

## Radiopharmaceuticals Used in Molecular Imaging

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### ABSTRACT

Molecular imaging technology can be used for many applications, including drug development, clinical investigations, and diagnostic techniques. Molecular imaging techniques depend upon molecular mechanisms operating *in vivo*. This imaging technique encompasses the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems. This technology uses the radiopharmaceuticals, intended for human use, which should be sterile, pyrogen-free, safe, and efficacious for specific indications. Nuclear medicine imaging methods or radionuclide imaging methods include positron emission tomography (PET), single photon emission computed tomography (SPECT) and hybrid imaging. Contrast to anatomical imaging, nuclear medicine techniques can provide physiological imaging and high sensitivity and specificity at sub-millimolar levels. This review aims to definite examples of radiopharmaceuticals which are used in molecular imaging with information of radiation, radioactivity, and radionuclide production. The radiopharmaceuticals like Technetium-99m (Tc-99m), Thallium-201 (Tl-201), Floro-18 (F-18), Gallium-67 (Ga-67), Gallium-68 (Ga-68), Iodine-123 (I-123), Iodine-131 (I-131), Nitrogen-13 (N-13), Rubidium-82 (Rb-82), Indium-111 (In-111), Oxygen-15 (O-15) and Carbon-11 (C-11) radionuclides are currently used in molecular imaging. In this review, we summarize these radiopharmaceuticals that have been widely used in clinical trials and elaborate them in terms of their applications in molecular imaging.

**Keywords:** Molecular imaging; radiopharmaceutical; nuclear medicine.

## Moleküler Görüntülemeye Kullanılan Radyofarmasötikler

### ÖZ

Moleküler görüntüleme teknolojisi, ilaç geliştirme, klinik araştırmalar ve teşhis teknikleri dahil birçok uygulama için kullanılabilir. Moleküler görüntüleme teknikleri, *in vivo* olarak işleyen moleküler mekanizmalara bağlıdır. Bu görüntüleme tekniği, insanlarda ve diğer canlı sistemlerde moleküler ve hücresele seviyelerde biyolojik süreçlerin görselleştirilmesini, karakterizasyonunu ve ölçülmesini kapsar. Bu teknoloji, steril, pirojensiz, güvenli ve belirli endikasyonlar için etkili olması gereken, insan kullanımı için tasarlanmış radyofarmasötikleri kullanır. Nükleer tıp görüntüleme yöntemleri ya da radyonüklid görüntüleme yöntemleri pozitron emisyon tomografisi (PET), tek foton emisyonlu bilgisayarlı tomografi (SPECT) ve hibrid görüntülemeyi içermektedir. Anatomik görüntülemenin aksine nükleer tıp teknikleri, milimolar altı seviyelerde fizyolojik görüntüleme ve yüksek hassasiyet ve özgüllük sağlayabilir. Bu derleme, moleküler görüntülemeye kullanılan radyofarmasötiklerin örneklerini radyasyon, radyoaktivite ve radyonüklid üretimi bilgileriyle tanımlamayı amaçlamaktadır. Teknesyum-99m (Tc-99m), Talyum-201 (Tl-201), Flor-18 (F-18), Galyum-67 (Ga-67), Galyum-68 (Ga-68), İyot-123 (I-123), İyot-131 (I-131), Nitrojen-13 (N-13), Rubidyum-82 (Rb-82), İndiyum-111 (In-111), Oksijen-15 (O-15) ve Karbon-11 (C-11) gibi radyonüklidler şu anda moleküler görüntülemeye kullanılmaktadır. Bu derlemede, klinik çalışmalarda yaygın olarak kullanılan bu radyofarmasötikleri özetlemekte ve moleküler görüntülemeye uygulamaları açısından detaylandırmaktayız.

**Anahtar Kelimeler:** Moleküler görüntüleme; radyofarmasötik; nükleer tıp.

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Geliş Tarihi / Received: 07.10.2020, Kabul Tarihi / Accepted: 25.12.2020

## INTRODUCTION

Molecular imaging is a diagnostic medical imaging method that uses radiopharmaceuticals to investigate the physiology and metabolism of the body in a cellular or molecular dimension. It has an opportunity to obtain more specific information about the desired region and to examine the physiology of that region in a molecular dimension. In the imaging of these molecular targets, radiopharmaceuticals with suitable physicochemical and radiological properties which are compatible with the imaging device mechanism are used. Radiopharmaceuticals consist of pharmaceutical part and radionuclide. Radionuclides have unstable nucleus. Their unstable property is caused by an excess of protons or neutrons. They decay to become stable and emit radiation. When they administered to body, emitted radiation is perceived by various cameras and detectors and converted into images on the computer. These images are called scintigraphy. There are some devices which are used in nuclear medicine application and the main devices of scintigraphy are positron emission tomography (PET) and single photon emission computed tomography (SPECT).

In this review, information about radiation, radioactivity, radionuclide production routes, definition of radiopharmaceuticals, molecular imaging, some radiopharmaceuticals that are frequently used in molecular imaging will be given.

## RADIATION AND RADIOACTIVITY

Some of atoms have stable and unstable nucleus. This feature is related to the number of protons and neutrons of atom has balanced. In a stable nucleus, in many cases the neutron number (N) is slightly higher than the number of protons (Z) or the number of neutrons and protons is equal, while the N/Z ratio increases in heavy nucleus. As the rate increases, a point is reached where the nucleus is no longer stable. Nuclides with too many neutrons tend to turn themselves into a proton by converting one neutron into a proton. This process is known as "beta decay" and results in the release of a negatively charged electron called a beta particle. Nuclides with many protons convert their excess protons into neutrons. These nuclides lose their positive charge by the positron emission, which is a positively charged electron. The event that the nucleus becomes more stable by releasing a proton or particle from an unstable state is called radioactivity or radioactive degradation. To stabilize natural or artificial radioactive nucleus, the particles released, and excess energy carried in the form of electromagnetic waves are released as radiation. This release continues until the core passes into stable structure. This transformation action is called atomic nucleus, which is the atomic nucleus that emits decay, changes, and radiation (1,2).

## RADIONUCLIDIC PRODUCTION ROUTES

Radionuclides used in nuclear medicine can be produced using generator, cyclotron, and nuclear reactor systems (3).

Radionuclide generator systems are based on the principle of the formation of a mother (product) radionuclide with a completely different chemical structure with the decay of the main radionuclide.

Systems separate the mother-daughter radionuclide pair by a special method and that make the daughter radionuclides ready for use are called generators. Technetium-99m (Tc-99m), Gallium-68 (Ga-68), Krypton-81m (Kr-81m), Rubidium-82 (Rb-82) and Indium-113m (In-113m) are generator products. Among these, Tc-99m is the most used radionuclide in imaging processes (3).

Radionuclides produced in cyclotron emit a positron and gamma rays. These radionuclides are artificially made in accelerator units called cyclotron, bombarding a stable substance in cyclotron with protons, deuterium, or helium nucleus. The obtaining isotope contains many protons. These radionuclides break down by throwing positrons during decay to stabilize. Positron collides with an electron when it travels through the tissue. Gamma ray (photon) occurs because of collision. The gamma ray that comes out of the body is detected simultaneously by two PET crystals and the image is created with the help of computers (4). Radionuclides which produced in cyclotron and formed images according to this mechanism are Carbon-11 (C-11), Nitrogen-13 (N-13), Oxygen-15 (O-15) and Fluor-18 (F-18) (3).

Radionuclides can also produce by nuclear reactor. Fission occurs in a nuclear reactor where neutrons are used to bombard fission nuclides such as Uranium-235 (U-235) or Plutonium-239 (Pu-239). Fission results in the splitting of the large nucleus into smaller fission fragments along with the release of gamma radiation and high energy neutrons. Neutron activation also takes place in a nuclear reactor. The neutrons are used to bombard stable nuclides to form other radionuclides (5). Some radionuclides such as Xenon-133 (Xe-133), Molybdenum-99 (Mo-99) and Iodine-131 (I-131) are produced in nuclear reactors (3).

## RADIOPHARMACEUTICALS

Radiopharmaceuticals are pharmaceutical formulations consisting of radioactive substances used in diagnosis and treatment. They are the main components of nuclear medicine application and used in nuclear medicine for 95% diagnosis and 5% treatment. In radiopharmaceutical development studies, a pharmaceutical that is selected according to retaining in a particular organ or participating in the physiological function of that organ and then suitable radionuclide is chemically linked to the selected pharmaceutical. This process is called "radiolabeling". Radiopharmaceuticals usually have no pharmacological effect, because in most cases they are used in tracer quantities. In these cases, they do not show any dose-response relationship (6) Because they are administered to humans, they should be sterile and pyrogen free and they are subject to all quality control measurements (such as pyrogenicity, sterility, toxicity) for conventional drugs. In addition, quality control tests related to radioactivity (radionuclidic purity, radiochemical purity, radiolabelling efficiency, biodistribution etc.) must be performed. The American Food and Drug Administration (FDA) classifies radiopharmaceuticals as drugs regardless of whether they are diagnostic or therapeutic agents (3).

## MOLECULAR IMAGING

Molecular imaging is defined as “non-invasive and repetitive imaging” of macromolecules and biological processes targeted in living organisms. Molecular imaging enables the imaging, characterization, and measurement of biological functions at the molecular or cellular level in the living organism. Thus, it is possible to define the changes in cell function (7).

Molecular imaging technology used in nuclear medicine includes specific imaging methods such as optical imaging and scintigraphy (8). Since these imaging techniques are based on physiological changes before anatomical changes, they play an important role in detecting diagnostic functional abnormalities. It also provides useful information in planning the treatment process and following the treatment. It prevents unnecessary examinations and difficult invasive procedures that can disturb the patient (9). In diagnostic imaging method in nuclear medicine, radiopharmaceutical, which is selected according to the target organ or tissue and given to the patient through various application methods, emits radiation in the region to be examined according to the specific degradation type of the radionuclide. This radiation is perceived by various cameras and detectors and converted into images on the computer. These images obtained with SPECT and PET devices. They are also called scintigraphy (8).

## DIAGNOSTIC RADIOPHARMACEUTICALS

In nuclear medicine, Tc-99m, Tl-201, F-18, Ga-67, Ga-68, I-123, I-131, N-13, Rb-82, In-111, O-15 and C-11 radionuclides are frequently used for molecular imaging. These radionuclides and the use of radiopharmaceuticals prepared from these radionuclides are summarized below.

### **Technetium-99m (<sup>99m</sup>Tc)**

Technetium isotopes turn into other elements, only <sup>99m</sup>Tc is artificially produced. Over 80% of radiopharmaceuticals currently in use contain this short-lived and semi-stable radionuclide. The half-life of <sup>99m</sup>Tc (6h) is an ideal time for radiopharmaceutical preparation, quality control and injecting to the patient for imaging studies. <sup>99m</sup>Tc emits 140 KeV gamma photons, does not contain particle radiation, is generator source and is the cheapest radionuclide (3,10). <sup>99m</sup>Tc is obtained from <sup>99</sup>Mo/<sup>99m</sup>Tc generator. It is obtained in the form of pertechnetate directly from the generator by elution using saline. This single charged anion is an iodide imitation due to its ionic charge and similarity in its current size. It can be given to the body in the form of sodium pertechnetate (Na<sup>+</sup>TcO<sub>4</sub><sup>-</sup>) by dissolving in saline without binding to any pharmaceutical (3,10). The sterile sodium pertechnetate solution is administered intravenously, for thyroid, salivary gland, ectopic gastric mucosa localization, cerebral, cardiac, and vascular scintigraphy, lacrimal canal scintigraphy, gastrointestinal bleeding scintigraphy, urine scintigraphy (11). In addition, <sup>99m</sup>Tc involvement in testicles is used in the evaluation of acute unilateral testicular pain (4). <sup>99m</sup>Tc can be used alone in the above indications, or it can also be used in various indications by connecting with different pharmaceutical parts.

### **Technetium Sulfur Colloid (<sup>99m</sup>Tc-SC)**

<sup>99m</sup>Tc-SC is a sterile dispersion of colloidal sulfur and emitting gamma ray and used in the imaging of the reticuloendothelial system (RES) (3). RES cell types include macrophages or macrophage precursors, endothelial cells in the liver, spleen and bone marrow sinusoids, and reticular cells of the lymphatic tissue and bone marrow. After intravenous administration, <sup>99m</sup>Tc-SC is phagocytized by RES and concentrates in lymph tissue, liver, spleen, and bone marrow. Thus, detection of the gamma-emitting colloid is performed with a gamma-ray scintillation camera (12).

### **Technetium Diethylene Triamine Penta Acetic Acid (<sup>99m</sup>Tc-DTPA)**

<sup>99m</sup>Tc-DTPA is the cheapest dynamic kidney scintigraphy radiopharmaceutical and is widely used today. In dynamic renal scintigraphy, the passage of radiopharmaceuticals from the kidneys with time is examined. Thus, perfusion of kidneys, glomerular and tubular functions, collecting system, bladder function, i.e. excretion functions of kidneys are evaluated (13). <sup>99m</sup>Tc-DTPA is excreted only by glomerular filtration without tubular excretion. It is one of the technetium radiopharmaceuticals which used for direct measurement of glomerular filtration rate (14,15).

### **Technetium Dimercaptosuccinic Acid (<sup>99m</sup>Tc-DMSA)**

Dimerkaptosuccinic acid (DMSA) is a static kidney scintigraphy (renal cortical scintigraphy) agent. Static kidney scintigraphy is performed to evaluate the kidney parenchyma. <sup>99m</sup>Tc-DMSA is the best radiopharmaceutical that displays the kidney parenchyma (13). DMSA is ideal for the evaluation of the kidney cortex, as it binds to sulfhydryl (-SH) groups in the proximal tubules of the renal cortex for a long time. It cannot be used in dynamic renal scintigraphy due to its slow involvement in the kidneys and minimal excretion (14).

<sup>99m</sup>Tc-DMSA scintigraphy is a suitable method for imaging the renal cortex with short-lived radioisotope. DMSA scintigraphy is a preferred imaging method to prove the presence of acute-chronic pyelonephritis or parenchymal damage due to kidney parenchymal abnormalities, to obtain information about cortical scar, relative kidney size kidney infarcts and congenital kidney anomalies (16). It is the most used radiopharmaceutical in pediatric applications of nuclear medicine for detecting scar and pyelonephritis (4).

### **Technetium Mercaptoacetyltriglycine (<sup>99m</sup>Tc-MAG3)**

<sup>99m</sup>Tc-MAG3 is one of the most used tubular radiopharmaceuticals. It is largely bound to proteins, and since it is excreted only from the proximal tubules, by the tubular delivery system, its clearance directly shows the tubular function. <sup>99m</sup>Tc-MAG3 is the first-choice radiopharmaceutical in diuretic renography and transplant kidney evaluation of infants in patients with impaired renal function (14).

### **Technetium Ethylenedicysteine (<sup>99m</sup>Tc-EDC)**

<sup>99m</sup>Tc-EDC is a good alternative agent to <sup>99m</sup>Tc-MAG3. While it is largely excreted from the tubules, it is partly filtered through glomerulus. It is preferred due to the low liver involvement in patients with renal failure (14).

**Technetium Glucoheptonate ( $^{99m}\text{Tc}$ -GHA)**

$^{99m}\text{Tc}$ -GHA is an approved radiopharmaceutical for the assessment of kidney function and impaired blood-brain barrier (10). It shows proximal tubules uptake in the kidneys. It is preferred in the evaluation of kidney lesions as it can show the blood supply, cortex, and excretory function of the kidney with a single injection (14).

**Technetium Iminodiacetic Acid ( $^{99m}\text{Tc}$ -IDA)**

In hepatobiliary system scintigraphy,  $^{99m}\text{Tc}$ -IDA derivatives are used for the diagnosis of various acute and chronic hepatobiliary diseases including acute gallbladder inflammation, biliary obstruction, gall leak and chronic gallbladder disease (10). Two radiopharmaceuticals for hepatobiliary imaging diagnostic administration have been developed in the United States:  $^{99m}\text{Tc}$ -diisopropyl IDA (Disophenin) and  $^{99m}\text{Tc}$ -bromotrimethyl IDA (Mebrofen). Disophenin and Mebrofen are available in a sterile kit under the names Hepatolite<sup>®</sup> and Choletec<sup>®</sup>, respectively. Mebrofen is preferred in patients with poor liver function as it shows better hepatic uptake and faster biliary excretion compared to Disophenin (17).

IDA radiopharmaceuticals are organic anions and transported to bile canaliculi with an active membrane transport system, like bilirubin. Unlike bilirubin, these compounds pass into the intestines without being conjugated or metabolized in the liver. Since  $^{99m}\text{Tc}$ -IDA is on the same path as bilirubin, it is subject to competitive inhibition with high serum bilirubin levels (17).

**Technetium Ethylenedicysteine ( $^{99m}\text{Tc}$ -EDC)**

$^{99m}\text{Tc}$ -EDC is a good alternative agent when compared to  $^{99m}\text{Tc}$ -MAG3. While it is largely excreted from the tubules, it is partly filtered through glomerulus. It is preferred due to the low liver involvement in patients with renal failure (14).

$^{99m}\text{Tc}$ -MAG3 and  $^{99m}\text{Tc}$ -EDC are the most used tubular radiopharmaceuticals. Both accumulate in the kidneys in a very short time and are quickly removed from the collecting system. Therefore, their image quality is very high. These tubular radiopharmaceuticals can be used successfully even with severe kidney function loss (14).

**Technetium Methoxyisobutylisonitrile ( $^{99m}\text{Tc}$ -MIBI)**

$^{99m}\text{Tc}$ -MIBI is the first technocyte-labeled myocardial perfusion agent approved by the FDA for clinical use in 1990. Radiopharmaceutical is a coordination complex consisting of 6-MIBI ligands surrounding the  $^{99m}\text{Tc}$ -radionuclide. Therefore, it is commonly referred to as 6-sestamibi.

Sestamibi is a lipophilic, monovalent cation. Due to its lipid structure, it passes the plasma and mitochondria membrane by passive diffusion and is protected intracellularly in the mitochondria region due to its negative transmembrane potential. This radiopharmaceutical is prepared from Cardiolite<sup>®</sup> (17).

$^{99m}\text{Tc}$ -sestamibi is generally used in the imaging of primary and secondary tumors of the lung, chest, thyroid, parathyroid, brain, melanoma, lymphoma, bone, and soft tissue in nuclear oncology (18). It is also approved by FDA in the detection of multiple drug resistance in cancer mediated by P-glycoprotein and protein-1 (19). MDR1 Pgp, encoded by the Multi-Drug Resistance gene, has the function of pumping most lipophilic and cationic strong cytotoxic agents out of the cell (20).  $^{99m}\text{Tc}$ -MIBI is one of

the  $^{99m}\text{Tc}$ -agents and investigates *in vivo* detection of MDR1 Pgp function and inhibition in tumors (18).

**Technetium Methylene Diphosphonate ( $^{99m}\text{Tc}$ -MDP) and Technetium Hydroxy Methylene Diphosphonate ( $^{99m}\text{Tc}$ -HMDP)**

$^{99m}\text{Tc}$ -MDP and  $^{99m}\text{Tc}$ -HMDP are most used radiopharmaceuticals in bone scintigraphy (13). After administration of these radiopharmaceuticals to the patients, diphosphonates bind to the hydroxyapatite crystals involved in the formation of the bone structure due to local blood flow and osteoblastic activity.

Bone formation (osteoblastic activity) and destruction (osteoclastic activity) show continuity in healthy bone (21). While radiopharmaceutical localization increases in areas where osteoblastic activity increases, it decreases in region where blood flow decreases, and osteolytic lesions occurs (4). Primary and secondary bone tumors, fractures, trauma, arthritis, degenerative changes of joints, neuropathic uptake, and pathological fractures due to osteoporosis are cases where high osteoblastic activity is observed.

Radiopharmaceuticals are administered intravenously as bolus injection and approximately 50% of the dose given to the patient accumulates in the bones. Thus, diphosphonates emitting gamma rays, marked with the accumulated  $^{99m}\text{Tc}$ , provide access to important physiological information such as bone blood flow and metabolism. The excretion of these radiopharmaceuticals occurs through the kidney (13).

**Technetium Hexamethylene Propylene Aminoxime ( $^{99m}\text{Tc}$ -HMPAO)**

$^{99m}\text{Tc}$ -HMPAO [ $^{99m}\text{Tc}$ -exametasim (Ceretek<sup>®</sup>)] is a lipophilic radiopharmaceutical. It is used to visualize brain perfusion by crossing the blood-brain barrier because it is lipophilic. After crossing the blood-brain barrier, it enters the neuron through passive diffusion and reacts with glutathione inside the cell and turns into a hydrophilic complex.

This complex binds to the mitochondria and the cell nucleus.  $^{99m}\text{Tc}$ -HMPAO is a radiopharmaceutical that is routinely used in nuclear medicine. It specifically used in radiolabeling of granulocytes. This creates a disadvantage in detecting chronic infections with mononuclear cell infiltration (22).

The infection focus can be investigated by marking the leukocytes of the patient with  $^{99m}\text{Tc}$ -HMPAO (3). The labeling of leukocytes with  $^{99m}\text{Tc}$ -HMPAO is performed by *in vitro* way.  $^{99m}\text{Tc}$ -HMPAO is kept for 10 min at room temperature with the leukocytes separated from the blood and centrifuged. Leukocytes are then washed and separated. Radiolabeled leukocytes are returned to the patient without waiting. Using the cellular migration mechanism, infected tissues and organs targeted by leukocytes are investigated (13).

**Macroaggregate Albumin ( $^{99m}\text{Tc}$ -MAA) or Human Serum Albumin ( $^{99m}\text{Tc}$ -HAM) Microspheres Labeled with  $^{99m}\text{Tc}$** 

$^{99m}\text{Tc}$ -MAA and  $^{99m}\text{Tc}$ -HAM are used in lung perfusion scintigraphy and lower extremity deep vein thrombosis to detect the region where pulmonary embolism develops. MAA particles form transient microemboli in lung capillaries and precapillary arterioles in the first pass. This condition, which forms the basis of perfusion

imaging, has no clinical significance. Since the particles are radiolabeled with  $^{99m}\text{Tc}$ , both lungs become visible with gamma rays. The perfusion defect areas are occurred because the radioactive agent cannot reach the area where the embolism appears (13).

#### **Thallium Chloride ( $^{201}\text{TlCl}$ )**

$^{201}\text{Tl}$  is a cyclotron product. It has a physical half-life of 73 h. While decaying to Mercury-201 ( $^{201}\text{Hg}$ ), it emits mainly X-rays ranging from 69-83 KeV, and gamma photons of 167 KeV and 135 KeV (17).

$\text{Na}^+\text{-K}^+$  homeostasis is protected by an energy-dependent process involving the  $\text{Na}^+\text{-K}^+$  ATPase (adenosine triphosphatase) pump on the myocardial cell membrane. Although  $^{201}\text{TlCl}$  is not a real chemically analogous  $\text{K}^+$  analogue, it behaves physiologically similar to  $\text{K}^+$ , and when administered intravenously, it enters the cell by passing the cell membrane with active transport with  $\text{Na}^+\text{-K}^+$  ATPase pump (17). This pump is only available in living cells. Therefore, only viable heart cells show  $^{201}\text{Tl}$  involvement. In other words, the involvement of radiopharmaceuticals in the heart depends on blood flow and the presence of living cells. Therefore, it is used to investigate viability. With effort, the  $\text{Na}^+\text{-K}^+$  ATPase pump in the ischemic cell membrane breaks down.  $^{201}\text{Tl}$  cannot enter the ischemic cell. After four hours, the membrane is recovered, and the ischemic cell begins  $\text{Tl-201}$  uptake. This is called redistribution. It shows a live but ischemic (hypoperfused) myocardium. It is the primary preferred perfusion agent in the demonstration of live myocardial tissue after infarction since it is redistributed and retained in the heart (13). Although the standard  $^{201}\text{Tl}$  redistribution and resting/stress sestamibi protocol on the same day or two days are the most frequently used administration, it is long and laborious. Therefore, the use of the rest  $^{201}\text{Tl}$  and stress  $^{99m}\text{Tc}$ -sestamibi protocol is possible with the use of dual isotopes. The combination of  $^{201}\text{Tl}$  and  $^{99m}\text{Tc}$ -sestamibi provides the most appropriate image resolution as well as the simultaneous evaluation of myocardial viability (23). Due to the long half-life of thallium, the limited dose can be given to patient. Its main photons have low energy (68-80 KeV). It is not an ideal agent in terms of image quality. The image study takes longer than other agents (up to 24 h). Due to such disadvantages, myocardial perfusion agents that are radiolabeled with  $^{99m}\text{Tc}$  are more preferred today (13).

#### **Fluorodeoxyglucose ( $^{18}\text{F-FDG}$ )**

$^{18}\text{F}$  is artificially produced in cyclotrons. The half-life is 110 min. It is the radionuclide that has the longest half-life and has the widest application area among positron emitting radionuclides. It can be transferred from the centers where it is produced to the places to be examined because of its suitable half-life. It is the most used PET radiopharmaceutical agent.  $^{18}\text{F-FDG}$  is glucose analog and shows the glucose utilization of the cell.  $^{18}\text{F-FDG}$  is transported into the cell by crossing the cell membrane with facilitated diffusion mediated by glucose transporter proteins [glucose transporter-1 (GLUT-1)]. It is phosphorylated by hexokinase enzyme to  $\text{FDG-6-phosphate}$ . It cannot go any further step of glucose metabolism and accumulates in the radiolabeled  $\text{FDG-6-phosphate}$  cell (24).

$\text{FDG}$  accumulation in the tissue is proportional to the use of glucose. In many cancers, the production of glucose-bearing proteins and hexokinase activity in the membrane of cancer cells increases compared to normal cells. Accordingly, the use of glucose is also increasing (9) because cancer cells have faster metabolism and  $\text{FDG}$  is more involved in these cells and the location of tumor tissue can be imaged (24).

#### **Sodium fluoride ( $^{18}\text{F-NaF}$ )**

$^{18}\text{F}$ -Sodium fluoride ( $^{18}\text{F-NaF}$ ) is a highly sensitive bone-seeking PET radiopharmaceutical and is considered as an excellent substitute for traditionally used  $^{99m}\text{Tc}$ -labeled tracers, because its favorable characteristics of negligible protein binding, and rapid blood pool clearance. Additionally, uptake of  $^{18}\text{F-NaF}$  reflects blood flow and bone remodeling, and  $^{18}\text{F-NaF}$  have been proposed for the use in detection of benign and malignant osseous abnormalities that also allows the regional characterization of lesions in metabolic bone diseases (25).

#### **Fluorothymidine ( $^{18}\text{F-FLT}$ )**

Cellular proliferation plays an important role in cancer and has been an important imaging target of PET radiopharmaceuticals, especially with the aim targeting of DNA synthesis.  $^{18}\text{F}$ -Fluorothymidine ( $^{18}\text{F-FLT}$ ) is widely investigated in oncologic setting comprising tumor detection, staging, restaging, and response assessment to treatment and  $^{18}\text{F-FLT}$  imaging has several clinical advantages including noninvasive procedure, three-dimensional tumor images and simultaneous detection of multiple tumor sites. Also,  $^{18}\text{F-FLT}$  is capable to evaluate tumor heterogeneity in day-to-day practice (25).

#### **$^{67}\text{Ga}$ ( $^{67}\text{Ga}$ ) Citrate and $^{68}\text{Ga}$ ( $^{68}\text{Ga}$ ) Citrate**

$^{67}\text{Ga}$  is a cyclotron product with a physical half-life of 77.9 h and a biological half-life of about 25 days. It is used as a specific agent in determining tumor and infection/inflammation foci in SPECT imaging.  $^{67}\text{Ga}$  is sensitive to many cancers, including hepatocellular cancer, sarcomas, and lung cancer. It exhibits biological behavior like iron and binds to the iron-bearing glycoprotein (transferrin) *via* the transferrin receptor (CD71) after intravenous injection. It is transported in the form of  $^{67}\text{Ga}$ -transferrin complex in circulation (17,22).  $^{67}\text{Ga}$  ionic form or transferrin receptors leak through the vascular epithelium in the infection site in CD71-bound form and bind with high affinity for abscess fluid and lactoferrin, which is abundant in neutrophils.  $^{67}\text{Ga}$  shows intense binding to organic materials (siderophores), which are involved in the transport of iron. In infected tissues,  $^{67}\text{Ga}$  is taken by siderophores and produced by microorganisms in low-iron environments, as if it were anchored and carried into the cell. Its biological half-life takes 2-3 weeks since it binds to serum proteins such as transferrin, haptoglobin, albumin and globulin.  $^{67}\text{Ga}$  attaches to the tissue with lymphocytes and macrophages through lactoferrin (26).

It has been shown to be intensely involved in soft tissue and brain tumors. Its uptake is an effective marker of some malignant tumors such as lymphoma, bronchogenic carcinoma, and Hodgkin's disease. Tumor uptake mechanism is not clear (3).

$^{67}\text{Ga}$ -citrate, which has been used successfully in SPECT applications, shows nonspecific involvement in aseptic

inflammation, tumor and trauma, as well as low image quality, although it has been studied with SPECT/CT, there are some disadvantages such as the time between injection and imaging requires as long as 48 to 72 h. Due to these negative properties, studies are carried out with PET agent  $^{68}\text{Ga}$ -citrate, which shows the same chemical properties instead of  $^{67}\text{Ga}$ .  $^{68}\text{Ga}$ -citrate gives a higher resolution image in a shorter time with PET device.

While it is necessary to wait 48 h after injection with  $^{67}\text{Ga}$  imaging, it is possible to take images within 30-60 min after injection with  $^{68}\text{Ga}$  (26). Although the disadvantages of  $^{68}\text{Ga}$ -citrate with the low image quality of  $^{67}\text{Ga}$ -citrate and long waiting time between application and imaging are overcome, there are disadvantages such as limited specificity of  $^{68}\text{Ga}$ . To develop more specific imaging agents, researchers have complexed peptides with  $^{68}\text{Ga}$  (27).

$^{68}\text{Ga}$  is a PET imaging agent produced from the generator. Its half-life is 68 min. It is supplied from Germanium-68 ( $^{68}\text{Ge}$ )/ $^{68}\text{Ga}$  generator. In this generator, the main radionuclide  $^{68}\text{Ge}$  is a girl product with a (III) valence of  $^{68}\text{Ga}$  (9).

In practice, three different somatostatin analogs are radiolabeled  $^{68}\text{Ga}$  and routinely used. DOTA is the chelating agent that allows the peptides to form a stable complex with  $^{68}\text{Ga}$ . There are  $^{68}\text{Ga}$  labeled somatostatin analogs, which are frequently used in practice; DOTA-D-Phe-Tyr3-octreotide (DOTA-TOC), DOTA-1-Nal(3)-octreotide (DOTA-NOC) and DOTA-D-Phe-Tyr3-octreotate (DOTA-TATE). These radiopharmaceuticals are used in the detection of neuroendocrine tumors. Somatostatin receptors on the tumor cell surface are targeted. Five different somatostatin receptor subtypes (SRs) are well-known: SRs-1, SRs-2, SRs-3, SRs-4, and SRs-5. SRs-2 is a potential targeting molecule and used in the diagnosis and treatment of neuroendocrine tumors. SRs-2, which is the most frequently expressed in neuroendocrine tumors, binds to DOTA-TATE (28).

#### Radioiodine $^{123}\text{I}$ and $^{131}\text{I}$

The half-life of  $^{123}\text{I}$  is 13.2 h. It is an ideal agent used in thyroid imaging due to its lack of beta particle emission, high thyroid involvement, and low radiation dose (159 KeV gamma ray). It is a cyclotron product. Although it is expensive and difficult to find, images with very good resolution and minimal background activity are obtained, it is not available for routine thyroid scintigraphy in our country (13).

$^{131}\text{I}$  has a long half-life (8.1 days), beta particle and gamma ray are emitted. The high radiation dose (364 KeV gamma ray) is not routinely used for imaging the thyroid gland due to the lack of image on the same day and poor image quality. It is very valuable in the diagnosis of metastasis and recurrence in thyroid cancer. It destroys follicle cells and is used for the treatment of hyperthyroid (Graves' disease, toxic nodular goiter) and thyroid cancers (13).

#### Metaiodobenzylguanidine ( $^{123}\text{I}/^{131}\text{I}$ MIBG) Radiolabeled with $^{123}\text{I}$ and $^{131}\text{I}$

Metaiodobenzylguanidine (MIBG) is a guanethidine analog and its structure is like noradrenaline (NA). It is re-uprelated to adrenergic presynaptic neurons such as NA as a false neurotransmitter. It is transported into the cell of granules that keeps catecholamine *via* ATPase

dependent proton pump and is localized in sympathoadrenergic tissues. Its uptake increases in pathological cases.

MIBG radiolabeled with  $^{123}\text{I}$  or  $^{131}\text{I}$  and is used in the diagnosis and treatment of adrenergic system tumors (pheochromocytoma) originating from adrenal medulla, adrenergic system tumors (paragangliomas) and extra adrenal tissues. It is also used in studies such as determining primary focus, staging the tumor, detecting metastases, investigating the efficacy of the treatment, and detecting residual tissue after treatment, and investigating relapse in follow-up (13).

#### Nitrogen-13 ( $^{13}\text{N}$ )

$^{13}\text{N}$  is the preferred as PET myocardial perfusion radiopharmaceutical because it has a very short physical half-life (10 min), superior imaging properties. It requires on-site cyclotron production. At physiological pH, its main form is ammonium ( $\text{NH}_4^+$ ). After injection, the myocardial cell spreads through the capillary membrane and converted to N-3 glutamine with glutamine synthetase. It is then included in the cellular pool of amino acids and held in tissues. Myocardial intake is proportional to the coronary blood flow. Although its physical half-life is short, it stays inside the heart with a relatively long biological residence time. This agent is also retained by the brain, liver, and kidneys. In the diagnosis of coronary artery disease, post-pharmacological stress studies are performed with protocols like those described for SPECT myocardial perfusion scintigraphy (17).

#### Rubidium-82 Chloride ( $^{82}\text{RbCl}$ )

Rubidium-82 is obtained from Strontium-82 ( $^{82}\text{Sr}$ )/ $^{82}\text{Rb}$  generator.  $^{82}\text{Rb}$  is a monovalent cation and the true analogue of potassium like TI-201. It is taken into the myocardium by active transport way  $\text{Na}^+/\text{K}^+$  ATPase pump. The short half-life (76 seconds) of  $^{82}\text{Rb}$  allows sequential myocardial perfusion studies before and after pharmacological interventions (17).

#### Indium Chloride ( $^{111}\text{InCl}$ )

$^{111}\text{In}$  is produced from cyclotron. During decay, it emits 173 and 247 KeV of two gamma photons (17) and has 67 h physical half-life.  $^{111}\text{In}$  allows late imaging, which is required in many situations. However, due to the unsuitable photon energy, there are disadvantages such as low-resolution images and waiting 18-30 h for imaging after injection. It is also used to radiolabel various compounds (26).

#### Indium Octreotide ( $^{111}\text{In-OCT}$ )

Octreotide (Sandostatin<sup>®</sup>) is a synthetic long-acting cyclic octapeptide with pharmacological properties that mimics the natural hormone, somatostatin. It binds to somatostatin receptors and is a stronger growth hormone, glucagon, and insulin inhibitor than somatostatin (29).  $^{111}\text{In}$ -octreotide is used in the somatostatin receptor scintigraphy for the visualization of neuroendocrine tumors with SPECT (13).

OctreoscanTM is FDA-approved radiopharmaceutical containing a somatostatin analog and contains pentetreotide [N-(diethylene triamine-N, N, N', N''-tetra acetic acid-N'' -acetyl) -D-phenylalanyl-L-hemisistyl-L-phenylalanyl-D-triophyl-L-lysyl-L-threonyl-L-hemisistyl-L-threoninol cyclic (2 → 7) disulfide] and  $^{111}\text{In}$  (9).

**<sup>111</sup>In 8-hydroxyquinoline (<sup>111</sup>In-auxin) Leukocyte**

<sup>111</sup>In-auxin has a fat-soluble neutral structure. It easily passes through the cell membrane and binds tightly to cytoplasmic components that strongly chelate indium, such as lactoferrin. Free 8-hydroxyquinoline (auxin) is then removed from the cell (30). It is used in the diagnosis of bacterial infections and unknown infections (9).

**<sup>15</sup>O-CO and <sup>15</sup>O-H<sub>2</sub>O**

<sup>15</sup>O-CO is one of the most common tracers used for noninvasively measuring oxygen consumption and blood volume. Additionally, <sup>15</sup>O-CO is crucial for the evaluation of acute stroke patients. Moreover, measurement of myocardial oxygen consumption is a useful tool to clarify the relationship between myocardial blood flow and oxygen extraction fraction because both oxygen extraction fraction and myocardial blood flow are important indicators in describing myocardial function (25).

Although the short half-life (123 sec) of <sup>15</sup>O results in the challenges in clinical use, <sup>15</sup>O-H<sub>2</sub>O is still the preferred tracer because of its ease production from generator, effectiveness, and safety for patient use. Particularly, PET with <sup>15</sup>O-H<sub>2</sub>O has been a standard method and most reliable approach for quantitative measurement of cerebral blood flow. Also, <sup>15</sup>O-H<sub>2</sub>O is capable to clinically investigate cerebral and myocardial perfusion, and tumor perfusion (25).

**<sup>11</sup>C-Methionine (<sup>11</sup>C-MET)**

Although increased cellular protein synthesis is often characterized in malignant growth, decreased protein synthesis is found in certain neurodegenerative disorders. Thus, the ability to in vivo visualize the protein synthesis rate is significant for clinical use. Protein synthesis is initiated universally with the amino acid, methionine. <sup>11</sup>C-labeled methionine (<sup>11</sup>C-MET) is used for imaging of rate of protein synthesis, but the short physical half-life of <sup>11</sup>C (20 min) limits its accessibility for PET scanning centers without a cyclotron. Clinically, <sup>11</sup>C-MET is used in imaging of brain, urinary, gynecological, liver and lung cancer (25).

**Sodium Acetate (<sup>11</sup>C-Ac)**

<sup>11</sup>C-Ac is used to imaging in prostate cancer, hepatocellular carcinoma, lung cancer, nasopharyngeal carcinoma, renal cell carcinoma, bladder carcinoma and brain tumors. Also, <sup>11</sup>C-Ac is used to clinically measure myocardial oxygen consumption (25).

**CONCLUSIONS**

During the past decade, great efforts have been made to develop radiopharmaceuticals for molecular imaging in clinical application. The radiopharmaceuticals have been developed to enable SPECT and PET imaging of some disease. Some of them have met the challenges required to qualify a radiopharmaceutical in molecular imaging. Furthermore, the molecular imaging community also may work with clinical trial groups and pharmaceutical industry, to support well-designed imaging as new radiopharmaceuticals. In this way, one or more of these radiopharmaceuticals may be ultimately progress to authorized approval and become widely used imaging agents in molecular imaging.

**Authors' Contributions:** Concept: G.A.E.; Design: G.A.E., E.M.; Data collecting: E.M., S.M.; Analysis and/or Interpretation: G.A.E., E.M.; Literature Review: S.M.; Manuscript Writing: S.M.; Critical Review: G.A.E., E.M.

**REFERENCES**

- Köklü N. Radyasyonun insan sağlığı üzerindeki etkileri ve tıpta uygulama alanları [Yüksek lisans tezi]. Konya: Selçuk Üniversitesi; 2006.
- Radyasyon, insan ve çevre. 1. baskı. Ankara: TAEK; 2009.
- Aşıkoğlu M, İlem-Özdemir D, Atlıhan-Gündoğdu E. Radyofarmasi. 4. baskı. İzmir: Ege Üniversitesi Yayınevi; 2016.
- Adalet I, Mudun A, Ünal SN, Türkmen C. Nükleer tıp. 1. baskı. İstanbul: İstanbul Üniversitesi Yayınevi; 2012.
- Currie GM, Wheat JM, Davidson R, Kiat H. Radionuclide production. Radiographer. 2011; 58(3): 46–52.
- Saha GB. Radiopharmaceuticals and instruments. In: Saha GB, editor. Fundamentals of nuclear pharmacy. 2nd ed. New York: Springer; 1984. p. 67-86.
- Bulte JWM, Kraitchman DL. Iron oxide MR contrast agents for molecular and cellular imaging. NMR Biomed. 2004; 17(7): 484–99.
- Teksöz S, Biber-Müftüler FZ. Nükleer tıpta kullanılan radyoizotoplar ve biyomedikal uygulamaları. Nucl Med Semin. 2019; 5(1): 10–4.
- Atlıhan-Gündoğdu E, Özgenç E, Ekinci M, İlem-Özdemir D, Aşıkoğlu M. Nükleer tıpta görüntüleme ve tedavide kullanılan radyofarmasötikler. J Lit Pharm Sci. 2018; 7(1): 24–34.
- Banerjee S, Ambikalmajan Pillai MR, Ramamoorthy N. Evolution of Tc-99m in diagnostic radiopharmaceuticals. Nucl Med Semin. 2001; 31(4): 260–77.
- Molybdenum-99/Technetium-99m production and use [Internet]. Washington (DC): National Academies Press (US); 2009 [Updated: 2019 Dec 17; Cited: 2019 Dec 17]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK215133/>
- Ponto JA. Stability of filtered technetium Tc-99m sulfur colloid. J Am Pharm Assoc. 2005; 45(1): 92-4.
- Hacıosmanoğlu T, Karaçavuş S, İnce S, Elboğa U. Nükleer tıp teknisyen notları. 1. baskı. İstanbul: Nükleer Tıp Derneği; 2014.
- Sağır S, Asa S, Kabasakal L. Böbrek sintigrafisinde kullanılan radyofarmasötikler. Turk Urol Sem. 2011; 2: 88–90.
- Gümüşer FG, Sayıt E. Klinik öncesi çalışmalarda kullanılan nefroüroloji modelleri ve görüntüleme. Nucl Med Semin. 2019; 5: 102-6.
- Yazılıtaş F, Öztekin Çelebi FZ, Özlü SG, Kargın Çakıcı E, Çınar HG, Ekşioğlu AS, ve ark. İdrar yolu enfeksiyonu tanılı çocuklarda ultrasonografi, teknesyum-99m dimerkaptosüksinik asit sintigrafisi ve voiding sistoüretrografi bulgularının uyumu. Turkish J Pediatr Dis. 2019; 13(4): 277–82.
- Ziessman HA, O'Malley JP, Thrall JH, editors. Nuclear medicine: The requisites. 4th ed. Philadelphia: Elsevier Inc; 2014.

18. Töre G. Malign hastalıkların değerlendirilmesinde Tc-99m MIBI sintigrafisi. *Nucl Med Semin.* 2004; 15(1): 65–8.
19. Rizk TH, Nagalli S. Technetium (<sup>99m</sup>Tc) sestamibi. [Internet]. StatPearls Publishing; 2020 [Updated: 2020 Jul 5; Cited 2020 Jul 15]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/31985941>.
20. Atalay M. Meme sintigrafisi (sintomamografi) yöntemleri. *SSK Tepecik Hast Derg.* 1999; 9(1): 16–23.
21. Aras M, Turoğlu HT. Benign ve malign kemik lezyonlarını değerlendirmede Tek Foton Emisyon Tomografi/Bilgisayarlı Tomografinin değeri. *Nucl Med Semin.* 2016; 2(1): 9–14.
22. Sağlam S. Kemik protez enfeksiyonlarının ayırıcı tanısında kemik sintigrafisi, işaretli lökosit sintigrafisi, HIG sintigrafisi etkinliklerinin karşılaştırılması [Uzmanlık tezi]. Isparta: Süleyman Demirel Üniversitesi; 2009.
23. Okudan B, Üçok FM. Günümüzden geleceğe nükleer kardiyoloji. *SDÜ Tıp Fak Derg.* 2005; 12(3): 57–61.
24. Savaş R. Akciğer kanserinde PET/BT. *Trd Sem.* 2014; 2(3): 326–39.
25. Huang Y-Y. An overview of PET radiopharmaceuticals in clinical use: Regulatory, quality and pharmacopeia monographs of the United States and Europe. In: Shahzad A, Bashir S, editors. *Nuclear medicine physics.* IntechOpen; 2018. doi: 10.5772/intechopen.79227.
26. Ertay T. Enfeksiyon-enflamasyon: Moleküler görüntülemeye kullanılan SPECT radyofarmasötikleri. *Nucl Med Semin.* 2016; 2: 63–70.
27. Palestro CJ. Molecular imaging of infection with positron emission tomography: Beyond fluorodeoxyglucose. *Nucl Med Semin.* 2016; 2: 71–8.
28. Özkan E, Soydal Ç. Nöroendokrin tümörlerde teranostikler. *Nucl Med Semin.* 2015; 2: 103–8.
29. Farooqui M, Rathore S, Ball T. Utility of Indium-111 octreotide to identify a cardiac metastasis of a carcinoid neoplasm. *Proc (Bayl Univ Med Cent).* 2016; 29(1): 76–8.
30. Signore A, Glaudemans AWJM, editors. *Nuclear medicine in infectious diseases.* Switzerland: Springer; 2020.