultaneously with the detectors. Random coincidences and scatter coincidences are assigned out of LORs and do not intersect the actual locations of the annihilations (Fig. 3.2). They are sources of noise, which reduce image contrast and increase statistical noise [3].

To eliminate some of the random and scattering events, septa made of tungsten or lead are inserted between the rings. These mainly allow direct coincidence events, avoiding photons from other parts of the body and thus minimizing losses due to dead time, and random and scattering events [2]. But over time the number of rings has increased, making it common to be able to remove the septa to acquire data through planes (3D mode). The 3D model greatly increases the sensitivity of the PET detection system [3], but so are the scatter and random events [8].

New detector developments with reconstruction and scatter correction algorithms have improved 3D PET performance significantly, such that most scanners are 3D-only nowadays [9].

3.5 PET Scanner Design

PET scanners are built from many small detectors placed in adjacent rings around the patient port. A typical PET system has a ring diameter of 60–90 cm and an axial extent of 10–25 cm and consists of up to 25,000 detectors [1].