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 $\gamma$-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 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 $\gamma$-emitting radiotracers for imaging of different types of cancer and infection. Some of them are shown in Table 1 below [2].

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

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

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.
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 (177Lu) and Yatrium-90 (90Y) [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.

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

| Targeted agent with labeled radiotracer | Emitting radiation | Cancer type/disease |
|----------------------------------------|-------------------|---------------------|
| Metastron (89SrCl2)                     | β-emitting        | Skeletal cancer     |
| Radium-223 dichloride                  | α-emitting        | Bone metastasis, breast and prostate cancer |
| Samarium-153-EDTMP                     | β-emitting        | Bone and prostate cancer |

3. SPECT—radiopharmaceuticals

Radiopharmaceuticals which are used to diagnose the cancer and infection by using the γ-emitting radionuclides such as 111In and 99mTc 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 (%) |
|-----------------------------|-------------------|-----------|--------------|----------------------------|
| Indium-111                  | 67.32             | Cyclotron | 0.171 MeV    | 90.5                       |
|                             |                   |           | 0.245 MeV    | 94                         |
| Technetium-99m              | 6.02              | 99mMo/99mTc | 140 keV     | 88.9                       |
| Iodine-123                  | 13.22             | Cyclotron | 159 keV      | 82.8                       |

### Table 3.
**Common properties of γ-emitting radionuclides.**
• Free from $\alpha$ and $\beta$ 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 $\gamma$-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 $^{99m}\text{Tc}$ labeled. The reason for using the $^{99m}\text{Tc}$ 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 $\gamma$-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 $^{99m}\text{Tc}$ 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 $^{99}\text{Tc}$ is 0.25 million years in its ground state. Oxidation state of technetium varies from $-3$ to $+7$
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 (TcF₆, TcCl₆ and TcBr₄, oxide, [TcO₂, Tc₂O₇], sulfides [Tc₂S₇], and pertechnetate99mTcO₄ 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.

\[
3\text{Tc}^{\text{+5}} + 2\text{Tc}^{\text{+4}} + \text{Tc}^{\text{+7}}
\] (1)

\[
3\text{Tc}^{\text{+6}} + \text{Tc}^{\text{+4}} + 2\text{Tc}^{\text{+7}}
\] (2)

The coordination number of the technetium during complex formation can be changed between 4 and 9.
6. Reducing agents and reduction of $^{99m}\text{TcO}_4^-$

Technetium generated by Moly generator presents in the form of sodium-pertechnetate ($^{99m}\text{Tc}\cdot\text{NaTcO}_4$). In this pertechnetate ion, the oxidation state of technetium is +7 and structure of the $^{99m}\text{TcO}_4^-$ 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 $\text{MnO}_4^-$ and perrhenate ion $\text{ReO}_4^-$ ion. Structure of the pertechnetate ion $\text{TcO}_4^-$ is shown in Figure 2.

Pertechnetate $^{99m}\text{TcO}_4$ 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 $^{99m}\text{TcO}_4$ form +7 oxidation state to lower oxidation state, a variety of reducing agents are employed such as stannous citrate ($\text{C}_{12}\text{H}_{10}\text{O}_{14}\text{Sn}_3$), stannous tartrate ($\text{C}_4\text{H}_4\text{O}_6\text{Sn}$), stannous chloride ($\text{SnCl}_2.2\text{H}_2\text{O}$), concentrated hydrochloric acid ($\text{HCl}$), dithionite ($\text{O}_4\text{S}_2^-$), ferrous sulfate ($\text{FeSO}_4$), and sodium borotetrahdride ($\text{NaBH}_4$). However, the most frequently used reducing agent in labeling of the compounds with technetium process is stannous chloride dihydrate ($\text{SnCl}_2.2\text{H}_2\text{O}$) [10]. Electrolysis can also be utilized as a method for reducing sodium-pertechnetate ($^{99m}\text{Tc}\cdot\text{NaTcO}_4$) and use zirconium as an anode and labeling compound. However, following common characteristics are being considered to choose a reducing agent in $^{99m}\text{Tc}$ 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 $^{99m}\text{TcO}_4$ with the help of stannous chloride is accomplished in acidic medium, and reaction is given below.

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

![Figure 2. Structure of pertechnetate ion $^{99m}\text{TcO}_4^-$.](image)
299mTcO4 + 16H+ + 6e99mTc+4 + 8H2O (4)

Overall reaction

299mTcO4 + 16H+ + 3Sn2+2 99mTc+4 + 8H2O + 3Sn+4 (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 99mTc such as 99mTc+3 and 99mTc+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 99mTc 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 99mTc. Compounds containing the electron donating group such as carboxylic group (\(-\text{COOH}\)), amines (\(-\text{NH}_2\)), hydroxyl (\(-\text{OH}\)), and thiol group (\(-\text{SH}\)) 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 99mTcO4.

- Complex of technetium in +5 oxidation state (Tc$^{+5}$). Technetium is present in this oxidation state in the form of complexes such as 99mTc-gluconate, 99mTc-glucepetate, and 99mTc-citrate. During these complexes formation, reduction of technetium (pertechnetate 99mTcO$^{4-}$) 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 TcO₂ and hexahalo is +4. The reducing agent which is used to reduce the pertechnetate ⁹⁹ᵐTcO₄⁻ from +7 oxidation state to lower oxidation state +4 (TcO₂.xH₂O) 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 InCl₃, InBr₃ InI₃ and InF₃, sulphide and oxide (In₂O₃). 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 | 1s²,2s²,2p⁶,3s²,3p⁶,3d¹⁰,4s²,4p⁶,4d¹⁰,5s²,5p¹ |
| Density gm/cm³ (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

| 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.

Table 6.
General radiopharmaceuticals developed based on SPECT imaging.
These $\gamma$-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 $\gamma$-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 $\beta$-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 | Labeling 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
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 (N₂S₂), 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 | ¹¹¹In | Human model | Tumor target | | [6] |
2. | HYNIC-Glu-Urea | ⁹⁹ᵐTc | Human model | Metastatic prostate cancer | | [6] |
3. | DTPA-AMB8LK | ¹¹¹In | Mice model | Pancreatic cancer | 23.6 ± 3.9% ID/g | [7] |
4. | Octreotide | ¹¹¹In | Human model | Neuroendocrine tumor (NETs) | 95% | [8] |
5. | Sestamibi | ⁹⁹ᵐTc | Human model | Parathyroid adenoma | Range from 85 to 95% | [8] |
6. | MDP | ⁹⁹ᵐTc | Human model | Bone metastases | Very sensitive | [8] |
7. | (Arg11)CCMSH | ⁹⁹ᵐTc | Mice model | Murine melanoma | 3.33 ± 0.50% ID/g | [9] |
8. | DOTA-Re(Arg11)CCMSH | ¹¹¹In | Mice model | Murine melanoma | 8.19 ± 1.63% ID/g | [9] |
9. | DTPA-octreotide | ¹¹¹In | Mice model | Lung cancer | Bm/B was 3.1 ± 0.6 | [19] |
10. | HYNIC-TOC | ⁹⁹ᵐTc | Human model | Metastatic neuroendocrine tumors | Sensitivity 87% | [10] |
11. | DTPA-octreotide | ¹¹¹In | Mice model | Somatostatin-receptor tumors: evaluation | 4.3% ID/g | [11] |
cancer in human and mice models [18]. In Table 8, a number of compounds which are labeled with $\gamma$-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. |
|---------|-------------------|----------------------|---------------------|-----------|---------------------|-------|
| 14.     | HYNIC-TOC         | $^{99m}$Tc           | Mice model          | Somatostatin-receptor tumors: evaluation | $5.8 \pm 9.6\%$ 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.
| Sr  no.| Labeled compound          | Labeled radioisotope | SPECT imaging model     | Pathology                           | Sensitivity/accuracy | Refs. |
|-------|--------------------------|----------------------|-------------------------|------------------------------------|---------------------|-------|
| 8     | Maraciclaitide           | $^{99mTc}$           | Human model             | Angiogenesis                       |                     | [16]  |
| 9     | 3P-RGD2                  | $^{99mTc}$           |                         |                                    |                     | [16]  |
| 10    | MSAP-RGD                 | $^{111In}$           |                         |                                    |                     | [1]   |
| 11    | His-annexin A5 C2AcH-$^{99mTc}$(CO)$_3$ |             | Apoptosis               |                                    |                     | [2]   |
|       | (Me) FGCDEVD             | $^{99mTc}$           |                         |                                    |                     | [16]  |
| 13    | DTPA-Ac-TZ14011          | $^{111In}$           | Chemokine receptor 3 expression |                                    |                     | [1]   |
| 14    | AMD3100                  | $^{99mTc}$           |                         |                                    |                     | [1]   |
| 15    | DTPA-Fab-PEG24-EGF       | $^{111In}$           | Epidermal growth factor receptor |                                    |                     | [1]   |
| 16    | Etarfolatide             | $^{99mTc}$           | Folate receptor         |                                    |                     | [1]   |
| 17    | DOTA-folate              | $^{111In}$           |                         |                                    |                     | [1]   |
| 18    | MIP1404                  | $^{99mTc}$           | Prostate-specific membrane antigen |                                    |                     | [1]   |
| 19    | DPA-alendronate          | $^{99mTc}$(CO)$_3$   | Bone imaging            |                                    |                     | [1]   |
| 20    | human umbilical tissue-derived cells | $^{111In}$ | Mice model             | Cerebral ischemia                  |                     | [17]  |
| 21    | $^{99mTc}$-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    | $^{99mTc}$-HHK           | Rat model            | Tumor microenvironment | High specificity                    |                     | [18]  |
| 23    | nanobody (Nb cl1) against CD206 radiolabeled | $^{99mTc}$ | Mice model             | Macrophages in tumor               |                     | [18]  |
| 24    | $^{99mTc}$-PyDA          | Mice model           | In vivo hypoxia targeting | Selective uptake                   |                     | [18]  |
| 25    | $^{99mTc}$-meropenem     | Mice model           | Tumor hypoxia tissue    |                                    |                     | [18]  |
| 26    | $^{99mTc}$-nitroimidazole | Mice model           | Differentiate from inflamed and infected tissues |                                    |                     | [18]  |
| 27    | $^{99mTc}$-SD32          | Mice model           | 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-$^{99m}$Tc | 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 ± 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 presynaptic 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]   |
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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