1 Introduction: Radiopharmaceuticals Play an Important Role in Both Diagnostic and Therapeutic Nuclear Medicine

1.1 Introduction: Use of Radioisotopes in Nuclear Medicine

As a foundation for a discussion of the development and use of therapeutic radiopharmaceuticals, it is first necessary to provide an introduction to the field of nuclear medicine and how radioisotopes are used in this board-certified clinical specialty for both diagnostic and therapeutic applications. In the field of nuclear medicine, unsealed radioactive agents known as radiopharmaceuticals are administered generally intravenously for either diagnostic or therapeutic applications (McCready 2000; Ercan and Caglar 2000). These specialists and their staff are specially trained in the safe handling, storage, and disposal of radioactive materials. Special licensing is required, radiopharmaceuticals must be approved by regulatory bodies for use, and certified radiopharmacists are required for the formulation and dispensing of these radioactive substances. Diagnostic applications in nuclear medicine use low activity tracer levels of generally gamma- or positron-emitting radioisotopes which are generally produced in nuclear reactors and accelerators (Chap. 5). In contrast, therapeutic applications utilize particle-emitting radionuclides for induction of radiotoxicity to kill cells in the targeted tissue. The substrate or targeting moiety (vector) to which the radionuclide is chemically attached is designed to favor the accumulation of the administered radiopharmaceutical at the targeted cell, tissue, or organ. The radiation emitted from the accumulated radioactivity is then detected by external measuring devices such as a gamma camera or positron emission tomographic camera to reconstruct images for diagnostic purposes. For therapeutic applications in nuclear medicine, particles emitted from radioactive decay of selected radioisotopes deliver cytotoxic levels of radiation to the target site. After site-specific accumulation of the radiopharmaceutical to the target site, cytotoxic ionizing radiation is delivered to induce un-repairable double-strand DNA breaks which result in subsequent cell death (Hoefnagel 1998; Aerts et al. 2014; Wheldon 1994). It should also be noted that in the form of sealed radioactive sources, therapeutic radioisotopes are also used in other clinical specialties, most notably in brachytherapy practiced in radiation oncology. In these applications, permanently often reusable sealed radioactive sources are introduced adjacent to the target tissue for limited time periods and then removed, or permanently implanted, such as well-established methods for treatment of prostate cancer (Connell and Hellman 2009; Gerber and Chan 2008). This book focuses on the description of unsealed radioactive materials which are used for nuclear medicine therapy.

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1.2 Key Examples of Nuclear Medicine

1.2.1 Nuclear Medicine Imaging

For imaging tissue anatomy, function, and metabolism, radioisotopes which decay by emission of gamma photons, X-rays, and positrons (β^+) are targeted to specific organs and disease entities (James and Gambhir 2012; Zanzonico 2012). The radiopharmaceutical agents are generally administered intravenously and for some applications either orally or by inhalation, with the radioactive agent then localizing in the targeted specific organ or tissue. The emission of radiation from the localized radioactive agent is then detected by scintillation cameras and other instruments and the detector data is then processed in the computer into either two-dimensional (planar imaging) or three-dimensional (tomographic imaging) images of the radiopharmaceutical distribution. These data can also be used for several important applications on organ function to quantitate time–activity curves or the uptake and release kinetics of radioactivity over time. Images obtained from stationary camera devices are referred as scintigraphs, while the use of a linear moving or rotating camera system in two dimensions is called a scan. The use of the latter tomographic technology is currently most widely used for many applications, where the gamma camera is rotated around the patient to obtain three-dimensional images (Kjaer 2006). The development and clinical applications of radioisotopes and radiopharmaceuticals in nuclear medicine are widely described in the literature (Bhattacharyya and Dixit 2011; Britton 1997; Ercan and Caglar 2000; Hoefnagel 1991; Leeds 1990; Penner et al. 2009; Volkert and Hoffman 1999).

Modern gamma cameras provide tomographic images, and this technology is commonly referred to as single-photon emission computed tomography (SPECT). Another major nuclear medicine imaging modality is positron emission tomography (PET) which provides very high-resolution images and detects the coincidence photon events which occur after positron emission of radioisotopes such as carbon-11 (^{11}C) and fluorine-18 (^{18}F). Nuclear medicine imaging is thus unique, because it provides information about both structural and functional changes involved in a disease process and offers unique opportunities and can determine the presence of metabolic and functional abnormalities based on biological changes mostly at the cellular level rather than changes in anatomy, which are often only detected at later stages of the disease. Traditional radiology-based imaging technologies such as X-ray computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI) are almost used exclusively for evaluation of anatomy. Nuclear medicine imaging using planar scanning, SPECT, and PET, however, can thus often reveal metabolic and physiological abnormalities generally not detected by static forms of anatomic imaging such as CT and US, although some unique physiologic applications are possible with the MRI modality. Important instrumental developments have progressed over the last two decades, however, by the combination of traditional anatomically based imaging modalities and radioisotope-based technologies. Current state-of-the-art imaging instruments are thus now widely used which simultaneously utilize both PET and SPECT in conjunction with MRI and CT in hybrid imaging instruments for accurate assessment of radiopharmaceutical targeting data with anatomical images (i.e., PET-CT, PET-MRI, SPECT-CT).

1.2.2 Molecular Imaging

Molecular imaging is a special nuclear medicine application where engineered radiopharmaceutical agents are specifically targeted for the detection and evaluation of functional changes at a specific cellular level, which allows monitoring of body function to measure specific chemical and biological processes (Bentzen and Gregoire 2011; Garden et al. 1989; Howard et al. 2015; Hunter and Eisbruch 2011; Maletz et al. 2012; Schlegel 2010; Simpson et al. 2009; Wolbarst and Hendee 2006). Molecular imaging can often uniquely identify disease processes at very early

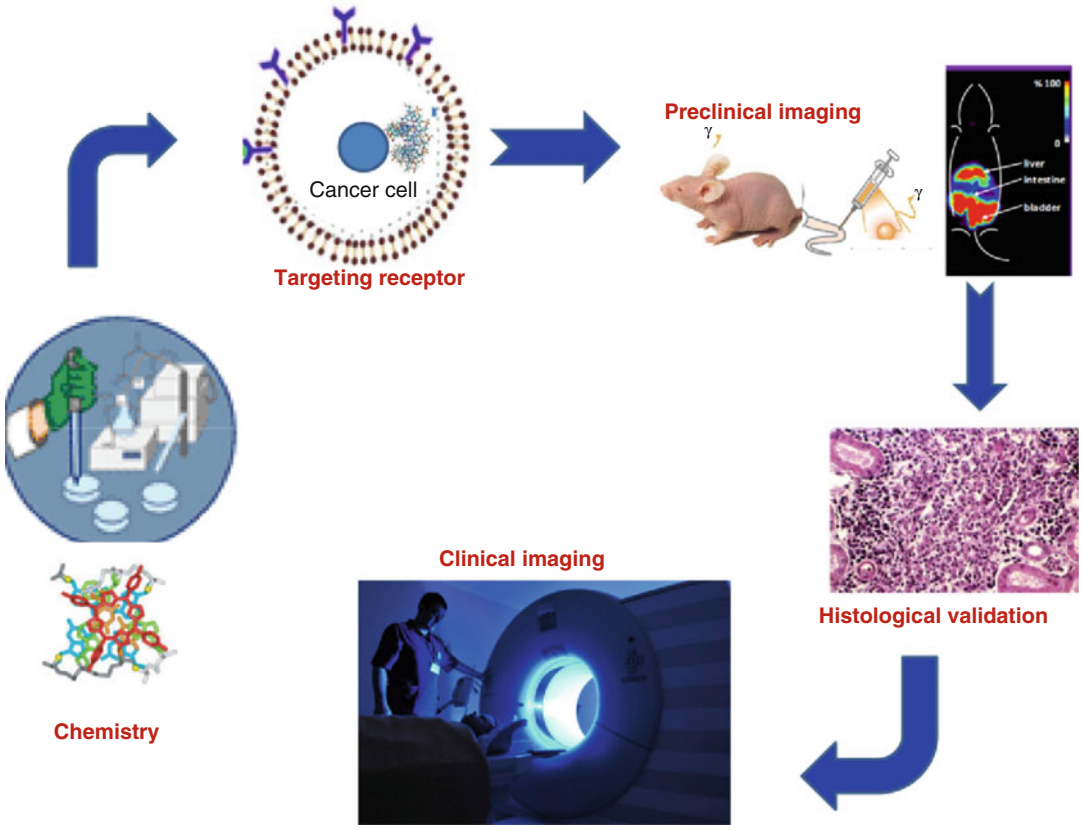

Fig. 1.1 The cycle of the development of molecular imaging agents

stages before clinical symptoms are observed. Several examples include the use of radiolabeled peptides to detect tumors. Nuclear medicine imaging thus plays a critical role at every phase of disease assessment, which includes diagnosis and staging, treatment planning, monitoring response to therapy, and monitoring recurrence and residual disease. In cancer management these technologies can detect disease conditions which may often be occult and be undetected by other imaging modalities. Imaging can also assess the severity of disease, including the degree of spread throughout the body. Although initial cancer staging has been historically accomplished by various diagnostic techniques such as CT and MRI, the relatively recent broad availability of SPECT and PET nuclear imaging technologies has resulted in new opportunities in cancer management, for example, for staging, upstaging, or downstaging specific cancer entities. In planning cancer treatment, nuclear medicine imaging often provides important information for selecting the most effective therapy based on the unique biologic characteristics of a particular patient and the molecular properties of the tumor. This "personalized" approach for patient management is important for evaluation of response to ongoing therapy, and such functional imaging technologies offer advantages not available through anatomic imaging alone. This critical advantage can allow midcourse alteration of treatment, if necessary, as opposed to the presentation of structural changes revealed by other imaging modalities. Nuclear imaging is also highly useful for detection of residual disease or surveillance for recurrence (Akkas et al. 2014; de Haas et al. 2012; Kostakoglu et al. 2013; Kurdziel et al. 2008). The key components which comprise the development of molecular imaging (MI) agents are depicted in Fig. 1.1.

1.2.3 In Vivo Function Tests

In this process a radiopharmaceutical is administered, and the adsorption, distribution, metabolism, and excretion (ADME) properties are documented (Dalvie 2000; Giron et al. 2008). Functional processes that can be assessed include tissue blood flow and metabolism, protein–protein interactions, expression of cell receptors in normal and abnormal cells, cell–cell interactions, neurotransmitter activity, cell trafficking and homing, tissue invasion, and programmed cell death. By providing information on these processes, nuclear medicine imaging offers a broad array of tools for probing normal and disease-related states of tissue function and response to treatment. The time–activity curves of the organs of interest are obtained which reflect organ function. In vivo quantification of radiopharmaceuticals has great potential as a tool in assessing the function of an organ or organ systems. Key examples include kidney function tests, neurological disorders, cardiovascular disease, bile flow, lymphatic drainage, thyroid structure and function, small-bowel transit gastric emptying assessment, acute GI bleeding, hepatic hemangiomas, reticuloendothelial function renal, artery stenosis, and inflammatory bowel disease (Alazraki 1993; Bomanji and Siraj 1995; Eberlein et al. 2011; El-Maghraby et al. 2006; Ganz and Serafini 1989; Messa et al. 1995; Notghi and Harding 1995; Prvulovich and Bomanji 1998; Ross 1991).

1.2.4 Nuclear Medicine Therapy

The primary focus of this book is the use of unsealed radioactive sources for nuclear medicine therapy, which is commonly referred to as radionuclide therapy (RNT). In this therapeutic modality, high activity levels of generally particle-emitting radioisotopes attached to tissue-targeting agents are administered to deliver high radiation doses to targeted tissues. Principal established clinical applications include cancer therapy (Chaps. 9 and 10), treatment of metastatic bone pain (Chap. 12), and treatment of inflammatory processes such as rheumatoid arthritis (Chap. 14). Key examples of developing technologies using therapeutic radiopharmaceuticals include treatment of nonmelanoma skin cancer in delicate anatomical areas (Chap. 13) and therapy of hyperplasia which often occurs after arterial angioplasty (Chap. 15). These applications and the radiopharmaceuticals which are employed are discussed in subsequent chapters. A large variety of disease-targeting radiopharmaceuticals to which are attached radionuclides which emit alpha (α), beta (β^-), or Auger (AE)/conversion (CE) electron particulate radiation are used for RNT. Unlike conventional external beam therapy—under the purview of radiation oncology—RNT is practiced in the nuclear medicine arena and targets diseases at the cellular rather than on a gross anatomical level (Cuaron et al. 2009: Dash et al. 2013; Eary 1991; Gabriel 2012; Srivastava and Dadachova 2001; Yeong et al. 2014). This concept is a blend of a tracer moiety that mediates a site-specific accumulation followed by induction of cytotoxicity with the short-range biological effectiveness of the particulate radiation. The proximal contact between the radionuclide and the cells targeted for destruction enables the absorbed radiation to be concentrated at the target site with the minimal injury to adjacent healthy tissue.

1.3 Radiopharmaceuticals

In contrast to the common use of nonradioactive therapeutic routine pharmaceuticals, radiopharmaceuticals are generally administered at subpharmacologic dose in very high specific activity (radioactivity/unit mass). Radiopharmaceuticals can consist in some instances of a radionuclide in ionic form—such as iodine-131 (^{131}I) for treatment of thyroid cancer or strontium-89 (^{89}Sr) for bone pain palliation (Chap. 12)—but these agents are generally represented by pharmaceutical targeting agents to which the radioisotope is chemically attached. These carrier molecules are represented by a broad range of molecules, which include chelating agents, small molecules, drugs, peptides, proteins, or particles. Similar to

conventional pharmaceuticals, the radiopharmaceutical targeting agents are administered by oral, intra-arterial, intravenous, intratumoral, intra-portal, and intracavity routes. The administered radiopharmaceuticals accumulate in the organ or tissue of interest through a variety of well-established known biological mechanisms, for which these agents are designed and developed. The radionuclides attached to the radiopharmaceuticals provide the radiation component (radioactivity), while the carrier molecule targets specifically diseased tissues or cells. These radiopharmaceutical carrier molecules to which radionuclides are attached are often called vectors and often consist of small organic molecules such as a drug, carbohydrate, lipid, nucleic acid, peptide, fragment of antibody, or even very large whole antibodies (Cutler et al. 2013; Dash et al. 2013). The synthetic chemical and biological issues associated for vector selection, development, and preparation are challenging and key factors to provide these agents for preclinical evaluation with a goal of eventual clinical application and are based on the ability of radiopharmaceuticals to accumulate selectively on/or/in a cell, tissue, or organ.

The activity doses of radiopharmaceutical used for diagnostic imaging applications vary depending on the extent of accumulation at the target site, the residence time, release kinetics, type of investigation being conducted, and the imaging technology which is employed. The goal is to limit the activity levels which are required for imaging to minimize the radiation dose to no targeted tissues. Often millicurie (mCi) levels of radioactivity are adequate for diagnostic studies, whereas several hundreds of mCi of activity are often required for therapeutic applications. Radiopharmaceuticals are formulated in various chemical and physical forms and require production and dispensing under good manufacturing conditions (GMP). There are several hundred radiotracers which have been developed over the last decades which have potential radiopharmaceutical use in humans. The radioisotopes used for both diagnostic and therapeutic applications are generally produced in research reactors and accelerator facilities or are available from radionuclide generator systems, as described in Chaps. 5, 6, 7, and 8. Although some imaging and therapeutic agents are produced or dispensed in-house in a hospital-based radiopharmacy under carefully controlled conditions, most radiopharmaceutical agents are delivered for clinical use in a ready-to-use form by commercial manufacturers or from a central radiopharmacy.

Radiopharmaceuticals are available in a wide variety of chemical and physical forms which include radionuclides in inorganic forms, such as $Na^{131}I$ (thyroid therapy), $^{90}SrCl_2$ (bone pain palliation), and $Na^{99m}TcO_4$ (thyroid imaging). Radionuclides are generally attached by complexation to suitable chelating groups, and these entities are then used for imaging or therapy. Key diagnostic examples include ^{99m}Tc-MDP (methylene diphosphonate) for bone imaging and ^{99m}Tc-MIBI (methoxy isobutyl isonitrile), which is widely used for assessment of regional myocardial perfusion. In addition, radionuclides can be complexed to a suitable chelating agent which is attached to the targeting vector, and key examples in this class include ^{99m}Tc-Hynic-TOC (a somatostatin analog peptide) used for tumor detection and therapy management evaluation. In addition, another important strategy is covalent linkage of radionuclides to drug molecule, and examples include ^{131}I-MIBG (MIBG: metaiodobenzylguanidine) for the treatment of adrenal-based tumors, primarily in children. Finally, therapeutic radionuclides can also be attached by chemical chelation to a carrier vector such as ^{99m}Tc-UBI (UBI, ubiquicidin). Key examples of different types of widely used radiopharmaceuticals and their uses are provided in Table 1.1.

The development and use of radiopharmaceuticals is truly a multidisciplinary process. Key strategies for radiopharmaceutical development include a number of physiological issues which are required to insure that the expected targeting and kinetics are optimized. Radiopharmaceuticals should exhibit rapid blood clearance and, when appropriate, possess high membrane permeability to facilitate cellular accumulation. The agents should also exhibit slow metabolism before delivery and after accumulation at the target site and minimal accumulation in nontarget organs. In addition, limited transport and biochemical transformation should

Table 1.1 Examples of key diagnostic and therapeutic radionuclides and radiopharmaceutical agents used in nuclear medicine applications

Radionuclide	Agent	Chemical form	Application
Diagnostic radiopharmaceuticals			
^{18}F	^{18}F[FDG]	Vector-link	Imaging cell proliferation
^{123}I	^{123}I-MIBG	Vector-link	Imaging medullary carcinoma
^{99m}Tc	$Na^{99m}TcO_4$	Ionic	Thyroid scanning
^{99m}Tc	^{99m}Tc-MDP	CA	Bone imaging
^{99m}Tc	^{99m}Tc-DTPA	CA	Renal agent for estimation of glomerular filtration rate (GFR) estimation
^{99m}Tc	^{99m}Tc-MIBI	CA	Cardiac imaging
^{99m}Tc	^{99m}Tc-ECD	CA	Brain imaging
^{99m}Tc	^{99m}Tc-hynic-TOC	Vector-CA	Imaging neuroendocrine tumors
^{99m}Tc	^{99m}Tc-hynic-RGD	Vector-CA	Imaging neo-angiogenesis
^{99m}Tc	^{99m}Tc-UBI		Imaging infection
Therapeutic radiopharmaceuticals			
^{131}I	$Na^{131}I$	Ionic	Thyroid scanning, treatment of hyperthyroidism and thyroid cancer
^{131}I	^{131}I-MIBG		Treatment of medullary carcinoma
^{177}Lu	^{177}Lu-DOTATATE	Vector-CA	Treatment of neuroendocrine tumors
^{89}Sr	$^{89}SrCl_2$	Ionic	Bone pain palliation
^{90}Y	Zevalin®	Vector-CA	Treatment of non-Hodgkin's lymphoma

CA chelating agent, *Vector-CA* vector attached chelating agent

occur to facilitate kinetic modeling of the tracer. These data are generated from time–activity curves and serial imaging and allow an estimation of radiation dose to both target and nontarget organs. Radiopharmaceutical development encompasses a variety of disciplines and capabilities including radionuclide production (Chaps. 5, 6, 7, and 8) with subsequent radiochemical processing, purification, and analysis to provide the radionuclides with requisite purity. Other key capabilities and resources include the organic synthesis of chelating agents or vectors for radiolabeling with the appropriate properties, and the development of radiolabeling methods ensures high radiochemical yields. Rapid and efficient purification procedures are required to obtain high radiochemical purity of the final products. From a pharmaceutical perspective, reliable technologies are required for the routine production of sterile, pyrogen-free products with minimum inconvenience achieved either through kit formulation procedure or through the use of automated synthesis modules. Finally, simple quality control procedures are required to ensure the purity and assurance for human use.

1.3.1 Diagnostic Radiopharmaceuticals

The use of radiopharmaceuticals for imaging organ function and disease involvement is the unique capability of nuclear medicine. Radiopharmaceuticals used in diagnostic nuclear medicine procedures generally emit either gamma radiation or positrons, and the half-lives of radionuclides for imaging applications generally span from minutes to several hours. Although it is not a goal of this book to discuss these diagnostic agents in detail, Table 1.2 provides a

summary of commonly used radionuclides for diagnostic radiopharmaceuticals.

1.3.2 Nuclear Medicine Imaging

Radiopharmaceuticals are administered to patients and then redistributed by well-established physiological principles which depend on specific properties of the targeting agent. All radiopharmaceuticals are carefully designed and have well-defined properties which govern adsorption, distribution, metabolism, and excretion (ADME). Nuclear medicine imaging is conducted at defined time points which are evolved as the imaging protocols (Zanzonico 2012). Usually imaging commences after clearance of blood pool activity. The evolution of nuclear medicine imaging has taken many twists and turns as both equipment technology and new radiopharmaceuticals have been developed over the past decade. The commonly used planar, SPECT, and PET imaging techniques are discussed in more detail below.

Table 1.2 Key examples of radionuclides used for diagnosis in nuclear medicine

Radionuclide	Half-life	Emission
^{15}O	2.1 min	Positron
^{11}C	20.4 min	Positron
^{68}Ga	60 min	Positron
^{18}F	109.8 min	Positron
^{99m}Tc	6 h	Gamma
^{111}In	2.8 days	Gamma
^{123}I	13.2 h	Gamma

1.3.2.1 Planar Imaging

A schematic representation of planar and SPECT imaging principles is illustrated in Fig. 1.2. Detection and subsequent image reconstruction of gamma rays emitted by radiopharmaceuticals is accomplished by scintillation cameras also referred to as Anger or gamma cameras (Fig. 1.2a). The gamma rays emitted by the radionuclide are detected by the scintillation crystal, which is usually thallium-activated sodium iodide (Anger 1958; Erickson 1992; Tapscott 1998; Pexman 1973; Telander and Loken 1967). The ionizations produced within the sodium iodide crystals emit secondary radiations which are converted to light photons via sodium iodide scintillation detectors, and photodiodes then convert the secondary radiation to light photons which are amplified by a series of photomultiplier tubes before measurement as a current pulse. Reconstruction is accomplished using computer software which converts the current detected at different points corresponding to the crystal to images. These images are traditionally called scintigraphs and are displayed as two-dimensional views of the targeted site region of interest. Such 2D images, known as planar scintigrams, are often of poor quality due to the superposition of nontarget activity from the 3D body which restricts the measurement of organ function and prohibits accurate quantification of that function. However, in some cases, such as bone scintigraphy, planar imaging is a common and cost-effective application. Computer processing of the planar scintigrams can increase the accuracy with

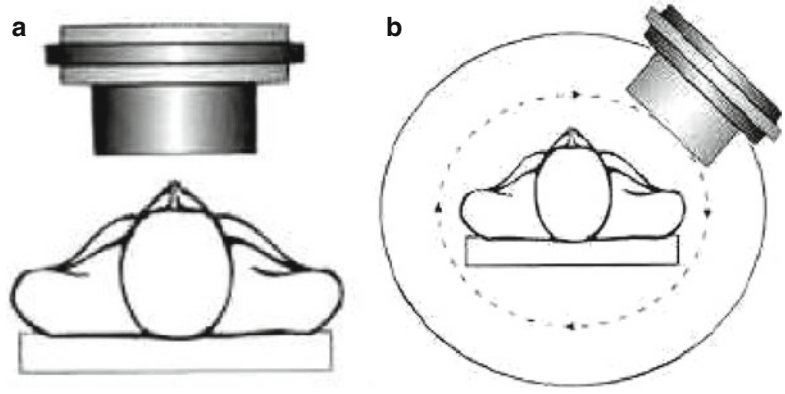

Fig. 1.2 Orientation and patient placement for planar and SPECT imaging. (**a**) 2D planar scan. (b) 3D SPECT, single-photon emission computed tomography

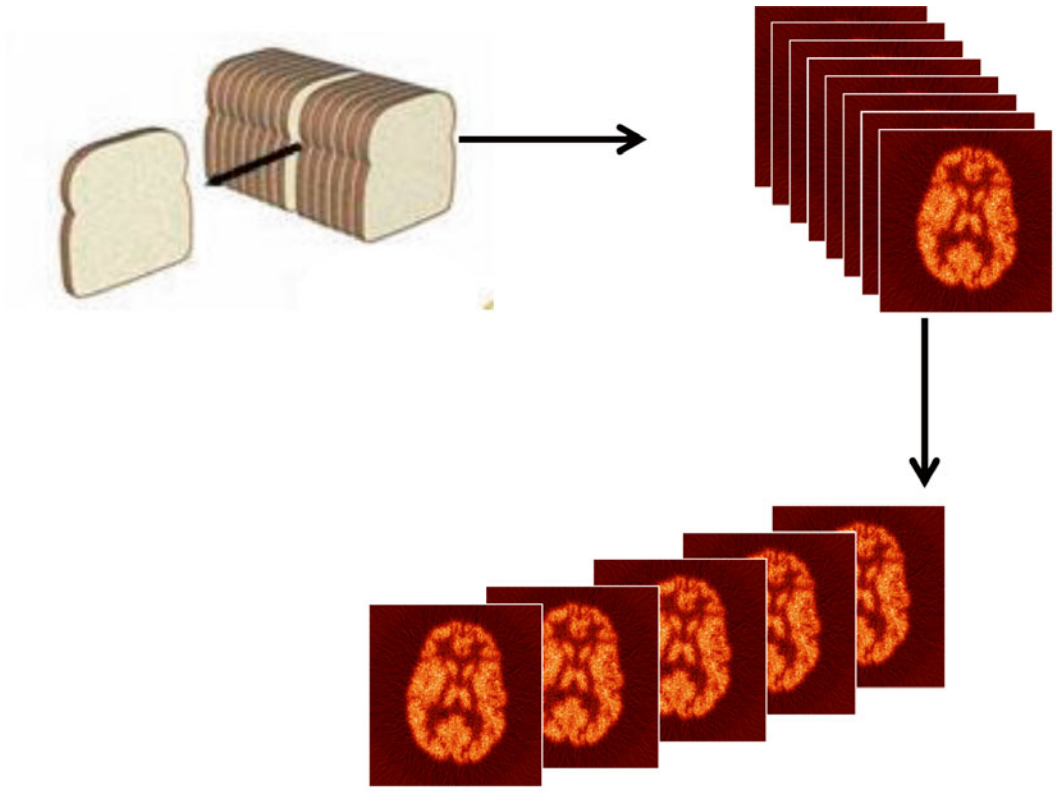

Fig. 1.3 The principal of single-photon emission computed tomography (SPECT)

which the image approximates the activity distribution, selectively enhance normal or abnormal structures of interest, and optimize the use of the display system presenting the image (MacIntyre et al. 1994; Zaidi 2006).

1.3.2.2 Single-Photon Emission Computed Tomography (SPECT)

SPECT is a 3D tomographic technique that uses the imaging data from many angles which are then reconstructed in different planes. SPECT uses a combination of a rotating gamma camera with a powerful computerized calculation system which allows the acquisition of cross-sectional images (Fig. 1.2b). This technique evolved to three-dimensional imaging acquisition which can be performed within a realistic time frame. SPECT has the capability for mapping physiological function and metabolic activity and thereby providing more specific information concerning organ function for the evaluation of function or physiology. The development of SPECT led to improved imaging of the heart, lung, liver, kidney, bone, and inflamed or infected tissues. SPECT also allows the identification of metastases and determination of the extent of a cancer. SPECT provides the activity distribution in different sections of the object at different depths and in turn to accurately determine the location of the lesion as well as metastasis.

SPECT is a technique whereby cross-sectional images of tissue function can be produced by reconstructing data in slices of the total organ thereby greatly minimizing the removal of the effect of overlying and underlying radioactivity as depicted in Fig. 1.3.

The functional information obtained by SPECT is complementary to planar images, obtained by projections of the organ under investigation (Eberl et al. 2006; Jaszczak 2006; Horger and Bares 2006; Schillaci 2006; Schillaci et al. 2007; Krausz and Israel 2006). Schematic representation of single-photon emission computed tomography

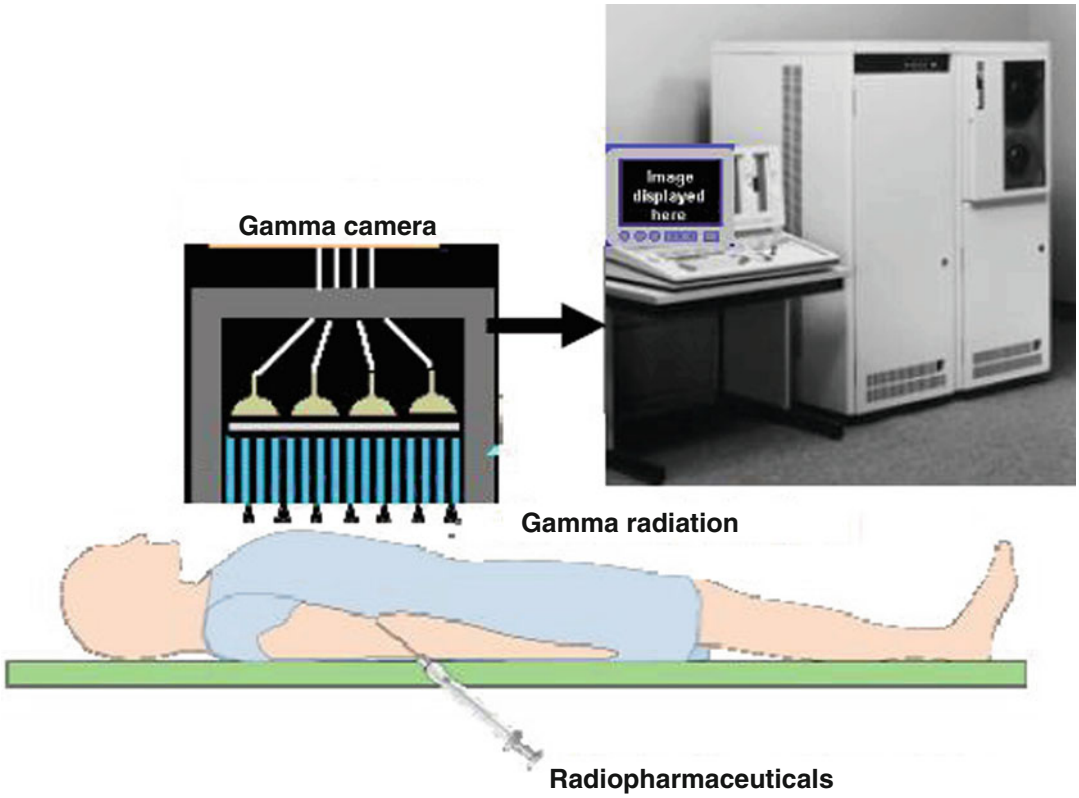

Fig. 1.4 Single-photon emission computed tomography (SPECT)

(SPECT) in a clinical setup is depicted in Fig. 1.4. The advantages of SPECT over planar scintigraphy include better spatial localization, improved detection of abnormal function, and, importantly, greatly improved quantification. In general SPECT images have poorer spatial resolution than the 2D images from which they are reconstructed. Of course capital costs and costs for maintenance of SPECT instrumentation are much higher than for planar imaging instruments.

Radioisotopes used for SPECT are limited to those that emit gamma rays with an energy range that is suitable for the gamma camera such as thallium-201 (^{201}Tl), technetium-99m (^{99m}Tc), and iodine-123 (^{123}I). The spatial resolution of SPECT systems is in the range of 10–14 mm.

1.3.2.3 Positron Emission Tomography (PET)

Positron emission tomography (PET) is a powerful diagnostic imaging modality which has become a dominant imaging method in the field of nuclear medicine (Coleman 1999; Gambhir 2002; Delbeke and Martin 2001; Kubota 2001; Mankoff and Bellon 2001; Mammatas et al. 2015; Mercer 2007; Wood et al. 2007; Riemann et al. 2008; Solomon et al. 2003). This technology requires radionuclides that decay with the emission of positrons (β^+). The concept of simultaneous detection (coincidence detection) is based on $\beta^+ + \beta^-$-annihilation by positron interaction with an electron from the surrounding environment after traveling a short distance (3–5 mm), resulting in the emission of two 511 keV gamma rays traveling in opposite directions. In PET, image acquisition is then based on the detection of the two gamma rays in a coincidence mode. A valid annihilation event requires a coincidence within 12 ns between the two detectors placed on opposite sides of the scanner. In a PET instrument, the patient is positioned within a ring of scintillation detectors. If two events are detected simultaneously in opposing detectors, it is

assumed that an annihilation occurred somewhere on an imaginary line connecting these two detectors. By acquiring a large number of such events, e.g., 10^6, tomographic reconstruction methods can be used to reconstruct two-dimensional images of the tracer distribution. Schematic representation of single detector ring of positron emission tomographic (PET) scanner is depicted in Fig. 1.5.

The higher sensitivity of this technology and its excellent quantification of regional tissue tracer concentrations are the distinct advantages of PET over SPECT, and these advantages have been harnessed to maximize the use of the tracer principle to visualize and measure biologic processes with PET (Zaidi 2006; Gholamrezanejhad et al. 2009). On the other hand, SPECT offers the possibility to widen the observational time window owing to the longer half-life of single-photon emitters and offers the possibility to observe biological processes in vivo several hours or days after administration of the labeled compound (Meikle et al. 2005).

A total of about 2350 fixed or mobile PET facilities are estimated to be in operation in the USA alone. SPECT and PET are not necessarily competitive with one another, but instead, have progressed on different parallel tracks with a focus on providing diagnosis information (Alavi and Basu 2008; Gholamrezanejhad et al. 2009; Jansen and Vanderheyden 2007; Mariani et al. 2008; Rahmim and Zaidi 2008). While both SPECT and PET have the capability for the detection of cancers and related metabolic abnormalities using the appropriate radiopharmaceutical agents, these technologies generally do not provide the anatomical information required for precise localization of lesions. For this reason, the most contemporary hybrid imaging systems encompass capabilities for the simultaneous registration of both PET images with computed tomography (CT) and magnetic

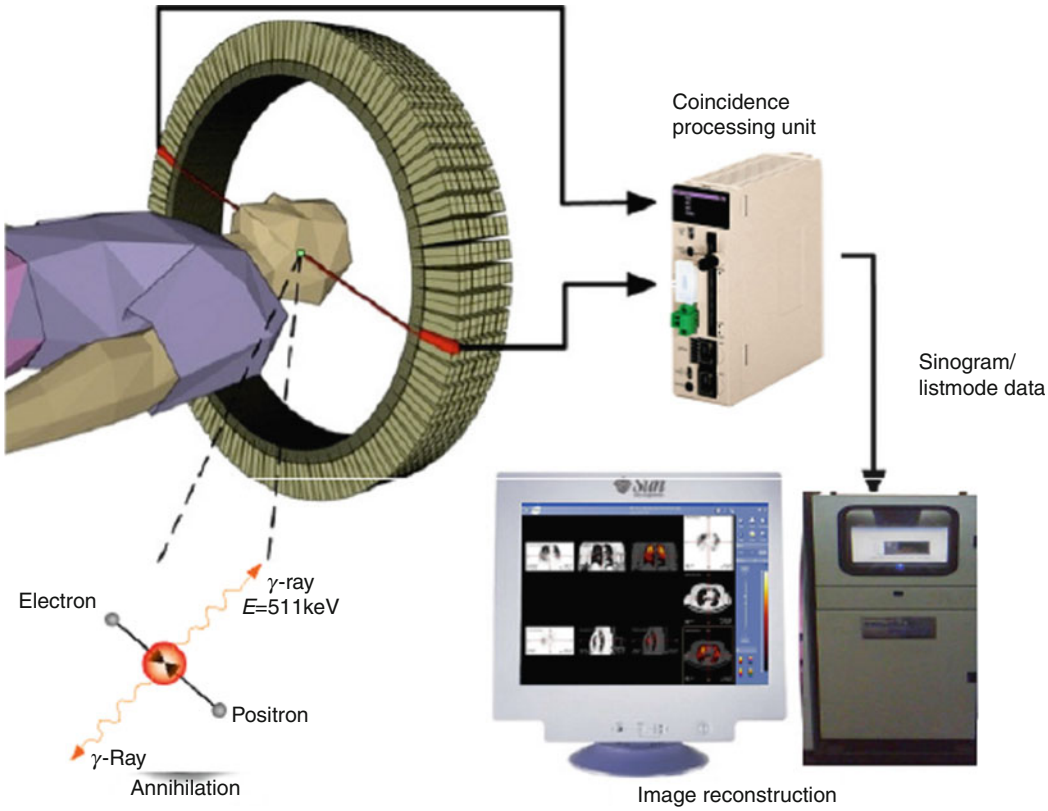

Fig. 1.5 Typical positron emission tomography (PET) system and patient orientation

resonance imaging (MRI) which offers excellent anatomic detail, in conjunction with the functional information provided by the PET capability. An earlier initial strategy involved software-based fusion of independently performed scintigraphic (PET or SPECT) and radiological images (CT), but these methods were time consuming and impractical for routine use. Introduction of hybrid PET-CT as well as PET-MR has now allowed co-registration of data from both the imaging modalities. The PET-CT and PET-MR images provide additional information which has greatly improved diagnostic accuracy and has greatly impacted patient management, especially for oncological applications (Beyer et al. 2011; Bockisch et al. 2009; Brandon et al. 2011; Chowdhury and Scarsbrook 2008; Delbeke and Sandler 2000; Delbeke et al. 2009; Keidar et al. 2003; Kuikka et al. 1998; Mariani et al. 2010; Patton et al. 2000; Schillaci et al. 2004; Utsunomiya et al. 2006).

1.4 Therapeutic Radiopharmaceuticals

In contrast to the goal of limiting tissue radiation dose for diagnostic applications, nuclear medicine therapy is designed to deliver therapeutic doses of ionizing radiation to specific disease sites for cure, disease control, or pain palliation. The ionizing radiation induces irreversible damage to nuclear DNA by induction of double-strand breaks, thereby inhibiting further proliferation of these cells (Fig. 1.6).

In radionuclide therapy, the biological effect is obtained by energy absorbed from the radiation emitted by the radionuclide. Therefore, a radionuclide used for targeted therapy must emit particulate radiations which have relatively short path lengths thereby depositing the radiation energy in a small volume of cells to spare surrounding nontarget tissues. Radionuclides used for targeted therapy decay by alpha, beta, or Auger electron emission, as described in

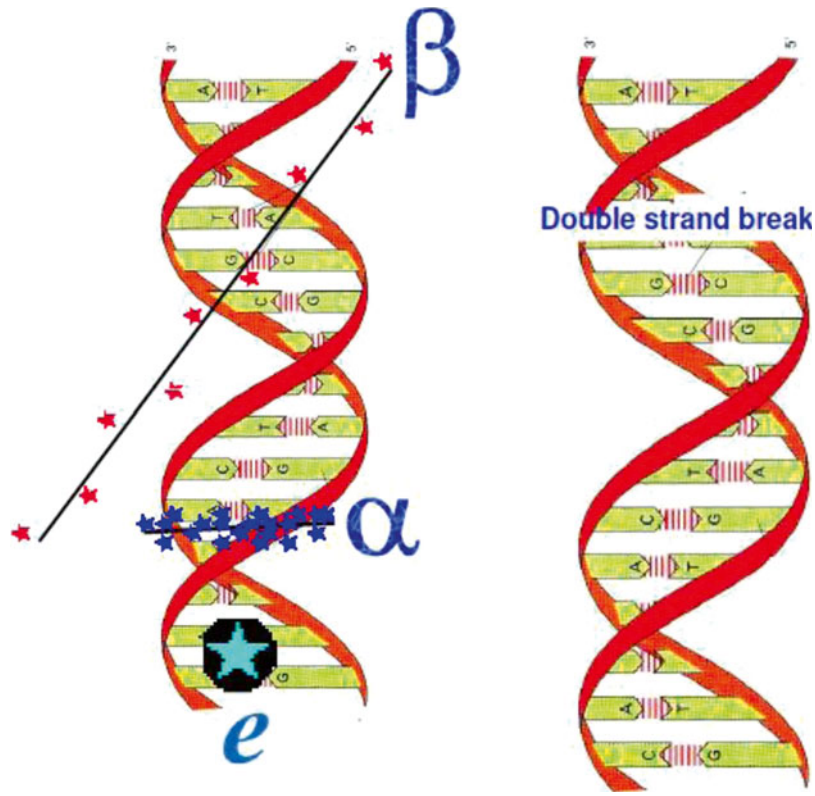

Fig. 1.6 Schematic of DNA strand breaks mediated by ionizing radiation

Chaps. 2, 3, and 4. Within each radionuclide category, there are multiple radionuclides with a variety of range in soft tissues, half-lives, and chemical properties which offer the attractive possibility of optimizing targeted radionuclide therapy to specific therapeutic applications. Production issues and availability and costs are also important parameters which are discussed in Chaps. 5, 6, 7, and 8. Unlike tumor-directed drugs and toxins, which kill only the directly targeted cells, a unique feature of many radioactive emissions (i.e., beta) is that they can often exert a "bystander" or "cross-fire" effect, potentially destroying adjacent tumor cells even if they are not targeted by the radiopharmaceutical. In most cases this characteristic is advantageous, since it is unusual for delivery of the therapeutic radiopharmaceutical to every target cell to be labeled, especially for therapy of solid tumors, because of blood supply and anatomical and physiological barriers. In other cases, dose delivery to only the targeted cell may be a necessity, such as the use of very short-range alpha-emitting radioisotopes (Chap. 3) for the treatment of blood-borne diseases such as some types of leukemia. A systemically administered targeted radiotherapeutic agent has the potential to eliminate primary tumor sites as well as metastases and other malignant cell populations which may be undetectable by diagnostic imaging.

The efficacy of a therapeutic radiopharmaceutical depends on the radiotoxic nature of the radiation emitted and the targeting ability of the radiopharmaceutical vector used for carrying the radionuclide to the disease sites. The choice of a radionuclide for use in therapeutic radiopharmaceuticals is based on several criteria. Radionuclides that decay by alpha-particle emission (α), beta-particle emission (β^-), electron capture (EC), and internal conversion (IC) leading to the emission of Auger and Coster–Kronig (C–K) electrons are suitable for radionuclide therapy. These radiations have high linear energy transfer (LET) and deliver localized radiation. The treatment efficacy with a particular radionuclide can vary depending on the size of the tumor to be treated and intratumor distribution of the tracer. In addition, the nature and energy of the particulate radiation must match with the uptake and distribution of the radiopharmaceutical. The size of the tumor or site/cavity for treatment should match with the appropriate tissue range of radionuclide emissions. Radionuclides that emit β^- particles can induce damage in a cell volume extending up to several millimeters, while alpha particles can induce damages within a few cell volumes. In contrast, Auger and C–K electrons are effective only when they are localized within the cell nucleus to damage DNA. The physical half-life of the radionuclide should also be matched with the in vivo biolocalization and clearance properties of the vector that is used for carrying the radionuclide to the site of interest. The decay product of the radionuclide should be preferably stable or have a very long half-life. The emission of gamma photons—preferably of low abundance—is also advantageous and allows imaging to track the radiopharmaceutical uptake as well as to allow biokinetic data for low-dose imaging for dosimetry estimates and for staging of disease state as well as for monitoring response to therapy. The radionuclide should be available at highest standards of purity, which include radionuclidic, radiochemical, and chemical purity, and should be available either carrier-free (i.e., every atom is radioactive) or with very high specific activity (SA, activity per unit mass). For practical considerations, the radionuclide should have favorable chemical properties enabling radiolabeling with wide range of biomolecules. As discussed in detail in Chaps. 5, 6, 7, and 8, large-scale cost-effective production feasibility ultimately decides the success of a radionuclide to emerge as a choice for therapy (Zimmermann 2013).

1.4.1 Traditional Applications of Therapeutic Radiopharmaceuticals

Therapeutic radiopharmaceuticals have traditionally been used in nuclear medicine for the treatment of a variety of various diseases which are briefly discussed as a prelude for the more detailed recent developments and the use of various newer agents described in detail in the

subsequent chapters. Phosphorous-32 as ^{32}P-orthophosphate ($^{32}PO_4^{3-}$) is an early example which has been traditionally used for the treatment of elderly patients with *polycythemia vera* and essential thrombocytopenia (low blood platelet count) and is one of the earliest applications of radionuclide therapy. However, this mode of therapy is now rarely followed due to the availability of other more recent modes of therapy. Use of ^{131}I for the treatment of thyroid cancer patients has been practiced for many decades and is a unique and still widespread therapeutic example of successful radionuclide therapy. Iodine-131 as sodium iodide is one of the remarkable radiopharmaceuticals and a magic bullet since about one third of the orally administered dose is taken up in a normal thyroid for direct in vivo incorporation into the thyroglobulin macromolecule. Such large concentration of radioactivity allows near total destruction of remnant cancer tissues post surgery. Stimulation of the thyroid by injection of recombinant thyroid-stimulating hormone enhances the efficacy of the therapy. This well-established and historical technology has been widely discussed in the literature and is not described in this book. Iodine-131 is also traditionally used for therapy of other types of cancer. Metaiodobenzylguanidine (MIBG) is a catecholamine analog similar to noradrenaline, which accounts for the uptake of this radiopharmaceutical in catecholamine storage vesicles. The ^{131}I-mIBG agent is used for the treatment of medullary carcinomas such as neuroblastoma and pheochromocytoma. This is an established specialized therapy which is not discussed in this book. However, the use of radiolabeled peptides for therapy of neuroendocrine gastroenteropancreatic (NE-GEP) tumors is described in detail in Chap. 10.

1.4.2 Current and New Therapeutic Applications

1.4.2.1 Peptide Receptor Radionuclide Therapy (PRRT)

The use of radiolabeled peptides for the targeting and treatment of receptors expressed on specific cancer entities is a rapidly growing clinical specialty (PRRT). The overexpression of many peptide receptors on human tumor cells compared to normal tissues makes these receptors attractive molecular targets for radiotherapy. The most commonly used peptide-based therapy is the use of somatostatin (SST) analogs for the treatment of neuroendocrine tumors (NETs). As discussed in Chap. 10, NETs usually overexpress somatostatin receptors, thus enabling the therapeutic use of somatostatin analogs able to reduce signs and symptoms of hormone hypersecretion, improve quality of life, and slow tumor growth. Peptide receptor radionuclide therapy is thus an effective treatment option for patients with well-differentiated somatostatin receptor-expressing neuroendocrine tumors. There are several analogs of somatostatin which have been synthesized and evaluated, and Tyr3-octreotate (TATE) and Tyr3-octreotide (TOC) predominantly target sst2 receptors. PRRT with ^{90}Y- or ^{177}Lu-labeled somatostatin analogs, DOTATOC and ^{177}Lu-DOTATATE, has demonstrated impressive results on tumor response, overall survival, and quality of life in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Besides somatostatin receptor-targeting peptides, as described in Chap. 10, there are multiple other radiopeptide analogs which are being developed as diagnostic and therapeutic agents. Some of these peptide analogs, including cholecystokinin, gastrin, gastrin-releasing peptide, arginine–glycine–aspartate (RGD) peptides, and glucagon-like peptide 1 analogs, have shown promise in preclinical studies.

1.4.2.2 Radioimmunotherapy

Radioimmunotherapy (RIT) uses large macromolecular monoclonal antibodies as vectors for transport of the radioactivity to cancer cells. The radiolabeled antibodies are directed against various antigens overexpressed on tumor cells or blood vessels formed during angiogenesis. RIT combines the synergistic effects of both radiation and immunotherapy with manageable local and systemic side effects. Radionuclides emitting β^--particles such as ^{90}Y and ^{131}I are used for RIT. The improved effectiveness of antibodies

labeled with beta-emitting radionuclides relates to the phenomenon of "cross-fire" or "bystander" effect, where tumor cells within close range of the targeted cell are also killed due to secondary radiations. Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of lymphoreticular malignancies which exhibit a wide range of aggressive behavior. The majority of NHLs are B-cell lymphomas, with the follicular and diffused large B-cell lymphomas constituting up to 50 % of NHL cases. The currently US FDA-approved therapeutic agent for the management of lymphomas is ^{90}Y ibritumomab tiuxetan (Zevalin®, Cell Therapeutics Inc, Seattle, WA, and Schering AG, Berlin, Germany; FDA approved in 2002). Earlier, ^{131}I tositumomab had been commercially available and also used for the same indication, but this agent no longer has market approval (Bexxar, GlaxoSmithKline, Research Triangle Parks, NC; FDA approved in 2003).

1.4.2.3 Treatment of Hepatocellular Carcinoma (HCC) and Hepatic Malignancies

As described in Chap. 11, hepatocellular carcinoma (HCC) is a malignant tumor of liver hepatocytes which may be present either as primary liver cancer or as metastatic/secondary liver tumors. Radioembolization by delivering β^--emitting radionuclides (transarterial radioembolization, TART) in colloidal form through the hepatic artery is one of the therapies for the treatment of these inoperable/non-resectable liver malignancies. Radioembolization exploits HCC preferential blood supply from the hepatic artery to deliver the radioactive particles which localize in hepatic end-arterioles thereby allowing localized delivery of therapeutic doses. Thus, this methodology essentially represents a flow-directed mode of treatment that is dependent on neo-angiogenesis. Lipiodol labeled with ^{131}I and lipiodol labeled with ^{90}Y are the two early agents used for this therapy. More recently, such therapy with ^{90}Y microspheres has emerged as the mainstream modality due to the availability of approved products. Commercially available microspheres formed from glass (TheraSphere®; MDS Nordion, Ottawa, ON, Canada) and microspheres made of resin (SIR-Spheres®; Sirtex Medical, Sydney, Australia) are the two commercially available microsphere devices in which ^{90}Y is incorporated. TheraSphere® consists of ^{90}Y embedded into glass microspheres of ~25 μm diameter size which is approved by the US Food and Drug Administration for the treatment of unresectable HCC. SIR-Spheres® consists of biocompatible resin-based microspheres containing ^{90}Y and was granted approval for metastatic colorectal cancer in 2002. In addition to these commercially available agents, a variety of new radiopharmaceuticals are being developed and evaluated for the treatment of HCC as described in Chap. 11.

1.4.2.4 Bone Pain Palliation Therapy

As discussed in detail in Chap. 12, bone metastases are a common complication and the principal cause of pain in cancer patients. Bone metastases may occur in almost all cancers at different frequencies; however, prostate, lung, and breast cancers have maximum probability for such metastases. Radiopharmaceutical treatment of metastatic bone pain is an effective modality that provides palliation of pain to multiple areas of the skeleton simultaneously without the significant soft tissue toxicity. A wide range of radionuclides, especially beta-emitting radionuclides such as ^{177}Lu, ^{32}P, ^{186}Re, ^{188}Re, ^{153}Sm, and ^{89}Sr, have been used for clinical management of bone pain. Of these, ^{32}P and ^{89}Sr are used in the inorganic ionic form, whereas the others are used in the form of complexes with bone-seeking chelates. More recently, ^{223}Ra (Xofigo®) has emerged as a leader in the treatment of bone pain from prostate cancer refractory to chemical castration.

1.4.2.5 Nonmelanoma Skin Cancer Therapy

Clinical implementation of a relatively new radionuclide-based technology described in Chap. 13 may offer the best therapeutic regimen for treatment of nonmelanoma skin cancers, especially in delicate areas of the face and neck regions where surgical removal can result in difficult to resolve scarring. Radioisotopes being evaluated for this application primary involve ^{188}Re and ^{32}P skin applications.

1.4.2.6 Radiosynovectomy: Therapy of Arthritis (Radiosynoviorthesis)

Another important clinical application of therapeutic radioisotopes is the treatment of inflamed synovial joints. This technique is referred to as radiosynovectomy or radiosynoviorthesis and involves the restoration of inflamed and damaged synovial membrane of the joints after intra-articular injection of radionuclide-based preparations to patients with rheumatoid arthritis. This technology is practiced essentially worldwide, except interestingly in the USA, because of regulatory fear of consequences of in vivo radioisotope leakage. In this procedure, a beta-emitting radionuclide in colloidal or particulate form is injected into the articular cavity to deliver radiation dose to the inflamed synovium without excessive irradiation of surrounding tissue. Chapter 14 discusses the agents used for this application. Since the synovial thickness of different joints, principally including the knee, wrist, and finger vary substantially, selection of a radionuclide for radiosynovectomy is critical and is therefore primarily based on the size of the joint to be treated. Thus, for smaller joints lower-energy β^- emitters such as ^{169}Er are preferable. Several other β^--emitters have been evaluated or have entered routine use for this indication and include ^{165}Dy, ^{166}Ho, ^{32}P, $^{186/188}$Re, ^{90}Y, and, more recently, ^{177}Lu.

1.4.2.7 Therapy of Arterial Restenosis following Balloon Angioplasty

Finally, an additional unique therapeutic radioisotope application involves the intraluminal application of beta-emitting radioisotopes, currently limited to ^{188}Re, for the inhibition of the hyperplastic response of smooth muscle cell proliferation following arterial wall damage after balloon angioplasty as described in Chap. 15.

1.5 Historical Timeline of Nuclear Medicine

Nuclear medicine is gifted with contributions from scientists across different disciplines including chemistry, biology, physics, engineering, and medicine. Nuclear medicine evolved into the current status thanks to a series of discoveries and landmark events. The following timeline highlights some important dates in the history of nuclear medicine:

1896 Henri Becquerel discovers radioactivity.

1897 Marie Curie isolates radium from pitchblende.

1903 Alexander Graham Bell suggested placing radium sources in or near tumors for therapeutic purposes.

1913 Frederick Proescher intravenously injects radium for therapy of various diseases.

1924 Georg de Hevesy performed the first radiotracer studies in animals using ^{210}Pb and ^{210}Bi.

1925 Herrman Blumgart and Otto Yens used bismuth-214 (radium-C) to determine the arm-to-arm circulation time in patients.

1932 Ernest Orlando Lawrence constructed the first cyclotron, providing high-energy particles suitable for radionuclide production.

1935 O. Chievitz and George de Hevesy administered phosphate labeled with phosphorus-32 to rats and demonstrated the renewal of the mineral constituents of the bone.

1936 John Hundale Lawrence first applied the artificial radionuclide ^{32}P to treat leukemia. (John 1936)

1938 John Livingood and Glenn Seaborg discovered iodine-131 and cobalt-60.

1938 Emilio Segre and Glenn Seaborg discovered ^{99m}Tc, which is still the mostly used radionuclide in nuclear medicine.

1939 Joseph Gilbert Hamilton, Mayo Soley, and Robley Evans published the first paper on the diagnostic uses of iodine-131 in patients.

1939 Charles Pecher observed uptake of strontium-89 in bone metastases.

1940 The Rockefeller Foundation funded the first cyclotron dedicated for biomedical radionuclide production at Washington University in St. Louis.

1941 Saul Hertz gave a patient the first therapeutic dose of iodine-130.

1942 Enrico Fermi demonstrated the first controlled chain reaction.

1946 Allen Reid and Albert Keston discovered iodine-125, which became important in the field of radioimmunoassay.

1946 Samuel M. Seidlin, Leo D. Marinelli, and Eleanor Oshry treated a patient with thyroid cancer with iodine-131, an "atomic cocktail."

1947 Benedict Cassen used radioiodine to determine whether a thyroid nodule accumulates iodine, helping to differentiate benign from malignant nodules.

1947 George Moore used iodine-131-labeled diiodofluorescein to "probe" the brain for tumors at surgery.

1949 B. Silverstone used phosphorus-32 to detect brain tumors at surgery with a probe detector.

1950 K.R. Crispell and John P. Storaasli used iodine-131-labeled human serum albumin (RISA) for imaging the blood pool within the heart.

1950 Abbott Laboratories sold the first commercial radiopharmaceutical (^{131}I-labeled human serum albumin).

1951 The US Food and Drug Administration approved $Na^{131}I$ for use with thyroid patients. It was the first regulatory approved radiopharmaceutical.

1951 Benedict Cassen, Lawrence Curtis, Clifton Reed, and Raymond Libby automated a scintillation detector to "scan" the distribution of radioiodine within the thyroid gland.

1953 Gordon Brownell and H.H. Sweet built a positron detector based on the detection of annihilation photons by means of coincidence counting.

1953 Robert F. Schilling invented a test of vitamin B12 absorption, which plays a key role in nuclear hematology.

1954 David Kuhl invented a photorecording system for radionuclide scanning. This development moved nuclear medicine further in the direction of radiology.

1955 Rex Huff measured the cardiac output in man using iodine-131 human serum.

1955 George V. Taplin used iodine-131-labeled rose bengal to image the liver. He also used radioiodinated hippuran to measure kidney function with scintillation detectors.

1957 The first ^{99}Mo/^{99m}Tc generator was constructed at the Brookhaven National Laboratory in the USA.

1957 H. Knipping used xenon-133 to measure lung ventilation.

1958 Hal Anger invented the scintillation camera, an imaging device that made possible to conduct dynamic studies.

1959 Solomon Berson and Rosalyn Yalow invented the technique of radioimmunoassay to detect insulin antibodies in human serum.

1959 Picker X-Ray Company delivered the first 3-inch rectilinear scanner.

1960 John McAfee and Henry Wagner imaged the kidneys with radiomercury-labeled chlormerodrin.

1961 Allis-Chalmers installed the first US "medical center" cyclotron at Washington University Medical School. The cyclotron was designed by M.M. Ter-Pogossian.

1962 David Kuhl introduced emission reconstruction tomography. This method later became known as SPECT and PET. It was extended in radiology to transmission X-ray scanning, known as CT.

1962 Nuclear Chicago delivered the first commercial Anger camera to Ohio State University.

1963 Henry Wagner first used radiolabeled albumin aggregates for imaging lung perfusion in normal persons and patients with pulmonary embolism.

1963 George V. Taplin developed albumin aggregates for study of phagocytosis by the reticuloendothelial system.

1963 B. Ansell and B.M. Cook used radiolabeled colloids for radiation synovectomy.

1964 The FDA exempted the "new drug" requirements for radiopharmaceuticals regulated by the Atomic Energy Commission.

1964 Paul Harper and Katherine Lathrup developed radiotracers labeled with Tc-99m for the study of the brain, thyroid, and liver.

1968 Henry Wagner and colleagues used xenon-133 ventilation scans to diagnose pulmonary embolism.

1969 C.L. Edwards reported the accumulation of gallium-67 in cancer.

1970 W.C. Eckelman and P. Richards developed Tc-99m "instant kit" radiopharmaceuticals. The first one was Tc-99m-DTPA.

1970 The FDA announced that it would gradually withdraw the exemption granted to radiopharmaceuticals and start regulating them as drugs. The change would be completed by January 20, 1977.

1971 Gopal Subramanian and John McAfee introduced Tc-99m-labeled phosphates for bone imaging.

1972 David Kuhl performed the first quantitative measurement of cerebral blood volume in living patients.

1973 H. William Strauss introduced the exercise stress-test myocardial scan.

1973 Elliot Lebowitz introduced thallium-201 for myocardial perfusion imaging, first proposed by Kawana.

1973 David Goldenberg demonstrated that radiolabeled antibodies against a human tumor antigen (CEA) could target and image human tumors in animals.

1976 John Keyes developed the first general purpose single-photo emission computed tomography (SPECT) camera.

1976 N. Firusian used strontium-89 to reduce pain from metastatic bone disease.

1976 Ronald Jaszczak developed the first dedicated head SPECT camera.

1977 The FDA required manufacturers to obtain an approved new drug application for new and existing radiopharmaceuticals. The requirements are essentially the same as those for other prescription drugs.

1977 New England Nuclear received FDA approval to distribute thallium-201 for myocardial perfusion and the diagnosis and location of myocardial infarction.

1978 David Goldenberg used radiolabeled antibodies to image tumors in humans.

1981 J.P. Mach used radiolabeled monoclonal antibodies for tumor imaging.

1981 K.A. Krohn, D.R. Vera, and S.M. Steffen developed the first Tc-99m-labeled receptor ligand.

1982 Steve Larson and Jeff Carrasquillo treated cancer patients with malignant melanoma using iodine-131-labeled monoclonal antibodies.

1983 William Eckelman and Richard Reba carried out the first successful SPECT imaging of a neuroreceptor in humans.

1983 Henry Wagner carried out the first successful PET imaging of a neuroreceptor using himself as the experimental subject.

1987 Medi-Physics received FDA approval to market the first brain perfusion imaging radiopharmaceutical, iodine-123 IMP.

1985 D.E. Troutner and W.A. Volkert discover ^{99m}Tc-PnAO, the first technetium-based tracer which crossed the blood-brain barrier (BBB).

1988 Ceretec® (^{99m}Tc-HMPAO) for brain perfusion introduced by Amersham was approved by the FDA for the diagnosis of stroke.

1989 The first positron-emitting radiopharmaceutical (^{82}Rb) has been approved for myocardial perfusion imaging.

1990 Alan Fischman used indium-111-labeled chemotactic peptides to detect foci of infection.

1990 Steve Lamberts and Eric Krenning imaged endocrine tumors with somatostatin receptor-binding radiotracers.

1992 The FDA approved the first monoclonal antibody radiopharmaceutical for tumor imaging.

1993 Medi-Physics/Amersham received FDA approval to market strontium-89 chloride for relief of bone pain.

1994 Mallinckrodt received FDA approval to market the first peptide radiopharmaceutical that binds somatostatin receptors for imaging granulomatous and autoimmune diseases.

1995 ADAC Laboratories shipped the first SPECT camera with coincidence detection capability, suitable for combined SPECT and PET imaging.

1996 PET became an accepted tool for brain studies.

1997 Validation of ^{123}I-*beta*-CIT in assessing dopamine transporters in the diagnosis of Parkinson's disease.

1998 FDG PET studies were for the first time used to assess the response of an initial dose of chemotherapy to predict the response to subsequent high-dose chemotherapy.

1999 Sentinel node studies approved by HCFA for improved diagnosis and management of cancers.

2000 The first commercial PET/CT is launched by CTI.

2000 *Time Magazine* recognizes Siemens Biograph as the invention of the year.

2001 16.9 million nuclear medicine procedures were performed in the USA.

2003 FDA gives approval to IDEC Pharmaceuticals for clinical use of Zevalin™, a radioimmunotherapy agent.

2004 FDA approves the use of Bexxar™ for use in lymphoma.

2007 There were 1.8 million PET or PET/CT procedures performed in this year in the USA only.

2008 The first hybrid PET/MRI system for humans, created by Siemens, was installed.

2008 Nuclear medicine has gone through a global crisis due to acute shortage of ^{99}Mo. This has impacted patient access to care.

2009 FDA in September 2009 approved ^{90}Y-ibritumomab tiuxetan as part of the first-line treatment of follicular non-Hodgkin's lymphoma.

2013 The US Food and Drug Administration (FDA) approved radium Ra 223 dichloride (Xofigo® Injection, Bayer HealthCare Pharmaceuticals Inc.) for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease.

The orphan drug designation has been granted by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use of gallium-68 DOTATATE as a diagnostic agent for the management of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

1.6 Summary

Nuclear medicine imaging and radionuclide therapy have been in use for over half a century, and this field continues to grow as new radiopharmaceuticals and upgraded imaging modalities emerge. With the availability of a large number of diagnostic agents, SPECT and PET are matured technologies and represent the mainstay of functional diagnostic imaging. While PET has seen the maximum growth in the last 15 years, the next phase of growth of nuclear medicine is expected to be in radionuclide therapy. Nuclear medicine therapy is not expected to be an answer for the treatment of all types of cancers and chronic disease entities, but there are other niche areas that will emerge wherein nuclear medicine therapy can offer better solutions with alternative technologies. For this reason, radionuclide therapy should not be regarded to be in competition with other treatment modalities. Nuclear medicine therapy is a multidisciplinary procedure that involves a close understanding between specialists in many areas, including nuclear medicine, oncology, surgery, interventional radiology, and radiopharmaceutical scientists. Diagnostic imaging together with radionuclide therapy will be capable of providing patient-specific therapy in many cases.

The full potential of targeted radionuclide therapy can only be realized if new developments in radionuclide technology and availability and carrier-targeting molecules continue to expand. With the appropriate combination of an optimally engineered targeting vector and a suitable radionuclide, the benefit of radionuclide therapy is expected to substantially increase. For a very long time, the use of ^{131}I for the treatment of thyroid cancer patients was the sole example of a therapeutic success based on radionuclide therapy. Advances in nuclear medicine are possible, thanks to the identification of new biological targets and the discovery of suitable targeting vectors, and many more new agents are expected to be available for radionuclide therapy. However, the difficulties and expense to

obtain regulatory approval for new radiopharmaceuticals in a timely manner will continue to be detrimental factors for enhancing the scope of radionuclide therapy. The subsequent chapters in this book address the broad topic of nuclear medicine therapy, in terms of its development, advances, current practices, and future directions.

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