Diagnostic Radiopharmaceutical Agents

Selcan TÜRKER*, A. Yekta ÖZER*°

Summary
Diagnostic medical imaging is a fundamental part of the practice of modern medicine. Today's clinical practice of nuclear medicine revolves primarily around the use of systemically administered gamma- or positron-emitting radiopharmaceuticals as diagnostic tools for imaging the human body. Radiopharmaceuticals consist of either a gamma- or a positron-emitting radionuclide bound to ligands, which cause selective accumulation in cancerous or diseased tissue. Using cameras designed to detect gamma photons leaving the patient's body, the nuclear medicine physician directly observes regional radiotracer distribution and kinetics. This allows the clinician to evaluate those aspects of tissue function involved in the body's handling of the administered agent. Nuclear medicine imaging is considerably more sensitive than most other imaging modalities (X-ray, CT, MRI) for identifying the presence and extent of malignancy, since biochemical changes monitored by positron emission tomography (PET) and single photon emission computed tomography (SPECT) generally precede anatomical changes. This article surveys the growing literature on diagnostic radiopharmaceutical imaging with radiopharmaceutical agents.

Key Words: Radiopharmaceutical agents, diagnostic medical imaging, nuclear medicine, gamma-emitting radionuclides, positron-emitting radionuclides

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1) INTRODUCTION

Radiopharmaceuticals are radioactive agents that have been used extensively in the field of nuclear medicine as noninvasive diagnostic imaging agents to provide both functional and structural informati-
Nuclear pharmacy is a specialty area of pharmacy practice dedicated to the compounding and dispensing of radioactive materials for use in nuclear imaging and nuclear medical procedures. These procedures use small amounts of radioactive material for the safe diagnosis, treatment and monitoring of disease.

The development of nuclear pharmacy as a specialty area followed the development of nuclear medicine as a recognized specialty in the early 1970s. As nuclear medicine evolved from an obscure research tool to a mainstream clinical diagnostic and therapeutic modality, so has the role of the practice of pharmacy in nuclear medicine also evolved. This is borne out by the fact that the majority of radiopharmaceutical doses are now being dispensed through a nuclear pharmacy. In the traditional view of the practice of pharmacy, a triangular relationship between physician, pharmacist, and patient exists (Fig.1).

Nuclear medicine imaging techniques have been an essential part of the treatment scheme in patients with a variety of disorders. Diagnostic nuclear imaging is used principally for bone, brain, kidney, liver, gall bladder, heart, lung and infection assessment. A list of diagnostic radiopharmaceuticals is given in Table 2.

![Figure 1. Traditional representation of the physician, pharmacist, and patient relationship.](image)

We discussed the labelled drug delivery systems, including liposomes and niosomes for diagnostic and therapeutic use in nuclear medicine, in our previous studies. In this review, we have focused on the diagnostic radionuclide imaging and diagnostic imaging agents that are used in clinical practice.

### 2) DIAGNOSTIC RADIONUCLIDE IMAGING

Nuclear medicine imaging is considerably more sensitive than most other imaging modalities [X-ray, CT (computerized tomography), MRI (magnetic resonance imaging)] for identifying the presence and extent of malignancy, since biochemical changes monitored by positron emission tomography (PET) and single photon emission computed tomography (SPECT) generally precede anatomical changes.

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Nuclear imaging techniques have been an essential part of the treatment scheme in patients with a variety of disorders. Diagnostic nuclear imaging is used principally for bone, brain, kidney, liver, gall bladder, heart, lung and infection assessment. A list of diagnostic radiopharmaceuticals is given in Table 2.
A diagnostic radiopharmaceutical is a drug that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles, photons, any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such a drug\(^2\). The nonradioactive portion of the diagnostic radiopharmaceutical is often an organic molecule such as a carbohydrate, lipid, nucleic acid, peptide, small protein, or antibody. As technology advances, new products may emerge that do not fit into these traditional categories (e.g., agents for optical imaging, magnetic resonance spectroscopy, combined contrast and functional imaging). It is anticipated, however, that the general principles discussed here could apply to these new diagnostic products\(^{13,14}\).

When radiopharmaceuticals are used to help diagnose medical problems, only small amounts are given to the patient. The radiopharmaceutical then passes through or is taken up by an organ of the body (organ selection depends on which radiopharmaceutical is used and how it is administered). The radioactivity is then detected, and images produced, by special imaging equipment. These images allow the nuclear medicine physician to study how the organ is working and to detect cancer or tumors that may be present in the organ. Some radiopharmaceuticals are used in larger amounts to treat certain kinds of cancer and other diseases. In those cases, the radioactive agent is taken up in the cancerous area and destroys the affected tissue. The dosages of radiopharmaceuticals used to diagnose medical problems will vary from patient to patient and depend on the type of test\(^{14,15}\).

Using cameras designed to detect gamma photons leaving the patient’s body, the nuclear medicine physician directly observes regional radiotracer distribution and kinetics. This allows the clinician to noninvasively evaluate those aspects of tissue function involved in the body’s handling of the administered agent. At typically administered levels (10^{-6}–10^{-8} M), they can truly serve as tracer probes of tis-
sue biochemistry and/or physiology (functional imaging). The diagnostic information available from radionuclide imaging studies will often complement the information obtained via the more anatomically based diagnostic imaging modalities, such as X-ray, ultrasound (US), and MRI\textsuperscript{16}.

Radiotracer imaging will also, at times, allow detection of the physiologic basis of disease prior to the appearance of associated structural abnormalities detectable by X-ray, US, or MRI. The current clinical techniques for radionuclide imaging include conventional planar and tomographic (SPECT) methods for detection of gamma photons (typically in the range of 60–400 keV), and imaging by PET, where one detects the 511 keV photons produced by positron–electron annihilation. The most commonly used isotope in nuclear medicine is $^{99m}$Tc, which is readily and continuously available from a generator system. After performing quality assurance tests on the eluate, it can be used in the preparation of the final radiopharmaceutical products\textsuperscript{17}.

Today’s clinical practice of nuclear medicine revolves primarily around the use of systemically administered gamma- or positron-emitting radiopharmaceuticals as diagnostic tools for imaging the human body. Tables 3 and 4 show the wide varieties of gamma- and positron-emitting radionuclides, their decay characteristics and methods of production. Gamma-emitting radiopharmaceuticals are the cornerstone of current nuclear medicine practice, due to the widespread availability of appropriate radionuclides (e.g., $^{99m}$Tc, $^{67}$Ga, $^{111}$In, $^{123}$I, $^{131}$I), a diverse selection of radiopharmaceuticals, and the required imaging hardware\textsuperscript{16}.

In designing radiopharmaceuticals, important factors to consider include\textsuperscript{1,16}:

- Radionuclide decay mode and photon energy/energies
- Half-life
- Availability, since regular production and delivery to hospitals are essential
- Cost and availability
- Chemistry that can be adapted to radiopharmaceutical synthesis via simple procedures, so that sterile, pyrogen-free radiopharmaceuticals can be routinely and reliably prepared with minimal inconvenience.

### Table 3. Gamma-emitting Radionuclides\textsuperscript{1}

<table>
<thead>
<tr>
<th>Isotope</th>
<th>$T_{1/2}$ (h)</th>
<th>Production methods</th>
<th>Decay mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{67}$Ga</td>
<td>78.26</td>
<td>Cyclotron</td>
<td>EC (100%)</td>
</tr>
<tr>
<td>$^{123}$I</td>
<td>13.0</td>
<td>Cyclotron</td>
<td>EC</td>
</tr>
<tr>
<td>$^{111}$In</td>
<td>193.4</td>
<td>Reactor</td>
<td>$\beta^-$</td>
</tr>
<tr>
<td>$^{68}$Tl</td>
<td>73.1</td>
<td>Cyclotron</td>
<td>$\gamma$ (16)</td>
</tr>
<tr>
<td>$^{99m}$Tc</td>
<td>6.0</td>
<td>$^{99}$Mo/$^{99m}$Tc Generator</td>
<td>IT (100%)</td>
</tr>
<tr>
<td>$^{111}$In</td>
<td>67.9</td>
<td>Cyclotron, $^{111}$Cd(p,n)$^{111}$In</td>
<td>EC (100%)</td>
</tr>
</tbody>
</table>

### Table 4. Positron-emitting Radionuclides\textsuperscript{1}

<table>
<thead>
<tr>
<th>Isotope</th>
<th>$T_{1/2}$ (h)</th>
<th>Production methods</th>
<th>Decay mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{64}$Cu</td>
<td>0.4</td>
<td>Cyclotron, $^{64}$Ni(p,n)$^{64}$Cu</td>
<td>$\beta^+$ (93%)</td>
</tr>
<tr>
<td>$^{64}$Cu</td>
<td>3.3</td>
<td>Cyclotron, $^{64}$Ni(p,n)$^{64}$Cu</td>
<td>$\beta^+$ (62%)</td>
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<tr>
<td>$^{62}$Cu</td>
<td>0.16</td>
<td>$^{62}$Zn/$^{62}$Cu Generator</td>
<td>$\beta^+$ (98%)</td>
</tr>
<tr>
<td>$^{64}$Cu</td>
<td>12.8</td>
<td>Cyclotron, $^{64}$Ni(p,n)$^{64}$Cu</td>
<td>$\beta^+$ (19%)</td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>1.1</td>
<td>$^{68}$Ge/$^{68}$Ge Generator</td>
<td>$\beta^+$ (90%)</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>1.83</td>
<td>Cyclotron, $^{18}$O(p,n)$^{18}$F</td>
<td>$\beta^+$ (97%)</td>
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<tr>
<td>$^{124}$I</td>
<td>100.3</td>
<td>Cyclotron, $^{124}$Te(p,n)$^{124}$I</td>
<td>$\beta^+$ (25%)</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20</td>
<td>Cyclotron, $^{11}$N(p,n)$^{11}$C</td>
<td>$\beta^+$ $\alpha$</td>
</tr>
<tr>
<td>$^{18}$N</td>
<td>10</td>
<td>Cyclotron, $^{18}$O(p,n)$^{18}$N</td>
<td>$\beta^+$ $\alpha$</td>
</tr>
<tr>
<td>$^{18}$O</td>
<td>0.03</td>
<td>Cyclotron, $^{18}$N(d,n)$^{18}$O</td>
<td>$\beta^+$ (99%)</td>
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<tr>
<td>$^{85}$Y</td>
<td>14.7</td>
<td>Cyclotron, $^{85}$Sr(p,n)$^{85}$Y</td>
<td>$\beta^+$ (33%)</td>
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Hereunder, diagnostic radionuclide imaging will be discussed under radionuclide brain imaging, cardiac radionuclide imaging and radionuclide tumor imaging subtitles.
2.1. Radionuclide Brain Imaging (RNBI)

Delivery of diagnostic agents to the central nervous system (CNS) poses several challenges as a result of the special features of CNS blood vessels and tissue fluids. Diffusion barriers exist between blood and neural tissue, in the endothelium of parenchymal vessels (blood-brain barrier, BBB), and in the epithelia of the choroid plexus and arachnoid membrane (blood-CSF barriers), which severely restrict penetration of several diagnostic systems. The anatomy of large vessels can be imaged using bolus injection of X-ray contrast agents to identify sites of malformation or occlusion, and blood flow quantities can be derived, although relative measures in different CNS regions may be useful in diagnosis.

The role of radionuclide imaging methods in CNS tumor patients at the time of diagnosis involves the following:

1. Evaluation of the patient with a questionable mass on MRI/CT,
2. Differentiation of active neoplasm from tumors of maldevelopmental origin,
3. Verifying uptake at diagnosis so the method can be effectively used during follow-up, or,
4. Prognostic grading of the tumor that will complement information obtained from histopathologic study.

There are SPECT imaging as well as PET imaging agents suitable for these purposes. Blood pool imaging is of limited clinical use and is performed with 99mTc-labelled red blood cells in SPECT and with 15O-labelled water in PET. The major clinical indication for RNBI is cerebral perfusion imaging.

2.2. Cardiac Radionuclide Imaging

Cardiac radionuclide imaging is easily tolerated and relatively easy to perform, requires only moderately expensive equipment, and exposes patients to less radiation than comparable X-ray studies. Heart failure is a disease with significant morbidity and mortality. Some patients may have an improved prognosis because of increased myocardial viability within areas of left ventricular dysfunction.

The early diagnosis of cardiovascular diseases is of great importance. 201Tl and different 99mTc complexes are used in studies of myocardial perfusion. New 99mTc-labelled agents have gained considerable popularity in recent years and include 99mTc-labelled sestamibi and tetrofosmin. These are lipophilic, cationic substances and accumulate in the myocardium in proportion of flow. Typically, myocardial perfusion images are obtained at stress and at rest. Nuclear myocardial perfusion imaging determines levels of ischemia and viability and predicts numerous outcomes. Resting radionuclide perfusion testing with 201Tl- or 99mTc-labelled agents provides viability data and is readily available and inexpensive with high sensitivity and specificity.

Myocardial perfusion imaging can be used for initial evaluation of certain patients with chest pain (i.e., mainly those with pain of uncertain origin) to determine the functional significance of coronary artery stenosis or collateral vessels seen on angiography and to follow up procedures such as bypass surgery, transluminal angioplasty or thrombolysis.

Radionuclide evaluation of cardiac performance based on left and right ventricular function can be done by first-transit studies or gated-imaging studies performed over several minutes. Although first-transit studies are rapid and relatively easy, especially when evaluating ventricular function at rest and on exercise, gated-imaging studies better delineate the cardiac blood pool and ventricular wall motion and are more widely used.

2.3. Radionuclide Tumor Imaging

Diagnostic imaging in oncology fulfills several purposes: to locate the tumor and any metastases; to plan treatment and therapy regimens; to monitor response to therapy; and to identify residual or recurrent tumor. Diagnosis and staging determine treatment options and prognosis of the disease. In general, malignant cells tend to concentrate the radiot-
racers more avidly than benign cells. Therefore, the use of the ‘tumor to background ratio’, with a ratio of more than 1.5-1.7 to be attributed to malignant lesions, has been found useful in this distinction. Several radiotracers have been shown to concentrate into tumors, which makes them useful in the detection of sites with tumor involvement. The development of new and improved tumor selective radiopharmaceuticals is clinically desirable as a means of:• Detecting and/or confirming the presence and location of primary and metastatic lesions,
• Probing biochemical features of neoplastic tissue that have implications for tumor staging and/or treatment planning,
• Monitoring tumor response to treatment.

3. DIAGNOSTIC NUCLEAR IMAGING AGENTS

3.1. 99mTc-Labelled Radiopharmaceuticals

Many 99mTc-containing radiopharmaceuticals have become available for clinical use, including perfusion agents for the heart [99mTc-MIBI (Cardiolite®)] and the brain [99mTc-ECD (Neurolite®) and 99mTc-HMPAO (Ceretec®)], as well as an agent that images renal function (99mTc-MAG3)25. In this section we discuss some of the 99mTc-labelled radiopharmaceuticals.

3.1.1. 99mTc-HMPAO (99mTc-hexamethyl-propylene amine oxime)

99mTc-HMPAO is a lipophilic compound with the ability to cross the BBB and to accumulate in the brain proportional to blood flow. The mechanism of 99mTc-HMPAO retention in tissues is related to its conversion from a lipophilic form to hydrophilic derivatives. The cellular content of glutathione, a reducing agent present in the CNS, appears to be one of the determinants of 99mTc-HMPAO retention through the conversion mechanisms. Other factors appear to mediate the flow-independent accumulation of 99mTc-HMPAO, including changes in redox state of cells, metabolic alterations, and formation of a complex with proteins in subcellular organelles.

The nature of the cells in which 99mTc-HMPAO conversion and its subsequent retention take place is still undetermined. In vitro studies performed in brain slices do not allow the establishment of a cellular localization of 99mTc-HMPAO retention. Studies in neuronally-enriched cultures show a moderate degree of retention in this cell type. Astrocytes, another important cell type in the CNS, outnumber neurons by a factor of five to ten; they possess specialized processes called end-feet which almost entirely cover the surface of intraparenchymal capillaries. This feature suggests that astrocytes could represent a privileged site of 99mTc-HMPAO uptake and retention as it penetrates within the brain parenchyma26.

The contribution of intravascular tracer to the image is therefore relatively small, and the resultant cerebral blood flow (CBF) maps reflect predominantly perfusion in the brain parenchyma27.

Gökçora and co-workers28 performed 99mTc-HMPAO SPECT in young patients with Down’s syndrome and compared perfusion patterns defining the relationship to the primary language areas and Alzheimer disease-related perfusion abnormalities.

Dagar and co-workers investigated the receptor targeting ability of vasoactive intestinal peptide (VIP) grafted sterically stabilized liposomes that encapsulate a radionuclide (99mTc-HMPAO) in an animal model with fully developed breast cancer. The data showed that 99mTc-HMPAO encapsulating VIP sterically stabilized liposomes can be successfully used for the targeted imaging of breast cancer29.

3.1.2. 99mTc-MIBI

The injected radiotracer shows high affinity for areas of high metabolism, as is commonly seen with tumor cells. The tracer is taken up in areas of increased metabolism in the breast and surrounding lymphatic areas. This is indicative of primary breast cancer, as well as the metastatic spread to the surrounding lymph nodes. 99mTc-MIBI is the most frequently used tracer and has become the paradigm of
this new class of compounds suitable for breast imaging. The $^{99m}$Tc-MIBI is a nonmetabolized metallolopharmaceutical used clinically for myocardial perfusion studies and for the imaging of a variety of human tumors. The current sensitivity and specificity rates for breast scintigraphy with $^{99m}$Tc-MIBI depend on a number of factors including lesion size and site.

The mechanism of uptake by the cells of $^{99m}$Tc-sestamibi is not entirely clear, but it seems to be related to the concentration of mitochondria inside the cells and the electrochemical gradient across the cell membrane. Malignant tumor cells maintain higher mitochondrial and plasma transmembrane potentials secondary to increased accumulation of MIBI.

Some studies have found MIBI to be inferior to $^{201}$Tl for identifying viability, but others have found the two to be comparable.

### 3.1.3. $^{99m}$Tc-pyrophosphate ($^{99m}$Tc-PYP)

Bone scanning agents (e.g., $^{99m}$Tc-pyrophosphate) accumulate at these sites, probably secondary to membrane breakdown and microcalcification. Images usually become positive 12 to 24 h after an acute myocardial infarction (MI) combined with $^{201}$Tl/PYP tomography employed to identify the infarct-related vessel in patients with acute MI. Studies demonstrate that combined $^{201}$Tl/$^{99m}$Tc-PYP SPECT is highly accurate for identification of the infarct-related artery in acute MI, even in patients with multivessel disease.

### 3.1.4. $^{99m}$Tc-methylene diphosphonate (MDP)

Of patients diagnosed with breast, prostate or lung cancer, 50% eventually develop skeletal metastases. The most frequently requested diagnostic nuclear medicine procedure is the MDP bone scan. The bone-scan, unlike X-ray procedures that reflect mineral content, outlines physiological processes such as the functional reaction of bone to traumatic, inflammatory, or neoplastic injury. It was reported that $^{99m}$Tc-MDP was a superior bone agent because of its rapid clearance from the blood and soft tissues, and from that time it became the most common agent for high-resolution clinical skeletal scintigraphy in patients with different bone diseases. The $^{99m}$Tc-MDP bone scan can detect lesions long before radiographs of the skeleton become abnormal. The $^{99m}$Tc-labelled diphosphonates show fast blood clearance, reduced soft tissue uptake and increased normal bone uptake. The first diphosphonate used clinically as a $^{99m}$Tc bone-scanning agent was 1-hydroxyethylidene diphosphonate (HEDP), which was eventually replaced by MDP due to its faster blood clearance and higher skeletal affinity.

#### 3.1.5. $^{99m}$Tc-tetrofosmin

$^{99m}$Tc-tetrofosmin, a hydrophobic cationic compound, was designed originally as a radiopharmaceutical for myocardial perfusion imaging, $^{99m}$Tc-tetrofosmin is an extremely stable complex and offers possible formulation advantages over other $^{99m}$Tc complexes, such as room temperature reconstitution from a lyophilized kit. $^{99m}$Tc-tetrofosmin is a lipophilic agent and is seen in the mitochondria similar to the mechanism seen with MIBI. However, its exact localization in the tumor cells is not yet entirely understood.

### 3.2. Iodine Labelled Radiopharmaceuticals

#### 3.2.1. Folate Conjugates

The folate receptor or folate binding protein is attractive as a potential molecular target for radionuclide delivery, since it is overexpressed by a number of tumor cell types (e.g., breast, ovarian, cervical, colorectal, renal and nasopharyngeal), but shows only limited expression in normal tissues.

Retention of a radioactive folate conjugate, folate-diethylenetriaminepentaacetic acid (DTPA)-$^{111}$In, into the brain of mice was observed, although repeated injections or prolonged release via an osmotic pump of the compound did not result in increased brain uptake. Both fluorescence and radioimaging results demonstrate specific uptake of small molecular we-
endocrine tumors. The 131I-labelled agent is also a noradrenaline-like substance, and when stored in neurons of the sympathetic nervous system. Cardiac imaging with this agent may be of diagnostic and potentially salvageable myocardium. These agents are not yet routinely available for clinical use.

3.2.2. Iodine-123 (123I)-Labelled Fatty Acids

123I-labelled fatty acids detect an ischemic myocardium. The normal cardiac muscle uses fatty acid metabolism as its main source of energy; the ischemic myocardium switches to glucose metabolism. Resting radio-labelled fatty acid distribution compared with that of a perfusion agent may approach the gold standard of 18F-FDG as an indicator of viable and potentially salvageable myocardium. These agents are not yet routinely available for clinical use.

3.2.3. 123I Metaiodobenzylguanidine (123I-MIBG)

Meta-iodobenzylguanidine, a structural analog of guanidine, is an adrenergic blocking agent. Like guanidine, MIBG enters the adrenergic tissue and is concentrated in the catecholamine storage vesicles of adrenergic nerve endings and the adrenal medulla. MIBG accumulates in tumors of the neural crest tissue and adrenal medulla such as pheochromocytomas, non-functioning paragangliomas, carcinoid tumors, neuroblastomas and certain neuroendocrine tumors. MIBG has also been used for imaging the medullary carcinoma of the thyroid, retinoblastoma melanoma and bronchial cell carcinoma.

MIBG is a noradrenaline-like substance, and when labelled with 131I or 123I can be used to image neuroendocrine tumors. The 131I-labelled agent is also used in much higher doses for therapeutic purposes in these tumors. The presence of MIBG uptake on the diagnostic scan provides good evidence that the tumor can be treated with high efficacy using this approach and, in addition, the therapeutic dose of the agent can be calculated based on uptake on the diagnostic scan.

123I-MIBG, a neurotransmitter analog, is taken up and stored in neurons of the sympathetic nervous system. Cardiac imaging with this agent may be used in the evaluation of patients with cardiomyopathies and for the early detection of cardiac toxicity from chemotherapy (e.g., doxorubicin). Tagging with 123I allows for imaging of adrenergic nerve terminals both in the heart and in other tissues, with the use of either planar imaging or SPECT. MIBG has enabled noninvasive in vivo visualization of adrenergic receptor density and activity in post-MI, post-heart transplantation and congestive heart failure patients, shedding light on the pathophysiology of these diseases.

3.2.4. Cyto-Toxic Agents Labelled with Radioactive Iodine

There are three major reasons for the interest in cytotoxic agents labelled with radioactive iodine, particularly anti-metabolites:

- Previous studies have demonstrated a substantial incorporation of radiolabelled IudR into DNA of tumors and proliferating tissues,
- Low background radioactivity is achieved one or more days after intravenous administration due to rapid renal excretion of the major radiolabelled metabolite, iodide,
- The comparatively long physical half-life of iodine radioisotope 125I (60 days) is appropriate for longer studies.

In one study, the optimization of the labelling of a thymidine analog, cytarabine, with 125I is described. The results revealed that this new tracer, 125I-cytarabine, has a high affinity for localization in tissues of high proliferation rate, 60-mins post administration. Also, the labelled compound was cleared quickly from most of the body organs and concentrated in the bladder, 60-mins post administration. These findings suggest that 125I-cytarabine allows imaging and treatment of cancer. 125I-cytarabine meets most of the requirements to be used as a successful diagnostic and therapeutic agent: it is a low molecular weight molecule that diffuses readily in tissues, and it will not induce an antibody response, thereby lending itself to repeated injection of continuous infusion.
3.3. Indium Labelled Radiopharmaceuticals

3.3.1. [Indium-111-({\textsuperscript{111}In})-DTPA] Octreotide

Peptides have fast clearance, rapid tissue penetration and low antigenicity and can be produced easily. For evaluation of tumor receptor expression, different radiolabelled peptide analogs, such as somatostatin, cholecystokinin, gastrin, bombesin, substance P, vasoactive intestinal peptide and neuropeptide analogs have been introduced. The most commonly used receptor-targeting agents are the variety of analogs of somatostatin\textsuperscript{36}.

[Indium-111-({\textsuperscript{111}In})-DTPA] octreotide was the first radiolabelled peptide approved by FDA for use in tumor imaging. Octreotide is an 8-amino acid analog of somatostatin, which binds on specific receptors constituted by membrane glycoproteins. Beyond diagnostic applications, octreotide may be useful in peptide receptor radionuclide therapy using high activities of \textsuperscript{111}In\textsuperscript{37}.

3. CONCLUSION

Applications including assessment of blood flow and metabolism, receptor imaging, elucidation of the pathophysiologic process, and evaluation of the role of labelled therapeutic agents and the potential of these techniques are in the development of novel biological therapies. Functional imaging with radiolabelled tracers will play an increasingly important role in modern medicine and the impact will be substantial in the management of patients with various disorders. Overall, radiopharmaceuticals are currently a rapidly growing field thanks to the combined developments in radiopharmaceuticals and instrumentation.

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