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Chapter

Single-Photon Emission Computed Tomography (SPECT) Radiopharmaceuticals

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Abstract

Nuclear medicine techniques have a great deal of advantage of using gamma radiation emitter radiolabeled compounds to diagnose the long list of infectious and malignant disorders in human systems. The gamma emitter radionuclide-labeled compounds are associated with single photon emission computed tomography (SPECT) camera. SPECT camera mainly offers the detection and analysis of gamma rays origin to furnish the imaging of defective organs in the body. There are about 85% radiopharmaceuticals in clinical practice which are being detected by SPECT camera. The following chapter is an update about the SPECT radiopharmaceuticals that were developed and tried for infection and cancer diagnosis.

Keywords: ^{99m}Tc-antibiotics, SPECT imaging, radiopharmaceuticals, nuclear medicines, infection imaging

1. Introduction

Nuclear medicine technique (NMT) is a detection process that helps in obtaining diagnostic results at molecular level of a disease. The technique is carried out by administrating target-specific radioisotope-labeled organic/biomolecule to patient and collecting the gamma signals through scintillating camera to diagnose the infected organ/tissues. In contrast to advanced instrumental procedures such as magnetic resonance imaging (MRI) and computed tomography (CT) scan, NMT offers a wide range of detection limit. For example, NMT starts working from molecular level when no morphological changes appear; however MRI and CT do this job at the appearance of morphological changes in diseased tissues.

NMT works by administration of radiolabeled molecules (commonly known as radiopharmaceuticals) to patients and acquisition of radiation collected through scintillation camera. There are two main components of radiopharmaceuticals: the organic/biomolecule and the radioisotope. The former approaches diseased cells/tissues and accumulate there at diseased cells and the latter part emits radiation to indicate the position of diseased area.

Diagnosis through NMT means the image of internal body organs like heart, kidney, lungs, breast, brain, bones, tissues, or whole body using γ-emitting radiopharmaceuticals; for example, indium-111 (^{111}In) and technetium-99m (^{99m}Tc) labeled molecules. These radionuclides are labeled with a variety of compounds including drugs, organic species, peptides, proteins, and antibodies and then

Targeted agent with labeled radiotracer	Emitting radiation	Cancer type/disease
Bombesine indium-111	γ-emitting	Endocrine organ tumor
Pentadecapeptide Technetium-99m	γ-emitting	Breast and prostate cancer, gastro-entero-pancreatic tumors and lung cancer
Oxdronate-^{99m}Tc	γ-emitting	Bones disease
Tilmanocept technetium-99m	γ-emitting	Breast cancer, melanoma and oral Cavity cancer
Pertechnetate technetium-99m	γ-emitting	Urinary and bladder thyroid cancer
Iodinated bombesin I-125	γ-emitting	Endocrine cancer cell growth in endocrine organ breast, prostate, ovaries and testes
Bombesine rhenium-188	γ-emitting	Prostate tumor
FDG-F-18	γ-emitting	Soft tissue cancer and prostate cancer
Oxdronate-^{99m}Tc	γ-emitting	Bones disease

Table 1.
Gamma-emitting radiotracer for diagnostic imaging of different types of cancer and infection [1].

injected into the patient's body. Intravenously administrated radiopharmaceuticals accumulate in specific body part or organ for which it is prepared and scans are obtained by single photon emission computed tomography (SPECT) camera [1]. Scan generated by SPECT camera gives very fruitful information regarding disease and tumor, which makes it easier for doctors to make decision about treatment strategies.

A large number of compounds have been labeled with γ-emitting radiotracers for imaging of different types of cancer and infection. Some of them are shown in **Table 1** below [2].

2. Radiopharmaceuticals

In radiopharmaceuticals, there is a radioactive component which is used for the diagnosis and treatment of different malignancies. Only 5% of radiopharmaceuticals are used for therapeutic purposes while the remaining has diagnostic applications. Radiopharmaceutical has two components: first one is pharmaceutical part and the second is radiotracer as shown in **Figure 1**.

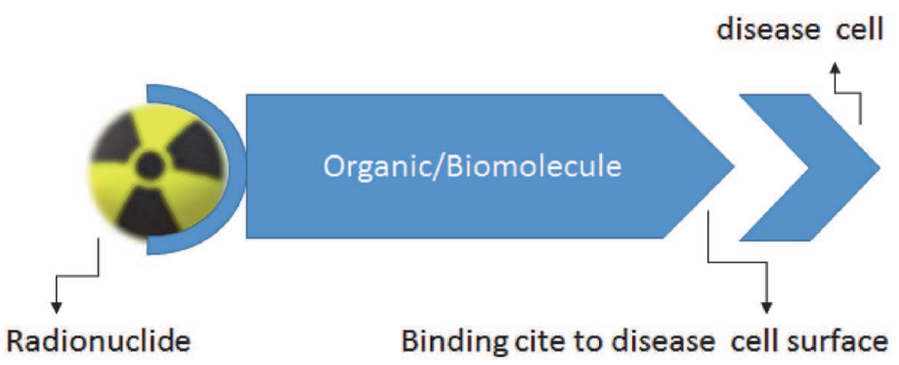

Figure 1.
Radiopharmaceutical and its design.

Targeted agent with labeled radiotracer	Emitting radiation	Cancer type/disease
Metastron ($^{89}SrCl_2$)	β-emitting	Skeletal cancer
Radium-223 dichloride	α-emitting	Bone metastasis, breast and prostate cancer
Samarium-153-EDTMP	β-emitting	Bone and prostate cancer

Table 2.
Commonly used radiopharmaceuticals for therapeutic purpose [4].

Effectiveness of the radiopharmaceutical depends upon both parts. In order to prepare a good and efficient radiopharmaceutical, the first step involves the selection of a pharmaceutical component which is very critical [3]. Pharmaceuticals that have a preferable accumulation in targeted body organ, tissues, or cells should be selected. After the selection of pharmaceutical component, pharmaceutical is labeled with a suitable radiotracer. The radiopharmaceutical is subjected to administration after a routine quality control procedure. There are many disease targeted radiolabeled agents or compounds that are commonly used for diagnosis and therapeutic purpose. From diagnostic point of view, disease-targeted agents (either a drug or any other compound) are labeled with γ-emitting radiotracer, and for therapeutic purpose, these agents are labeled with β and α radiotracer like lutetium-177 (^{177}Lu) and Yatrium-90 (^{90}Y) [4]. In **Table 2**, some of the disease-targeted agents (radiopharmaceuticals) are shown which are used for diagnostic imaging and therapeutic purpose of different diseases and cancers.

3. SPECT—radiopharmaceuticals

Radiopharmaceuticals which are used to diagnose the cancer and infection by using the γ-emitting radionuclides such as ^{111}In and ^{99m}Tc are known as SPECT radiopharmaceuticals. The radiotracer which is used for diagnostic purposes should have following properties [5]:

- Easy availability at nuclear medicine center
- Low cost
- Short effective half-life then labeled pharmaceutical
- Carrier free
- Nontoxic

γ-emitting radiotracer	Half-life (hours)	Generator	Gamma energy	Abundance of γ-emission (%age)
Indium-111	67.32	Cyclotron	0.171 MeV 0.245 MeV	90.5 94
Technetium-99m	6.02	$^{99m}Mo/^{99m}Tc$	140 keV	88.9
Iodine-123	13.22	Cyclotron	159 keV	82.8

Table 3.
Common properties of γ-emitting radionuclides.

- Free from α and β particles emission (with little emission)
- Biological half-life not greater than time of study
- Suitable energy range
- Chemically reactive to form coordinate covalent bonds with the compound which is to be labeled

Common properties of γ-emitting radionuclides for SPECT imaging are given in **Table 3**.

4. Characteristic of technetium-99m for labeling

More than 85% of radiopharmaceuticals which are being used to diagnose the cancer and infection are ^{99m}Tc labeled. The reason for using the ^{99m}Tc is due to following characteristics:

- Half-life of technetium is 6 hours which is sufficient to examine the catabolic as well as anabolic processes which occur in patient and minimal radiation exposure time to the patients [6].
- Energy of the γ-rays emitted by technetium is very low (140 keV) which does not greatly damage the soft tissues of the patient body, although they have low energy but can be detected by any sensitive gamma camera [7].
- Its excretion rate from the patient body is very fast.
- Its short half-life enables us to get the imaging information very quickly.
- Technetium is very reactive to make complex with compounds.
- Decay of technetium takes place through isomeric transitions due to which electrons and gamma radiation of low energy is emitted. Therefore, beta radiation exposure to patent is negligible.
- Due to the emission of same energy levels of gamma radiation, the detector alignment becomes very accurate as no beta radiation is emitted.
- Most important property of technetium is that its oxidation state can be changed according to the desired targeted body organ and parts, which makes it possible to develop a biological technetium labeled compound which can accumulate in high amount on that targeted organ and part of body which is under investigation [8].

5. Chemistry of ^{99m}Tc and oxidation state for labeling

Technetium belongs to transition metal family; its electronic configuration and physical properties are shown in table given below (**Table 4**). There are 22 isotopes of the technetium, but none of them is stable in nature. Half-life of ^{99}Tc is 0.25 million years in its ground state. Oxidation state of technetium varies from −3 to +7

Properties of technetium	Values
Atomic number	43
Atomic mass (amu)	98
Electronic configuration	$1s^2,2s^2,2p^6,3s^2,3p^6,3d^{10},4s^2,4p^6,4d^6,5s^1$
Density gm/cm^3 (at 25°C)	11.5
Oxidation state	−3, −1, 0, +1,+2,+3,+4,+5,+6,+7 (+4 and +7 are more stable)
Melting point in Kelvin	2430.15
Boiling point in Kelvin	5150.15
Occurrence	Solid state (naturally)
Electronagetivity	1.9
First, second, and third ionization energy (kJ/mol)	702, 1472, and 2850, respectively
Electron affinity (kJ/mol)	58
Heat of vaporization kJ/mol	660
Group	VIIB (7)
Metal category	Transitions metal
Period	Fifth
Color	Silvery gray
Numbers of isotopes	Twenty-two

Table 4.
Physical and chemical properties of technetium.

as shown in **Table 4** below. This happens due to the 4d and 5s loss or gain of electrons by 4d orbital. Different types of ligands which are used to label the technetium and chemical conditions under which labeling process is accomplished are responsible for steadiness of such types of oxidation state. It is observed that technetium is found in nature in the form of halides (TcF_6, $TcCl_6$ and $TcBr_4$, oxide, [TcO_2, Tc_2O_7], sulfides [Tc_2S_7], and pertechnetate $^{99m}TcO_4^-$ in +4 to +7 oxidation states). Oxidation states of smaller values such as −1, +2, +3 are naturally stabilized during complex formation with varieties of ligands; for example, +3 oxidation state is stabilized by the chelating agent, methylene diphosphate [9]. Without the use of these chelating agents in complex formation, the oxidation state will not remain constant and technetium would oxidize to +4 oxidation state and eventually change to +7 oxidation state which is most stable state in complex. The +5 and +6 oxidation of technetium is habitually charged to +4 and +7 oxidation states as shown in the following Eqs. 1 and 2 which is most stable regardless of their proportion.

$$3Tc^{+5}\ 2Tc^{+4+}\ Tc^{+7} \tag{1}$$

$$3Tc^{+6}\ Tc^{+4} + 2Tc^{+7} \tag{2}$$

The coordination number of the technetium during complex formation can be changed between 4 and 9.

6. Reducing agents and reduction of $^{99m}TcO_4^-$

Technetium generated by Moly generator presents in the form of sodium-pertechnetate (^{99m}Tc-$NaTcO_4$). In this pertechnetate ion, the oxidation state of technetium is +7 and structure of the $^{99m}TcO_4^-$ is pyramid tetrahedron in which Tc atom is present in the center of the tetrahedron with +7 oxidation state and four oxygen atoms located at the apexes of the triangular pyramid. This geometry and oxidation state is identical to the permanganate ion MnO_4^- and perrhenate ion ReO_4^- ion. Structure of the pertechnetate ion TcO_4^- is shown in **Figure 2**.

Pertechnetate $^{99m}TcO_4$ is a nonreactive molecule and cannot be used directly for labeling; therefore, it is necessary to reduce the pertechnetate from +7 oxidation state to lower oxidation state for labeling purposes. For the reduction of the pertechnetate $^{99m}TcO_4$ form +7 oxidation state to lower oxidation state, a variety of reducing agents are employed such as stannous citrate ($C_{12}H_{10}O_{14}Sn_3$), stannous tartrate ($C_4H_4O_6Sn$), stannous chloride ($SnCl_2.2H_2O$), concentrated hydrochloric acid (HCl), dithionite ($O_4S_2^{-2}$), ferrous sulfate ($FeSO_4$), and sodium boro tetrahdride ($NaBH_4$). However, the most frequently used reducing agent in labeling of the compounds with technetium process is stannous chloride dihydrate ($SnCl_2.2H_2O$) [10]. Electrolysis can also be utilized as a method for reducing sodium-pertechnetate (^{99m}Tc-$NaTcO_4$) and use zirconium as an anode and labeling compound. However, following common characteristics are being considered to choose a reducing agent in ^{99m}Tc chemistry.

- It should give effectual reduction at compassionate pH environment.
- It should have long shelf life mean remain unaffected when they are stored for long time.
- It should not incorporate within the final product of the complex.
- It should give well-defined oxidation state in order to generate intrinsic complex.
- It should not interfere with complex formation procedure.

Reduction of pertechnetate $^{99m}TcO_4$ with the help of stannous chloride is accomplished in acidic medium, and reaction is given below.

$$3Sn^{+2}\ 3Sn^{+4} + 6\ e \qquad (3)$$

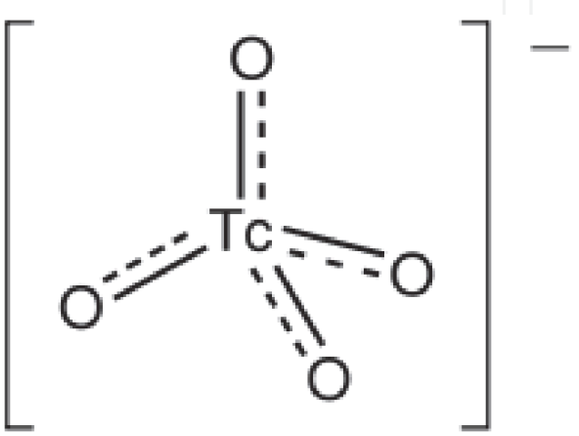

Figure 2.
Structure of pertechnetate ion $^{99m}TcO_4^-$.

$$2^{99m}TcO_4 + 16H^+ + 6e^{99m}Tc^{+4} + 8H_2O \quad (4)$$

Overall reaction

$$2^{99m}TcO_4 + 16H^+ + 3Sn^{+2\ 99m}Tc^{+4} + 8H_2O + 3Sn^{+4} \quad (5)$$

It is clear from the Eq. 4 that technetium reduces from higher oxidation state +7 to lower oxidation state +4. Under different chemical and physical conditions, other oxidation state of ^{99m}Tc such as $^{99m}Tc^{+3}$ and $^{99m}Tc^{+5}$ are likely to be formed or a mixture of all these oxidation states could possibly exist. Stannous chloride as a reducing agent is usually used in a very small amount while ^{99m}Tc is commonly administrated in the concentration $\sim 10^{-9}$ M.

7. Labeling of chelating agents with reduce technetium

Technetium-99m after reduction forms reactive species and attains the ability to bind with a variety of chelating agents to generate the labeled product. In order to form the additive bond, normally, chelating agent donates the lone pairs of the electrons to make coordinate covalent bond with ^{99m}Tc. Compounds containing the electron donating group such as carboxylic group (—COOH), amines ($—NH_{2)}$, hydroxyl (—OH), and thiol group (—SH) are good chelates such as DTPA (diethylenetriamine pentaacetic acid) and gluceptate.

8. Oxidation state of technetium for labeling

Technetium is found in variable oxidation states ranging from −1 to +7, but it frequently forms complexes in +5 oxidation state. A number of technetium complexes with other oxidation states also exist in increasing order [10]. Complex of technetium in +6, +2 and zero oxidation state are not synthesized because they are not fruitful for medical purpose. Different complexes of technetium that they from in different oxidation states are as follows:

- Complex of technetium in +7 oxidation state (Tc^{+7}). Technetium naturally occurs in this state, and it is most stable and nonreactive toward any chelating agent in this oxidation state. Technetium in +7 oxidation state is found in the form of technetium heptasulfide and pertechnetate $^{99m}TcO_4$.

- Complex of technetium in +5 oxidation state (Tc^{+5}). Technetium is present in this oxidation state in the form of complexes such as^{99m}Tc-gluconate, ^{99m}Tc-glucepetate, and ^{99m}Tc-citrate. During these complexes formation, reduction of technetium (pertechnetate $^{99m}TcO^{-}_4$) from +7 oxidation state to lower oxidation state +5 is accomplished with stannous chloride in an aqueous medium. It is observed that technetium in +5 oxidation state have tendency to form the complex with sulfur containing molecules (dithiols) in solid state. In these sulfur complexes, four sulfur atoms are located at the corner of the square planes and oxygen atom at the apex of square pyramid. Compounds with six coordination number are preferably formed in the aqueous medium, and molecules exhibit more stable structure in the form of octahedral geometry. Diaminodithiol (DATA) is one of the best examples of such compounds. In these complexes, oxidation state of technetium is +5 and complexes are neutral and stable in this oxidation state.

- Complex of technetium in +4 oxidation state (Tc^{+4}). Oxidation state of technetium in complexes of TcO_2 and hexahalo is +4. The reducing agent which is used to reduce the pertechnetate $^{99m}TcO_4$ from +7 oxidation state to lower oxidation state +4 ($TcO2.xH_2O$) is zinc with HCl. However, 20% of technetium reduces to technetium metal by this method. In technetium-99m-hydroxyethylidene diphosphonate (HEDP) complex, it is observed that the oxidation state of technetium is changeable which is highly dependent upon the pH of the method which is used to synthesize the complex. In acidic medium, the oxidation state of technetium is +3; in alkaline medium, it is +5; and in neutral medium, it is +4 [11]. This means that a slight change in pH can change the oxidation state of technetium pointing to the fact that they may exist as a mixture of all oxidation states like +3, +5 and +4 in technetium-99m-hydroxyethylidene diphosphonate (HEDP) complex.

- Complex of technetium in +3 oxidation state (Tc^{+3}). A number of technetium-99m complexes exist with +3 oxidation state in acidic medium. These complexes include DTPA (diethylenetriamine pentaacetic acid, ethylenediamine tetraacetic acid (EDTA), DMSA (dimercaptosuccinic acid) and hepatobiliary iminodiacetic acid. However, the oxidation state of technetium in the complex EDTA and DTPA become +4 in alkaline as well as in neutral medium. A variety of technetium complexes in which technetium exists in +3 oxidation state are used for myocardial scanning. These include complexes of technetium-99m with phosphine, arsine and BATOs (boronic acid adduct of technetium dioxime comples).

- Complex of technetium in +1 oxidation state (Tc^{+1}). This oxidation state is stabilized with the help of coordinate covalent bond with different types of ligands in aqueous medium. In this oxidation state, compounds are usually stable in water and air.

9. Chemistry of indium and oxidation state for labeling

Indium belongs to aluminum which are naturally occurring transition metals. Its chemical and physical properties are enlisted in **Table 5**. Indium is a soft silvery white metal which is not found in free elemental form but found in the form of combined state such as halides $InCl_3$, $InBr_3$ InI_3 and InF_3, sulphide and oxide (In_2O_3). Indium exists in three oxidation state +3, +2 and +1 but indium in +3 oxidation state it appears more stable. Thirty-nine isotopes of indium have been reported but only three

Properties of indium	Values
Atomic number	49
Atomic mass (amu)	114.818
Electronic configuration	$1s^2,2s^2,2p^6,3s^2,3p^6,3d^{10},4s^2,4p^6,4d^{10},5s^2,5p^1$
Density gm/cm^3 (at 25°C)	7.31
Oxidation state	+1,+2,+3, (+3 more stable)
Melting point in Kelvin	429.75
Boiling point in Kelvin	2353.15
Occurrence	Solid state (naturally)
Electronegativity	1.78

Properties of indium	Values
First, second and third ionization energy (kJ/mol)	558, 1820, 2704, respectively
Electron affinity (kJ/mol)	29
Heat of vaporization kJ/mol	23.2
Group	IIIA (13)
Metal category	Poor metal (posttransitional)
Period	5th
Color	Silvery white
Natural isotopes (two)	Indium-113 and Indium-115
Artificial isotope	39 in number but Indium-111 and Indium-113 are important

Table 5.
Physical and chemical properties of indium.

isotopes such as indium-111, indium-113 and indium-115 are commonly found. Indium-111 with half-life of 66.32 hours are used in radiopharmaceutical for imaging purpose [12]. γ-radiation emitted by indium-111 have an energy of 247 keV and 172 keV and the percentage of γ-radiation emitted by indium-111 is 90.6% with minimal β-radiation emission that make the indium −111 a good imaging radiotracer.

Sr no.	Labeled compound	Labeled radioisotope	SPECT imaging model	Pathology	Sensitivity/ accuracy	Refs.
1.	Oxyquinolone-labeled leukocytes	^{111}In	Human model		90%	[1]
2.	Exametazime-labeled leukocytes	^{99m}Tc	Human model	Reticuloendothelialsystem visualization	90%	[1]
	Sulfur colloid	^{99m}Tc	Human model	osteomyelitis		
3.	Methylene diphosphonate	^{99m}Tc	Human model		High sensitivity low specificity	[2]
4.	Labeled leukocytes	^{111}In	Human model			[2]
5.	HMPAO labeled leukocytes	^{99m}Tc	Human model			[2]
6.	Biotin	^{111}In	Human model	Spinal infection	93%	[2]
7.	UBI	^{99m}Tc	Human model	Soft tissue and bone infection	95%	[3]
8.	MDP	^{99m}Tc	Human model	Marrow imaging		[4]
9.	HMPAO-labeled leukocyte	^{99m}Tc	Human model	Prosthetic joint infections	91%	[5]

Table 6.
General radiopharmaceuticals developed based on SPECT imaging.

These γ-emitting radionuclide labeled compounds can be utilized to identify the exact position and location of the infection in different parts and organs such as brain, arteries, joints, bones and tissues. In **Table 6**, a number of compounds bound with γ-emitting radionuclides (indium-111 and technetium-99m) along with their sensitivity and imaging purpose are shown.

10. Methods of radiolabeling

The radiolabeling of antibiotics, drugs, peptides, proteins and organic species with different radiotracer has increased reasonably from imaging point of view in medical, biochemical and other associated fields. In the field of medical imaging, compounds are labeled with two types of radionuclides: (a) compound labeled with those radionuclide that emitted the gamma radiation and have large number of application and especially used for in vivo imaging of a number of organs and (b) secondly, the compounds are labeled with radionuclide that emitted the β-radiation and have limited in vitro study and therapeutic treatment of the disease site. During the labeling process of a compound with a radiotracer, atoms or group of atoms of compound are replaced by different or similar atoms or group of atoms of the radiotracers [13]. In order to obtain, certain type of the labeling, the labeling process is carried out under constant conditions of temperature, pressure and incubation time. There are mainly six methods for labeling of the compound with radiotracer as shown in **Table 7**.

Isotopic exchange	Labeling of the compounds with C-14, S-35, I-135 labeling of T3 and T4 and H-3.
Labeling with bifunctional Chelating Agent	In-111 DTPA albumin Tc-99m DTPA antibody
Introduction of foreign label	Labellng of the proteins with I-125. Tc-99m labeled radiopharmaceuticals Labeling of the hormones with I-125 Labeling of the cells with In-111 F-18 fluorodeoxyglucose
Biosynthesis	Labeling of the compounds with C-14 Co-57 cyanocobalamin Se-75 selenomethionine
Excitation labeling	Labeling of the compounds with I-223 from Xe-123 decay Labeling of the compounds with Br-77 from Kr-77 decay
Recoil labeling	Iodinated compounds Compounds label with H-3

Table 7.
Methods for labeling of the compound with radiotracers [13].

11. Direct method labeling without bi-functional chelating agent

In this type of labeling process, there is no need of bi-functional chelating agents or metal cheater. These are discussed below.

11.1 Isotopes exchange labeling

In this method, some atoms from the compound which is to be labeled is replaced by isotope of the same atom of the element having different atomic mass

(more or less) such as I-123, I-124, I-125, I-127, and I-131. the compound is labeled with isotope of the same element so the compound to be labeled and radiolabeled are similar in biological properties, except for the energy emitted from different isotopes of the same element which is used for labeling [14]. This method used for in vitro study. Examples of isotope exchange labeling reactions are labeling of the triiodothyronine (T3) with I-125, labeling of thyroxine with I-125, and labeling with C-14, S-35 and H-3 labeled compounds [15].

11.2 Introduction of a foreign label

In this process of labeling, a molecule of known biological function is labeled with a radionuclide. This labeling occurs by forming covalent bond or co-ordinate covalent bond. The attaché radiotracer is unknown (foreign) to the molecule, and labeling does not occur due to the exchange of its isotope. In most of these types of compounds, chelation is the cause for bond formation. In such bonds, more than one atom donates a pair of electrons to the foreign acceptor atom that is mostly a transition metal. Majority of Tc-99m labeled compounds are developed by this process such as binding of Tc-99m with DTPA, gluceptate, etc.

11.3 Biosynthesis

The biosynthesis method involves the growth of the microorganisms in a culture medium that contains the radiotracer. When microorganisms (bacteria) grow in such a medium, the radiotracer is introduced into the metabolites that are produced by the metabolic activity of the organism. This metabolite is then chemically separated. Example of such product is preparation of ^{57}Co-B12 by using a bacterium *Streptomyces griseus*.

11.4 Recoil labeling

It is of limiting interest and cannot be preceded on large scale for labeling because it has low specific activity of the bounded molecule. The method involves generation of recoil ions or atoms as particles are emitted by the nucleus. These generated atoms or ions then form a bond with the targeted molecule. This high energy of recoil atoms gives poor yield.

11.5 Excitation labeling

Radioactive and very reactive daughter ions that are produced by nuclear decay process are used in excitation labeling process. In β-decay and electron capture processes, there is a production of highly energetic charged particle ions which have the ability to label the compound of interest. When Kr-77 undergoes the decay process, it yields Br-77. These (Br-77) energetic ions are able to bind the compound of interest when exposed to it [16]. A number of proteins are labeled with I-123 when protein is exposed to Xe-123 which decays into energetic I-123 and label the protein. Main disadvantage of this method is poor yield.

12. Indirect method labeling using bi-functional chelating agent

A chelating agent is a substance that has the ability to form multiple bonds with a single metal ion, thus acts as a multidendate ligand. Bi-functional chelating agent is that which has two are more separate covalent or coordinate covalent bonds with a ligand which is polydendate in nature. The labeling process using bi-functional

chelating agent involves the bond formation at two sites: one bond is formed by the bi-functional chelating agent with macromolecule such as protein and antibody and other bond is formed with metal ion such as Tc-99m. There are many bi-functional chelating agents being used currently; however, most important are diethylene-triamine pentaacetic acid (DTPA), metallothionein, diamide dimercaptide (N_2S_2), dithiosemicarbazone, and hydrazinonicotinamide.

There are two types of labeling process by using bi-functional chelating agent.

(a) Tc-99m chelate method: In this method, a chemical is used to carry out chelation (such as diamidodithiol and cyclam) and labeling of macromolecules such as protein by forming the bond between chelating agent and protein (macromolecule).

(b) Indirect chelater antibody method: In this method, bi-functional chelating agent forms a bond with macromolecule and then it reacts with metal ion to form the complex known as metal-chelator-macromolecule complex. By using indirect chelator antibody method, a number of antibodies are labeled. The biological function of the antibodies may be affected due to the presence of the chelating agent; therefore, it is necessary to check the labeling products before a clinical trial. It is no doubt that the prelabeled chelating method gives pure metal-chelate- complex with precise structural study. However, the main drawback of this method is that it is a lengthy procedure and gives poor yield [17].

These SPECT-radiopharmaceuticals can also be developed for early and accurate diagnosis of cancer in different body parts and organs. A variety of drugs and compounds such as peptides, proteins, antibodies, and organic species were labeled with radionuclides such as indium-111 and technetium-99m, and these radiolabeled compounds are used for the successful and accurate diagnosis of different types of

Sr. no.	Labeled compound	Labeled radioisotope	SPECT imaging model	Pathology	Sensitivity/ accuracy	Refs.
1.	Anti-PSMA nanobody	^{111}In	Human model	Tumor target		[6]
2.	HYNIC-Glu-Urea	^{99m}Tc	Human model	Metastatic prostate cancer		[6]
5.	DTPA-AMB8LK	^{111}In	Mice model	Pancreatic cancer	23.6 ± 3.9% ID/g	[7]
6.	Octreotide	^{111}In	Human model	Neuroendocrine tumor (NETs)	95%	[8]
7.	Sestamibi	^{99m}Tc	Human model	Parathyroid adenoma	Range from 85 to 95%	[8]
8.	MDP	^{99m}Tc	Human model	Bone metastases	Very sensitive	[8]
9.	(Arg11)CCMSH	^{99m}Tc	Mice model	Murine melanoma	3.33 ± 0.50% ID/g	[9]
10.	DOTA-Re(Arg11) CCMSH	^{111}In	Mice model	Murine melanoma	8.19 ± 1.63% ID/g	[9]
11.	DTPA-octreotide	^{111}In	Mice model	Lung cancer	Bm/B was 3.1 ± 0.6	[19]
12.	HYNIC-TOC	^{99m}Tc	Human model	Metastatic neuroendocrine tumors	Sensitivity 87%	[10]
13.	DTPA-octreotide	^{111}In	Mice model	Somatostatin-receptor tumors: evaluation	4.3%ID/g	[11]

Sr. no.	Labeled compound	Labeled radioisotope	SPECT imaging model	Pathology	Sensitivity/ accuracy	Refs.
14.	HYNIC-TOC	^{99m}Tc	Mice model	Somatostatin-receptor tumors: evaluation	5.8 ± 9.6% ID/g	[11]
15.	HMPAO	^{99m}Tc	Mice model	Neuroblastoma	88%	[12]
16.	Oxine	^{111}In	Mice model	Neuroblastoma	80%	[12]
17.	Rhenium sulfide colloidal nanoparticles	^{99m}Tc	Rabbit model	Sentinel lymph node	Radiolabeled 98.5 ± 0.5%	[13]
18.	TDMPP complex	^{111}In	Mice model	Tumor imaging		[14]
19.	DOTA conjugate - TA138	^{111}In	Mouse model	Tumor imaging	9.39% ID/g	[15]

Table 8.
SPECT-radiopharmaceuticals using Tc-99m and In-111 for cancer imaging.

cancer in human and mice models [18]. In **Table 8**, a number of compounds which are labeled with γ-emitting radiotracer for SPECT imaging of different types of cancer with accuracy are shown.

SPECT-radiopharmaceuticals are not only used to identify infections and malignancies but are equally used to know the effectiveness of the treatment strategy which is used to cure the infections and tumors. That means, we can employ the SPECT-radiopharmaceuticals for follow-up strategy to know about the effectiveness of a treatment methods. A large numbers of radiolabeled compounds are being used to identify the effects of previous treatment strategy, for example, pentetreotide is labeled with indium-111 to follow-up of the neuroendocrine tumor therapy (tumor generated due to the hormonal cell and nerves system) in gastrointestinal tract, lungs, pancreas, and rest of the body (**Table 9**).

Sr no.	Labeled compound	Labeled radioisotope	SPECT imaging model	Pathology	Sensitivity/ accuracy	Refs.
1	Nano-colloids	^{99m}Tc	Human model	Breast cancer and melanomas	Well accepted	[16]
2	Radio-colloid	^{99m}Tc	Human model	Breast cancer, head/neck malignancies, prostate cancer and gynecological malignancies		[16]
3	Pentetreotide	^{111}In	Human model	Neuroendocrine tumors	95%	[16]
4	Capromab	^{111}In	Human model	Biochemical disease-free survival and disease-specific survival in primary prostate cancer	46%	[16]
5	Medronate	^{99m}Tc	Human model	Bone imaging		[16]
6	Labeled white blood cells	^{111}In	Human model	Inflammation imaging		[16]
7	Labeled white blood Cells	^{99m}Tc	Human model	Inflammation imaging		[16]

Sr no.	Labeled compound	Labeled radioisotope	SPECT imaging model	Pathology	Sensitivity/ accuracy	Refs.
8	Maraciclatide	^{99m}Tc	Human model	Angiogenesis		[16]
9	3P-RGD2	^{99m}Tc				[16]
10	MSAP-RGD	^{111}In				[1]
11	His-annexin A5 C2AcH-	^{99m}Tc(CO)3		Apoptosis		[2]
12	(Me) FGCDEVD	^{99m}Tc				[16]
13	DTPA-Ac-TZ14011	^{111}In		Chemokine receptor 3 expression		[1]
14	AMD3100	^{99m}Tc				[1]
15	DTPA-Fab-PEG24-EGF	^{111}In		Epidermal growth factor receptor		[1]
16	Etarfolatide	^{99m}Tc		Folate receptor		[1]
17	DOTA-folate	^{111}In				[1]
18	MIP1404	^{99m}Tc		Prostate-specific membrane antigen		[1]
19	DPA-alendronate	^{99m}Tc(CO)3		Bone imaging		[1]
20	human umbilical tissue-derived cells	^{111}In	Mice model	Cerebral ischemia		[17]
21	^{99m}Tc-pHLIP		Mice model	Lewis lung carcinoma (LLC), lymph node carcinoma of the prostate (LNCaP) and prostate adenocarcinoma	adequate imageability and correlation with tumor extracellular acidity	[18]
22	^{99m}Tc-HHK		Rat model	Tumor microenvironment	High specificity	[18]
23	nanobody (Nb cl1) against CD206 radiolabeled	^{99m}Tc	Mice model	Macrophages in tumor		[18]
24	^{99m}Tc-PyDA		Mice model	In vivo hypoxia targeting	Selective uptake	[18]
25	^{99m}Tc-meropenem			Tumor hypoxia tissue		[18]
26	^{99m}Tc-nitroimidazole		Mice	Differentiate from inflamed and infected tissues		[18]
27	^{99m}Tc-SD32			Breast tumor cells		[18]

Table 9.
SPECT-radiopharmaceuticals using Tc-99m and In-111 for follow-up imaging.

Sr no.	Labeled compound	Labeled radioisotope	SPECT imaging model	Pathology	Sensitivity/ accuracy/ efficiency	Refs.
1.	HMPAO	^{99m}Tc	Human model	Painful prosthetic hip	39% (SD 12%)	[20]
2.	Tropolonate	^{111}In	Human model	Painful prosthetic hip	63% (SD 14%)	[20]
3.	EDDA/HYNIC-TOC	^{99m}Tc	Human model	Cancer diagnosis	High tumor to organ ratio	[21]
4.	P829 peptide	^{99m}Tc	Human model	Neuroendocrine tumors	91%	[22]
5.	Pentetreotide	^{111}In	Human model	Neuroendocrine tumors	65%	[22]
6.	labeled leukocyte	^{111}In	Human model	Osteomyelitis	91%	[23]
7.	HYNIC-TOC	^{99m}Tc	Human model	Metastatic neuroendocrine tumors	Sensitivity 87%	[10]
8.	HYNIC-OC	^{99m}Tc	Human model	Tumor	0.70 ± 0.13%ID/g	[24]
9.	HYNIC-TOC	^{99m}Tc	Human model	Malignancies	3.85 ± 1.0	[24]
10.	HYNIC-TATE	^{99m}Tc	Human model	Tumor	3.99 ± 0.58%ID/g	[24]
11.	DTPA-OC	^{111}In	Human model	Tumor	0.99 ± 0.08%ID/g	[24]
12.	DOTA-TATE	^{111}In	Human model	Tumor	4.12 ± 0.74%ID/g	[24]
13.	Depreotide	^{99m}Tc	Human model	Lung cancer	Immuno-histochemical correlations 98%	[25–28]
14.	DTPA	^{99m}Tc	Human model	Graves' disease	Specificity 89%	[29]
15.	HDP	^{99m}Tc	Human model	Bone imaging		[30]
16.	Tetrofosmin	^{99m}Tc	Human model	Glioblastoma multiforme	L/N ratio of 4.7	[31]
17.	ECD	^{99m}Tc	Human model	Alzheimer's patients		[32]
18.	MAA	^{99m}Tc	Human model	Liver perfusion imaging	100%	[33–35]
19.	Mebrofenin	^{99m}Tc	Human model	Hepatobiliary Scintigraphy		[36]
20.	HSA-DTPA	^{99m}Tc	Human model	Gastrointestinal bleeding	70%	[34]
21.	GHA	^{99m}Tc	Human model	Brain-scanning	85%	[37]
22.	MDP	^{99m}Tc	Human model	Cerebral infarction		[38]
23.	DMSA	^{99m}Tc	Human model	Acute pyelonephritis		[39]

Sr no.	Labeled compound	Labeled radioisotope	SPECT imaging model	Pathology	Sensitivity/ accuracy/ efficiency	Refs.
24.	Pyrophosphate	^{99m}Tc	Human model	Amyloidoses	97%	[40]
25.	Sulfur Nanocolloid	^{99m}Tc	Human model	Lymphatic drainage from prostate	3.9–5.2 mSv/MBq	[41]
26.	Oxine-labeled leukocytes	^{111}In	Human model	Liver cysts	87.5%	
27.	HMPAO-labeled leukocyte	Tc-99m	Human model	Abscess		[42]
28.	MAA-and HAS Microspheres	^{99m}Tc	Human model	Liver-lung shunt		[35]
29.	HSA-DTPA	^{99m}Tc	Human model	Gastrointestinal bleeding	100%	[34]
30.	Labeled bone marrow mesenchymal stem cells	^{111}In	Human model	Acute brain trauma model		[43]
31.	Oxine	^{111}In	Human model	Diagnostic imaging	80%	[42]
32.	HMPAO	^{99m}Tc	Human model	Diagnostic imaging	88%	[42]
33.	Sulfur Nanocolloid	^{99m}Tc	Human model	Mapping of lymphatic drainage from the prostate		[41]
34.	HMPAO-labeled leukocyte	^{99m}Tc	Human model	Prosthetic joint infections	91%	[5]
35.	Labeled chimeric monoclonal antibody Nd2	^{111}In	Human model	Pancreatic cancer	100%	[44]
36.	Labeled GnRH-I tracer	^{111}In	Human model	Tumor imaging	Efficiency $11.8 \pm 1.9\%$	[45]
37.	Oxine labeled mesenchymal stem cells	^{111}In	Human model	Cirrhosis		[46]
38.	TRODAT-1	^{99m}Tc	Human model	Parkinson disease	Target the pre-synaptic dopamine transporter (DAT)	[47]
39.	Depreotide	^{99m}Tc	Human model	Lung cancer and other pulmonary malignancies	96.6%	[4]
40.	Prostascint	^{99m}Tc	Human model	Prostate cancer	Approved	[4]
41.	Zevalin	^{111}In	Human model	Diagnosis of non-Hodgkin's lymphoma	Approved for use	[4]
42.	CEA scan	^{99m}Tc	Human model	Colon cancer	Approved	[4]
	Octreo Scan	^{111}In	Human model	Neuroendocrine tumors		[4]
43.	Depreotide	^{99m}Tc	Human model	Lung cancer		[4]

Sr no.	Labeled compound	Labeled radioisotope	SPECT imaging model	Pathology	Sensitivity/ accuracy/ efficiency	Refs.
44.	Annexin-V	^{99m}Tc	Human model	Acute myocardial infarction and chemotherapy response monitoring		[4]
45.	Neuroligands	^{99m}Tc	Human model	Neuropsychiatric patients		[4]
46.	EC-MN	^{99m}Tc	Human model	Hypoxia		[4]

Table 10.
Clinical trials study of different SPECT radiopharmaceuticals.

A number of SPECT-radiopharmaceuticals are being used in clinical trials which are producing very fruitful results for the diagnosis of different types of cancers and infections in human beings (**Table 10**). These radiolabeled compounds help doctors obtain useful and precise information at a very early stage of the disease to identify the extent of problem and to take timely decisions about the treatment strategies.

Future prospect

There is a need to develop more accurate, sensitive, precise, and reliable SPECT-radiopharmaceuticals to identify the malignant infections and tumors at an early stage in order to overcome the infectious diseases and cancer all over the world. If cancer is diagnosed at an early stage, it would be easier to plan the exact treatment strategy ahead of time. Considerable advancements have been made during last decades in SPECT-radiopharmaceuticals that may take the place of instrumental imaging techniques and therapeutic strategies. In combination with existing technologies, NMT may help a lot in the diagnostic and therapeutic advancement of clinical detection methods.

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References

[1] Payolla FB et al. Radiopharmaceuticals for diagnosis in nuclear medicine: A short review. Eclética Química Journal. 2019;**44**:11-19

[2] Navalkissoor S et al. Single-photon emission computed tomography–computed tomography in imaging infection. Nuclear Medicine Communications. 2013;**34**:283-290

[3] Sathekge M et al. Molecular imaging in musculoskeletal infections with (99m)Tc-UBI 29-41 SPECT/CT. Annals of Nuclear Medicine. 2018;**32**(1):54-59

[4] Imam SK. Molecular nuclear imaging: The radiopharmaceuticals (review). Cancer Biotherapy & Radiopharmaceuticals. 2005;**20**(2): 163-172

[5] Kim HO et al. Usefulness of adding SPECT/CT to 99mTc-hexamethylpropylene amine oxime (HMPAO)-labeled leukocyte imaging for diagnosing prosthetic joint infections. Journal of Computer Assisted Tomography. 2014;**38**(2):313-319

[6] Su H-C et al. Evaluation of 99mTc-labeled PSMA-SPECT/CT imaging in prostate cancer patients who have undergone biochemical relapse. Asian Journal of Andrology. 2017;**19**(3): 267-271

[7] England CG et al. Molecular imaging of pancreatic cancer with antibodies. Molecular Pharmaceutics. 2016;**13**(1): 8-24

[8] Abikhzer G, Keidar Z. SPECT/CT and tumour imaging. European Journal of Nuclear Medicine and Molecular Imaging. 2013;**41**(Suppl 1):S67-S80

[9] Miao Y, Benwell K, Quinn TP. 99mTc- and 111In-labeled alpha-melanocyte-stimulating hormone peptides as imaging probes for primary and pulmonary metastatic melanoma detection. Journal of Nuclear Medicine. 2007;**48**(1):73-80

[10] Artiko V et al. The clinical value of scintigraphy of neuroendocrine tumors using (99m)Tc-HYNIC-TOC. Journal of BUON. 2012;**17**(3):537-542

[11] Gabriel M et al. An intrapatient comparison of 99mTc-EDDA/HYNIC-TOC with 111In-DTPA-octreotide for diagnosis of somatostatin receptor-expressing tumors. Journal of Nuclear Medicine. 2003;**44**(5):708-716

[12] Cusso L et al. Combination of single-photon emission computed tomography and magnetic resonance imaging to track 111in-oxine-labeled human mesenchymal stem cells in neuroblastoma-bearing mice. Molecular Imaging. 2014;**13**

[13] Dar U et al. In house development of (99m)Tc-rhenium sulfide colloidal nanoparticles for sentinel lymph node detection. Pakistan Journal of Pharmaceutical Sciences. 2013;**26**: 367-373

[14] Sadeghi S et al. Development of (111)In-labeled porphyrins for SPECT imaging. Asia Oceania Journal of Nuclear Medicine & Biology. 2014;**2**(2): 95-103

[15] Harris TD et al. Structure-activity relationships of 111In- and 99mTc-labeled quinolin-4-one peptidomimetics as ligands for the vitronectin receptor: Potential tumor imaging agents. Bioconjugate Chemistry. 2006;**17**(5): 1294-1313

[16] Gnanasegaran G, Ballinger JR. Molecular imaging agents for SPECT (and SPECT/CT). European Journal of Nuclear Medicine and Molecular Imaging. 2014;**41**(Suppl 1):S26-S35

[17] Arbab AS et al. Tracking of In-111-labeled human umbilical tissue-derived cells (hUTC) in a rat model of cerebral ischemia using SPECT imaging. BMC Medical Imaging. 2012;**12**(1):33

[18] Abadjian MZ, Edwards WB, Anderson CJ. Imaging the tumor microenvironment. Advances in Experimental Medicine and Biology. 2017;**1036**:229-257

[19] Schmitt A et al. Differences in biodistribution between 99mTc-depreotide, 111In-DTPA-octreotide, and 177Lu-DOTA-Tyr3-octreotate in a small cell lung cancer animal model. Cancer Biotherapy & Radiopharmaceuticals. 2005;**20**(2):231-236

[20] Aktolun C et al. Technetium-99m and indium-111 double labelling of granulocytes for kinetic and clinical studies. European Journal of Nuclear Medicine. 1995;**22**(4):330-334

[21] Decristoforo C et al. 99mTc-EDDA/HYNIC-TOC: A new 99mTc-labelled radiopharmaceutical for imaging somatostatin receptor-positive tumours; first clinical results and intra-patient comparison with 111In-labelled octreotide derivatives. European Journal of Nuclear Medicine. 2000;**27**(9):1318-1325

[22] Lebtahi R et al. Detection of neuroendocrine tumors: 99mTc-P829 scintigraphy compared with 111In-pentetreotide scintigraphy. Journal of Nuclear Medicine. 2002;**43**(7):889-895

[23] Palestro CJ et al. Osteomyelitis: Diagnosis with (99m)Tc-labeled antigranulocyte antibodies compared with diagnosis with (111)In-labeled leukocytes—initial experience. Radiology. 2002;**223**(3):758-764

[24] Storch D et al. Evaluation of [99mTc/EDDA/HYNIC0]octreotide derivatives compared with [111In-DOTA0,Tyr3, Thr8]octreotide and [111In-DTPA0]octreotide: Does tumor or pancreas uptake correlate with the rate of internalization? Journal of Nuclear Medicine. 2005;**46**(9):1561-1569

[25] Herlin G et al. Quantitative assessment of 99mTc-depreotide uptake in patients with non-small-cell lung cancer: Immunohistochemical correlations. Acta Radiologica. 2009;**50**(8):902-908

[26] Axelsson R et al. Role of scintigraphy with technetium-99m depreotide in the diagnosis and management of patients with suspected lung cancer. Acta Radiologica. 2008;**49**(3):295-302

[27] Shih W-J et al. 99mTc-depreotide chest SPECT demonstrates pulmonary metastases from renal cell carcinoma. Journal of Nuclear Medicine Technology. 2004;**32**(1):19-21

[28] Harders SW et al. Limited value of 99mTc depreotide single photon emission CT compared with CT for the evaluation of pulmonary lesions. The British Journal of Radiology. 2012;**85**(1015):e307-e313

[29] Szumowski P et al. Efficacy of (99m)Tc-DTPA SPECT/CT in diagnosing orbitopathy in graves' disease. BMC Endocrine Disorders. 2019;**19**(1):10-10

[30] Hirschmann MT et al. Assessment of loading history of compartments in the knee using bone SPECT/CT: A study combining alignment and 99mTc-HDP tracer uptake/distribution patterns. Journal of Orthopaedic Research. 2013;**31**(2):268-274

[31] Alexiou GA et al. The value of 99mTc-tetrofosmin brain SPECT in predicting survival in patients with glioblastoma multiforme. Journal of Nuclear Medicine. 2010;**51**(12):1923-1926

[32] Merhof D et al. Optimized data preprocessing for multivariate analysis applied to 99mTc-ECD SPECT data sets of Alzheimer's patients and asymptomatic controls. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2011;**31**(1):371-383

[33] Ahmadzadehfar H et al. The significance of 99mTc-MAA SPECT/CT liver perfusion imaging in treatment planning for 90Y-microsphere selective internal radiation treatment. Journal of Nuclear Medicine. 2010;**51**(8):1206-1212

[34] Kotani K et al. Diagnostic ability of 99mTc-HSA-DTPA scintigraphy in combination with SPECT/CT for gastrointestinal bleeding. Abdominal Imaging. 2014;**39**(4):677-684

[35] Grosser OS et al. Pharmacokinetics of 99mTc-MAA- and 99mTc-HSA-microspheres used in preradioembolization dosimetry: Influence on the liver–lung shunt. Journal of Nuclear Medicine. 2016; **57**(6):925-927

[36] de Graaf W et al. 99mTc-mebrofenin hepatobiliary scintigraphy with SPECT for the assessment of hepatic function and liver functional volume before partial hepatectomy. Journal of Nuclear Medicine. 2010; **51**(2):229-236

[37] Santra A, Kumar R, Sharma P. Use of 99m-technetium-glucoheptonate as a tracer for brain tumor imaging: An overview of its strengths and pitfalls. Indian Journal of Nuclear Medicine: IJNM: The Official Journal of the Society of Nuclear Medicine, India. 2015;**30**(1):1-8

[38] Guo J et al. Cerebral infarction on 99mTc-MDP SPECT/CT imaging. Clinical Nuclear Medicine. 2013;**38**:925-927

[39] Yoo JM et al. Diagnosing acute pyelonephritis with CT, 99mTc-DMSA SPECT, and Doppler ultrasound: A comparative study. Korean Journal of Urology. 2010;**51**(4):260-265

[40] Bokhari S et al. ^{99m}Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circulation. Cardiovascular Imaging. 2013;**6**(2):195-201

[41] Seo Y et al. Mapping of lymphatic drainage from the prostate using filtered 99mTc-sulfur nanocolloid and SPECT/CT. Journal of Nuclear Medicine. 2011; **52**(7):1068-1072

[42] Djekidel M, Brown RKJ, Piert M. Benefits of hybrid SPECT/CT for 111In-oxine- and Tc-99m-hexamethylpropylene amine oxime-labeled leukocyte imaging. Clinical Nuclear Medicine. 2011;**36**(7):e50-e56

[43] Yoon JK et al. In vivo tracking of 111In-labeled bone marrow mesenchymal stem cells in acute brain trauma model. Nuclear Medicine and Biology. 2010;**37**(3):381-388

[44] Sawada T et al. Preoperative clinical radioimmunodetection of pancreatic cancer by 111In-labeled chimeric monoclonal antibody Nd2. Japanese Journal of Cancer Research. 1999; **90**(10):1179-1186

[45] Zoghi M et al. Evaluation of 111In-labeled GnRH-I tracer for SPECT tumor imaging. Radiochemistry. 2019;**61**(2): 226-232

[46] Gholamrezanezhad A et al. In vivo tracking of 111In-oxine labeled mesenchymal stem cells following infusion in patients with advanced cirrhosis. Nuclear Medicine and Biology. 2011;**38**(7):961-967

[47] Zhu L, Ploessl K, Kung HF. PET/SPECT imaging agents for neurodegenerative diseases. Chemical Society Reviews. 2014;**43**(19):6683-6691