

# Radiopharmaceuticals and Their Various Application in Health Care System

Vaibhav Paraji Dhone\*<sup>1</sup> Sonal Shinde\*<sup>2</sup> Vikas B. Wamane \*<sup>2</sup>

<sup>1</sup> student, <sup>2</sup> Assistant Professor

**Abstract:** Radiopharmaceuticals made up of two words Radio and Pharmaceutical Radio means emission of radiation and Pharmaceutical means dosageform which emmit the radiation. these radiation are used for diagnostic and treatment purpose. use of radiopharmaceuticals, often known as radioactive pharmaceuticals, has increased during the past few decades. Radioactive substances known as radioisotopes are the basis of radiopharmaceuticals. Recent years have seen the use of radiopharmaceuticals for both medicinal and diagnostic applications. There are three different forms of radioactive decays, including alpha particles, beta particles, and gamma radiations, according to the decay of radioactive substances. Alpha particles have a large mass and charge, which prevents them from penetrating the skin and instead causes damage. They are made up of two protons and two neutrons. Beta particles can be used in therapy because they are less corrosive than alpha particles and have a lower mass and charge. They can also penetrate tissue more easily. Gamma radiations have no mass or charge so they can penetrate the deep tissue of organs so used in diagnosis by imaging using a gamma camera. The radiopharmaceuticals were established in the diagnostic purpose and treatment of several diseases as thyroid gland cancer, hyperthyroidism, bone pain metastasis This review article describes the radiation source used in healthcare system, diagnostic imaging technique, the diagnostics, therapeutic application as well as advantage and disadvantage of radiopharmaceuticals in healthcare system. The main aim of this review article is to various application of radiopharmaceuticals in healthcare system.

**Keywords:** - Radiopharmaceuticals, Imaging technique, nuclear medicine, Diagnostics.

## Introduction

**Definition:** Radioactive substance used in diagnosis, treatment of various diseases called radiopharmaceuticals. Radiopharmaceuticals are radioactive substances used in the fields of diagnosis and therapy<sup>1</sup>. Radiopharmaceutical Preparations containing radioisotopes are known as "radiopharmaceuticals," and they are used in medicine for either diagnosis or treatment<sup>2</sup>. However, radiopharmaceuticals differ from traditional pharmaceuticals in many ways, and this branch has grown into a specialty. Most frequently, radiopharmaceuticals are made by radiolabeling a target molecule with a desired radionuclide, although occasionally, inorganic ions such as radioiodine and <sup>99m</sup>Tcper technate, operate as the radiopharmaceuticals directly. Information gathering for diagnostic purposes is done with the aid of diagnostic radiopharmaceuticals. This might be done using static imaging which involves injecting a radiopharmaceutical into the body (in vivo), letting it localise in the area of interest, and then imaging it to get information on the size, shape, and location of the target tissues. Some examples are imaging of organs such as liver, thyroid to find the occurrence and extent of damage, tumors to find out their exact location and size. Therapeutic radiopharmaceuticals are employed in a similar way, but with an aim to achieve a therapeutic effect. Hyperthyroidism, thyroid cancer, polycythemia<sup>3</sup>. Radiopharmaceuticals are categorized into 4 main classes: research, diagnostic, environmental and therapeutic pharmaceuticals<sup>4</sup>. Basic imaging tools of medical diagnostics, which are daily used to acquire important information about diseases stage and localization, are computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET). Nowadays, the use of dual modalities, such as PET/CT and SPECT/CT, enables the scientists and clinicians to identify the physiological basis of disease and correlate it with the anatomical image<sup>5</sup>. There are different route of administration for radio pharmaceuticals, may be given orally parentally or installed into the eyes.<sup>6</sup> The global market of RPs is growing continuously and is expected to reach USD 5.2 billion by 2024 from an estimated USD 4.1 billion in 2019, growing at a CAGR of 4.7%.<sup>7</sup>

## History of Radiopharmaceuticals

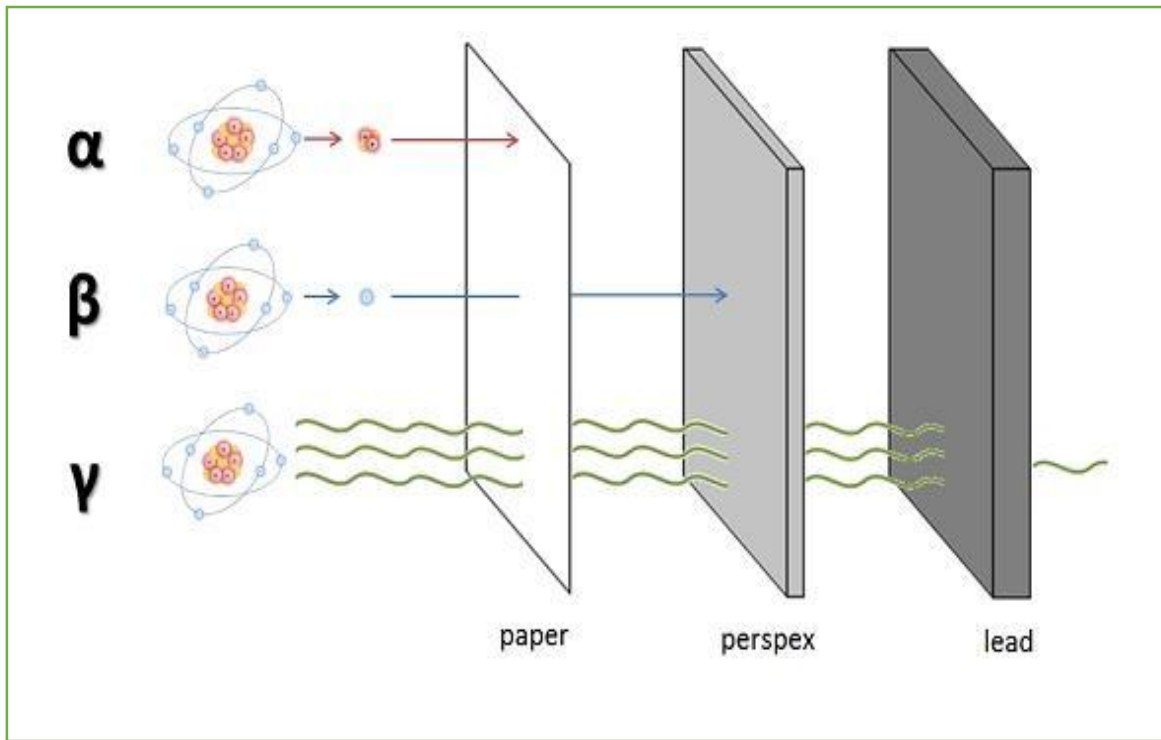
Radiopharmaceutical therapy began in 1941 with the efforts and insight of Saul Hertz, MD of MGH and also Arthur Roberts, PhD of MIT. From that beginning, I-131 has become an important agent for the treatment of thyroid disease.<sup>8</sup>

## Radiopharmaceuticals:-

The radiopharmaceuticals are radioactive substances which disintegrate instantaneously by emitting radiations.<sup>9</sup> The radioactive nuclides are like normal nuclides having the same number of protons with different numbers of neutrons. The emitted radiation may be in the form of alpha, beta, and gamma radiation<sup>10</sup>.

## Radioactivity:-

As shown in fig. (1), the different types of radioactive decays, which include alpha, beta, and gamma. The difference between the different types of radioactive decays is represented in table<sup>2</sup>.



• Fig.1: Types of radioactivity: alpha, beta, and gamma decay <sup>11</sup>

**Alpha particle**

Alpha particles are helium nuclei consisting of two protons and two neutrons, which means that when the radionuclide decays and emits an alpha particle, its atomic number will be decreased by 2 and also the atomic mass will be decreased by 4. Alpha particles are heavy and move slowly, so they have low penetration power, which allows them to be stopped by a sheet of paper (12). Due to the high mass of alpha particles, they cannot penetrate the outer layer of the skin when the body is exposed to them and do not cause a hazardous effect. However, when alpha particle emitters are inhaled, ingested, or injected, they cause a serious hazardous effect on internal organs due to the high charge of the alpha particles.

**Beta particle**

Beta particles resemble the electron in mass and charge, which indicates that they have a very small mass in comparison to protons or neutrons. Beta particles can be of negative charge (negatron) or positive charge (positron). Due to the low mass of beta particles, they have a penetration power higher than alpha particles, which allows them to penetrate a sheet of paper but be stopped by an aluminum sheet. Being charged, beta particles have a destructive effect on organs, but less than alpha particles. Therefore, they can be used in therapy, especially for the destruction of tumor tissue. <sup>13</sup>

**Gamma radiation**

Gamma radiations are emitted from a radioactive nuclide in the form of photons, not particles, which means they have no mass or charge. When radionuclides decay in the form of gamma radiations, the process is not accompanied by any change in the atomic number or the atomic mass. Being radiation, gamma rays have a higher penetrating power than beta particles due to their lack of mass. Gamma radiations can be used for diagnosis because they have no harmful effects as there is no charge in them.

An example of a radionuclide that decays into gamma radiation is technetium-99m. <sup>13</sup>

**Different Types Of Radioactive Decays Of Radiopharmaceuticals**

Types of decay	Alpha (α)	Beta (β)	Gamma (γ)	Reference
Structure and origin	Like helium nucleus emitted from the radionuclide	Like electron emitted from the radionuclide	Like waves emitted from the radionuclide	14
Charge	α <sup>2+</sup>	β <sup>-</sup> or β <sup>+</sup> ,	Zero	13

Mass	4	1/1836	Zero	13
Ionization degree in the human body	Highly ionized so cause a destructive effect and can't be used in nuclear medicine	Less than alpha particle can't be used for diagnosis but used for therapy	No ionization so can be used in imaging	14
Suitability for nuclear imaging	Not suitable	Not suitable	Highly suitable	13

Table :-1

**DIAGNOSTIC IMAGING TECHNIQUES:-**

**1] X-rays**

The most popular and commonly used diagnostic imaging method is X-ray imaging (radiographs). You will most likely receive an x-ray initially, even if you also require more complex diagnostics.



Fig:-2 in this x-ray of an ankle, the tibia and fibula bones are fractured. The pieces of bone are severely out of place. Photographic film or a digital x-ray sensor is placed between the x-ray machine and the area of your body being photographed. You must stay still as the device temporarily passes electromagnetic waves (radiation) into your body, exposing the film to reflect you're inside structure. X-ray exposure does not cause any harm at the current level.<sup>26</sup>

**2] CT (Computer tomography):-**



Fig: - 3 CT Scan

The basic idea behind CT is to measure the spatial distribution of the physical material that will be viewed from various angles and then create superposition-free images using this information. It is essentially an X-ray photography technique in which a single patient plane is scanned from several angles to produce a cross-sectional image of the interior structure of that plane. There are numerous diagnostic and therapeutic uses for a CT scan. By outlining specifics of the organs, including soft tissues and bones, it increases the accuracy of the diagnosis. A CT scan can help with surgical procedures, biopsies, and radiotherapies by providing information on the spread of an infection or tumour to other bodily parts.

**3] MRI (Magnetic resonance imaging):-**

Fig:-4 MRI (Magnetic resonance imaging)



Similar to a computerised tomography (CT) scanner, an MRI creates cross-sectional images of the body. Cross-sectional imaging of the body can be compared to slicing a loaf of bread to see the inside. Unlike a CT scan, MRI does not use X-rays. Instead, it uses a strong magnetic field and radio waves to produce The gut, pelvis, joints, brain, and spine are frequently examined with MRI technology. The blood vessels are examined using a specialised MRI test called Magnetic Resonance Angiography (MRA). Digital images that are crystal clear and in-depth of the human body.

**4] Echography/Ultrasound:-**



Fig: - 5 Echography/Ultrasound

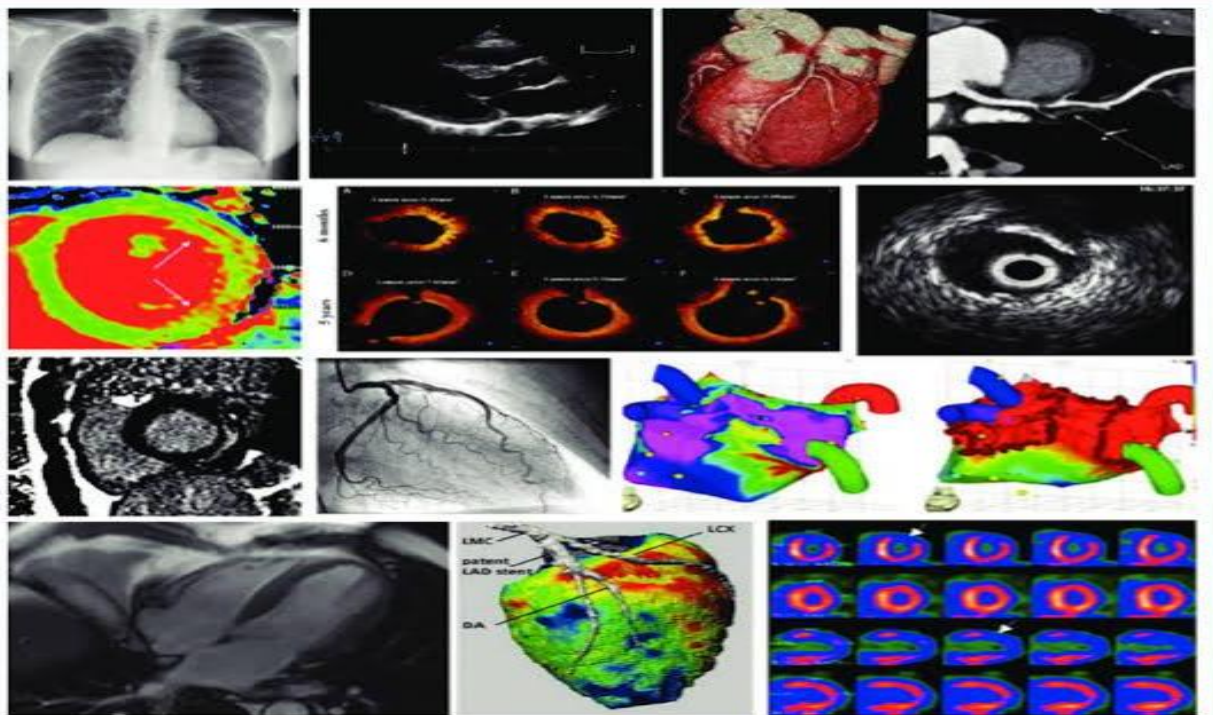
Ultrasound examines organs and body structures by using high frequency sound waves. They are used by medical practitioners to view the kidneys, liver, heart, blood arteries, and other organs. During pregnancy, doctors use ultrasound tests to examine the foetus. Contrary x-rays, ultrasound does not involve exposure to radiation.

A specialised technician or physician will slide a transducer over a portion of your body during an ultrasonic examination. The transducer emits sound waves, which are reflected by the tissues in your body. The transducer also records waves that return. Images are created from these sound waves.<sup>15</sup>

### 5] Cardiovascular Imaging:-

Fig: - 6 Different modalities of cardiovascular imaging

In cardiac imaging, radiopharmaceuticals are helpful as agents that provide details about the regional myocardial blood perfusion. To provide information at peak cardiac output, there were administered. The study involves stressing the patient with exercise in a



treadmill or giving i.v injection of dipyridamole. A technetium<sup>99m</sup> (<sup>99m</sup>Tc) labelled methoxy isobutyl isonitrile injection or thallium chloride injection is then administered, and imaging is performed.

### 6] bone imaging

This technique is frequently used to diagnose both primary and metastatic benign and malignant bone cancers. A diagnostic agent (often a single photon emitter) plus a therapeutic agent make up radiopharmaceuticals used for bone imaging.

Therapeutic radiopharmaceuticals are used in a different way than single photon bone imaging agents based on their particle emissions (mainly Beta). For the in vivo experiments, <sup>99m</sup>Tc labelled polyclonal human immunoglobulin (<sup>99m</sup>TcHIG) was employed as the radiopharmaceutical to show arthritic lesions by gamma scintigraphy.<sup>16</sup>

### 7] SPECT (single photon emission computed topography):

It was developed on the principles of planar imaging, which rotates gamma cameras around the patient while acquiring a series of planar images. The doctor can view activity distributions in crosssections of the human body because it produces three-dimensional images of nuclear activity dispersion.

### 8] PET (positron emission tomography):-

In recent decades, it has become a part of clinical practise. A radioactive isotope (a PET radionuclide) is administered to the patient during a PET imaging procedure. The isotope generates positrons during decay (particles with the mass of electrons but with a positive charge). Two gamma photons are produced as a result of the annihilation of both particles as a result of electron and positron interaction.

The resulting gamma rays are detected by a ring of several of detectors.<sup>16</sup>

### Commonly Used Radiation Sources

In the healthcare system, a variety of radiation sources are used.

External beam radiation therapy (EBRT or XRT) or teletherapy, brachytherapy or sealed source radiation therapy, and systemic radioisotope therapy or unsealed source radiotherapy are the three primary subcategories of radiation therapy. .

The differences relate to where the radiation source is located; external radiation is delivered from outside the body; brachytherapy uses sealed radioactive sources that are implanted precisely where the patient needs treatment; and systemic radioisotopes are administered orally or by infusion.

#### 1. External Beam Radiation

Each treatment involves a two to three minute beam of radiation being directed into the tumour from outside the body. Teletherapy or external beam radiation (EBRT) is the most popular type of radiotherapy. An external source of ionising radiation is focused at a specific area of the patient's body while they sit or lie on a couch. External beam radiotherapy (EBRT) sends radiation at the tumour from outside the body, in contrast to internal radiotherapy (brachytherapy), in which the radiation source is inside the body.

**2. Image-Guided, Intensity-Modulated Radiation Therapy**

Patients with prostate cancer, head and neck malignancies, cancers at the base of the skull, or cancers affecting portions of the brain are all treated with intensity modulated radiation treatment (IMRT). With IMRT, the tumour can be targeted with stronger radiation doses, especially close to important structures, increasing the likelihood of a cure and reducing late treatment effects. The incorporation of image

guided technology with IMRT allows doctors to track tumour position and location while the patient is actually on the treatment table. Image-guided IMRT offers more accurate coverage since it enables medical professionals to react quickly to any tumour movement and, if necessary, recalculate the radiation beams in the course of the therapy.

**3. Virtual Simulation and 3-Dimensional radiation Therapy**

By employing sophisticated CT and/or MRI scanners and planning software, it is now possible to outline tumours and nearby normal structures in three dimensions, revolutionising the way radiation therapy treatments are planned. Virtual simulation, the most basic form of planning, allows more accurate placement of radiation beams than is possible using conventional X-rays, where soft-tissue structures are often difficult to assess and normal tissues difficult to protect.<sup>15</sup>

**Applications of Radiopharmaceuticals in Healthcare System**

Sr.No	Elements	Application
1	Iodine-131	Treatment of thyroid gland disorders and Cancer.
2	Xenon-133	Diagnostic lung function imaging.
3	Molybdenum-99/ technetium-99m	Diagnostic imaging in oncology, cardiology and bone scanning, and the functional imaging of organs such as kidneys, liver, brain and lungs
4	Strontium-89	Treatment of painful bone metastasis
5	Lutetium-177	Treatment of tumours.
6	Holmium-166	Development of treatments for liver cancer and Blood Cancer.

Table:-2

**RADIOPHARMACEUTICALS:-**



Fig.7 applications of radiopharmaceuticals in the diagnosis, therapeutic Interventions, and monitoring of environments.<sup>17</sup>

**Application of Radiopharmaceuticals**

➤ **THE USE OF RADIOPHARMACEUTICALS IN DIAGNOSTICS**

Radiation used for diagnostic purposes must have enough energy to penetrate through tissues and reach the detecting equipment from within the body. The functions of the organs in the body vary. Throughout the investigation, the doctors determined the chemical compounds that each organ can ingest and absorb. The thyroid gland, for example, preferentially absorbs iodine, whereas the brain absorbs glucose and the bones absorb calcium. This concept is employed in radiopharmaceuticals, where the radioisotope is selectively up taken by certain organs after entering the body. A diagnostic radionuclide with a short half-life and decay through gamma radiation emission is suitable. Technetium-99 m is the perfect diagnostic radionuclide because it has a short half-life (6 hours), decays solely via gamma radiation, and is easily spotted by a gamma camera.

Radionuclide	Diagnostic use
Iodine-125	Used in diagnosis and evaluation of the glomerular filtration rate of kidneys
Fluorine-18	Used in positron emission tomography to assess alternations in glucose metabolism in brain and cancer
Gallium-67	Used in tumors imaging
Potassium-42	Used in determination of exchangeable potassium in coronary blood flow
Iodine-131	Used in studying the function of the thyroid gland
Xenon-133	Used to study the pulmonary ventilation
Sodium-24	Used to study sodium exchange
Chromium-51	Used in diagnosis of pernicious anemia
Selenium-75	Used to study the production of digestive enzymes
Holmium-166	Used in the diagnosis of liver cancer <sup>18</sup>

Table:3

### ➤ THERAPEUTIC APPLICATIONS OF RADIOPHARMA-CEUTICALS

Today, nuclear medicine provides close to one hundred procedures that are extremely beneficial to a wide range of medical disciplines, from oncology and cardiology to psychiatry, and as a result, several millions of people worldwide benefit each year. Health care applications of radioisotopes are more and can be widely classified Diagnostic and Therapeutic. Few therapeutic applications are described below.

#### • TREATMENT OF HYPERTHYROIDISM:-

<sup>131</sup>Iodine is used extensively for the treatment of hyperthyroidism. The treatment of benign and malignant diseases of the thyroid can be done with Iodine-131 (I-131). Radioiodine therapy has been used for a long time. In treating diseases such as hyperthyroidism, I-131 radionuclide settles in the thyroid tissue. It destroys the follicle cells with the beta particles it emits and stops the growth and activities of the thyroid cells.<sup>19</sup>

#### • TREATMENT OF THYROID CARCINOMA:-

radioiodine has been used to treat differentiated thyroid carcinoma, a malignancy that can spread to the bones, lungs, and other soft tissues. However, because it is slow-growing and the prognosis is generally favourable, patients can be followed up on for a long time. Repeated radionuclide imaging with radioiodine can be used to evaluate treatment response, and in advanced or resistant cases, more therapeutic doses of <sup>131</sup>I may be required.

#### • TREATMENT OF BONE TUMORS:-

Patients with prostate, breast, and lung cancer frequently have bone metastases, and for these patients, managing their bone pain is a crucial clinical problem. External beam radiotherapy, in combination with analgesic drugs, remains the mainstay of treatment but the proportion of the body that can be treated is limited. So many beta emitting radionuclides, in a variety of chemical forms, can be used for the treatment of bone metastases. <sup>32</sup>P, <sup>89</sup>Sr, <sup>186</sup>Rhenium and <sup>153</sup>Samarium have been carried out.<sup>16</sup>

### The Nuclear Medicine

Radiopharmaceuticals are pharmaceutical preparations that contain radioactive substances and radiolabel substances to be used either in diagnosis or therapy. The Society of Nuclear Medicine, state that 20 million nuclear medicine procedures are carried out in the United States every year.

#### **Advantages of Nuclear Medicine**

Providing information about the function and anatomy of the body The tests of nuclear medicine give complete information about the functions and anatomy of body organs. It serves as an effective tool for doctors to assess patient cases and choose the most appropriate course of action. From the scan of the body, it is easy to decide on the tumor is malignant or benign, the physician can determine if surgery is required or not, and it is easily discovering the presence of disease before the appearance of the symptoms<sup>20</sup>

#### • Determination of the cancer status

Nuclear medicine is a useful tool for determining the status of the tumor. The physician can know if the tumor is metastasized or returned after size Reduction<sup>21</sup>

#### • Nuclear medicine is important in bone metastasis

The bone pain source and the presence of bone cancer can be detected by nuclear medicine. Also, for an elderly patient, nuclear medicine serves as a tool for detecting the hidden features which resulted from osteoporosis<sup>22</sup>

#### • Nuclear medicine is important in heart disease (cardiology)

Nuclear medicine is used by the cardiologist to recognize the causes of certain symptoms like the breath shortage and chest pain. Also, the nuclear medicine used for diagnosis of coronary artery disease caused by high cholesterol level, which causes the block of the blood and oxygen supply to the heart<sup>23</sup>

### ADVANTAGES OF RADIOPHARMACEUTICAL IN HEALTHCARE SYSTEM

- It can be used as diagnosis and treatment of the patient.
- The pain can be relieved quickly.
- Cancer is typically curable.
- Is able to treat different disease sites.
- A therapy option that is readily available.

- Directly treats the tumor, especially useful For bone metastasis.
- A single dose is effective for some patients.
- Nuclear medicine tests can be performed on Children.
- Nuclear medicine techniques are fully safe and have no side effects.<sup>24</sup>

#### **DISADVANTAGES OF RADIOPHARMACEUTICAL IN HEALTHCARE SYSTEM**

- Patients may experience prolonged discomfort and inconvenience when many fractions are administered.
- Higher doses of the head and neck radiation can be associated with cardiovascular complication, thyroid dysfunction and pituitary axis dysfunction.
- Nuclear medicine tests are not recommended for pregnant women because unborn babies have a greater sensitivity to radiation than children or adults.
- Dental braces, permanent bridges, and tooth fillings may result in some distortion near the mouth.
- Can cause a few allergic responses.
- It has a radiation risk.
- Myelosuppression may occur.

#### **Conclusion**

Nowadays there are different types of radiopharmaceuticals are available and having an important role in diagnosis of disease. In the present era, there is an important role of radiopharmaceutical due to its correct and effective diagnosis of disease, advances in all imaging modalities changing the pattern of diagnostic imaging. Nowadays, the modern healthcare system will not be perfect without radiation source because of its effectiveness.

#### **Reference**

1. Nadugopal, B., Swain, S.S., Ojha, S.K. and Meher, C.P., 2017. Impact of Radiopharmaceuticals in Healthcare System. *PharmaTutor*, 5(8), pp.23-31.
2. Debnath, S. and Babu, M.N., 2015. Radiopharmaceuticals and their therapeutic applications in health care system. *Asian Journal of Research in Pharmaceutical Science*, 5(4), pp.221-226.
3. Nadugopal, B., Swain, S.S., Ojha, S.K. and Meher, C.P., 2017. Impact of Radiopharmaceuticals in Healthcare System. *PharmaTutor*, 5(8), pp.23-31.
4. Badria, F.A., 2022. Radiopharmaceuticals: On-Going Research for Better Diagnosis, Therapy, Environmental, and Pharmaceutical Applications. *Radiopharmaceuticals: Current Research for Better Diagnosis and Therapy*, p.3.
5. Ahmedova, A., Todorov, B., Burdzhiev, N. and Goze, C., 2018. Copper radiopharmaceuticals for theranostic applications. *European Journal of Medicinal Chemistry*, 157, pp.1406-1425.
6. Volkert WA, Hoffman TJ. Therapeutic radiopharmaceuticals. *Chem Rev* 1999;99:2269–92.
7. Kaushik, D., Jangra, P., Verma, R., Purohit, D., Pandey, P., Sharma, S. and Sharma, R.K., 2021. Radiopharmaceuticals: An insight into the latest advances in medical uses and regulatory perspectives. *Journal of Biosciences*, 46(1), pp.1-25.
8. 8)
9. Kost SD, Dewaraja YK, Abramson RG, Stabin MG. VIDA: a voxel-based dosimetry method for targeted radionuclide therapy using geant4. *Cancer Biother Radiopharm* 2015;30:16–26.
10. Del Guerra A, Panetta D. Fundamentals of natural and artificial radioactivity and interaction of ionizing radiations with the matter. In: *Nuclear Medicine Textbook*. Springer; 2019. p. 3–19.
11. Parigger CG, Dackman M, Hornkohl JO. Time-resolved spectroscopy measurements of hydrogen-alpha,-beta, and gamma emissions. *Appl Opt* 2008;47:G1–G6
12. Lassmann M, Eberlein U. Targeted alpha-particle therapy: imaging, dosimetry, and radiation protection. *Ann ICRP* 2018;47:187–95.
13. Maulany GJ, Manggau FX, Jayadi J, Waremra RS, Fenanlampir CA. Radiation detection of alfa, beta, and gamma rays with geiger muller detector. *Int J Mech Eng Technol* 2018;9:21–7.
14. Magill J, Galy J. Radioactivity radionuclides radiation. Vol. 1. Springer Science and Business Media; 2004.
15. Tayal, S., Batham, S., Solanky, N. and Hait, A., 2019. IMPACT OF RADIOPHARMACEUTICAL ON HEALTH: A REVIEW ABOUT AUTHOR.
16. Nadugopal, B., Swain, S.S., Ojha, S.K. and Meher, C.P., 2017. Impact of Radiopharmaceuticals in Healthcare System. *PharmaTutor*, 5(8), pp.23-31.
17. Badria, F.A., 2022. Radiopharmaceuticals: On-Going Research for Better Diagnosis, Therapy, Environmental, and Pharmaceutical Applications. *Radiopharmaceuticals: Current Research for Better Diagnosis and Therapy*, p.3.h
18. Vagahasiya, T.K., Malaviya, M.K., Kotadiya, R.J., Vas, R. and Gohil, V.K., 2021. RADIOPHARMACEUTICAL IN NUCLEAR PHARMACY & MEDICINE AND THEIR THERAPEUTICS APPLICATION IN HEALTH CARE SYSTEM.1
19. Akgun, E., Ozgenc, E. and Gundogdu, E., 2021. Therapeutic Applications of Radiopharmaceuticals: An Overview. *FABAD Journal of Pharmaceutical Sciences*, 46(1), pp.93-104.
20. Hughes DK. Nuclear medicine and infection detection: the relative effectiveness of imaging with <sup>111</sup>In-oxine-, <sup>99m</sup>Tc-HMPAO-, and <sup>99m</sup>Tc-stannous fluoride colloid-labeled leukocytes and with <sup>67</sup>Ga-citrate. *J Nucl Med Technol* 2003;31:196–201.
21. 3. Tryciecky EW, Gottschalk A, Ludema K. Oncologic imaging: interactions of nuclear medicine with CT and MRI using the bone scan as a model. In: *Seminars in nuclear medicine*. Elsevier; 1997. p. 142–51
22. Vassiliou V, Andreopoulos D, Frangos S, Tselis N, Giannopoulou E, Lutz S. Bone metastases: assessment of therapeutic response through radiological and nuclear medicine imaging modalities. *Clin Oncol* 2011;23:632–45.



23. Nakajima K, Matsumoto N, Kasai T, Matsuo S, Kiso K, Okuda K. Normal values and standardization of parameters in nuclear cardiology: Japanese Society of Nuclear Medicine working group database. *Ann Nucl Med* 2016;30:188–99.
24. M.J. Welch and C.S. Redvanly; *Hand book of Radiopharmaceuticals: Radiochemistry and Application* , eds, New York, NY:J, Wiley, 2003.
25. Kara Duncan Weatherman; *Clinical use of Radiopharmaceuticals*, BCNP.
26. <https://orthoinfo.aaos.org/en/treatment/x-rays-ct-scans-and-mris/>