**Nuclear Medicine: Future and Challenges**

**Preeti Singh1 and Deepak Singh2**

**1Department of Physical Sciences, Ravindra Nath Tagore University, Bhopal, India**

**2Department of Nuclear Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India**

**Abstract:**

Nuclear medicine plays a significant role in the health management in developing countries, just as it does in other parts of the world. Nuclear medicine professionals had to become proficient in the multimodality study interpretation since the development of PET/CT, SPECT/CT, and PET/MRI significantly altered the field. However, there are several difficulties that may be readily avoided while practicing nuclear medicine in the underdeveloped countries. The sustainability of radioisotope production is currently a critical subject that is receiving a lot of attention. Nuclear medicine will likely be more crucial for both diagnostic and therapeutic purposes in the near future. If we commit to training and aiding the upcoming generation of nuclear medicine researchers, technicians, and physicians, and if we create a programme to fund nuclear medicine research. If we spend money building the plant's infrastructure.

**Keywords**: Nuclear medicine, Radioisotopes, SPECT and PET

1. Introduction

There is a long list of Nobel laureates, who have used radioisotopes for medical diagnosis and treatment. German physicist Wilhelm Konrad Roentgen was awarded the first-ever Nobel Prize in Physics in 1901 for the discovery if X-rays. Many scientists proposed that when phosphorescence develops over time, materials that glow when exposed to visible light may also release X-rays. The introduction of PET/CT, then SPECT/CT, and PET/MRI profoundly changed the field and required nuclear medicine specialists to gain expertise in the multimodality study interpretation. The editors of the Journal of Nuclear Medicine have produced a supplement that examines the most important issues and future opportunities for the sector.

In the United States, Netherlands and various European countries, nuclear medicine is commonly used in radiology. After the introduction of multimodality imaging, this integration made sense from a logistical and financial standpoint. Enhancing early cancer detection and localisation is the aim of multimodal or multiplexed imaging (Kobayashi et al., 2010). Today's theranostics require training in and experience with clinical skills, which shows a close relationship with medical oncology or radiation oncology. Theranostics, which employs the same receptor for imaging and therapy, has already had a significant influence on nuclear medicine operations (Turner, 2019). Because of its encouraging results, big pharma was lured to Lutathera and PSMA-617, as seen by Novartis' acquisition of both medications for a combined USD 6.0 billion. After decades of ignorance, Wall Street is suddenly informed about the developments and potential of nuclear medicine.

Due of the rapid development of machine learning in the interpretation of medical images, the future of radiography as a clinical discipline has been pessimistically prophesied ((Capobianco et al., 2020, Guiot et al., 2021, Kocak et al., 2019). Nensa et al. (2019) discuss the advantages and drawbacks of application of Artificial Intelligence in nuclear medicine. With the advent of digital PET allowing for speedy dynamic picture acquisition, advances in algorithms, deep learning, and computing power have kindled the potential of establishing clinical evidence and relevance for radiomics. Hatt et al. (2020) assert that data are also pictures; they provide a summary of notable advancements over the last five years and also provide a glimpse into the future. Today's growing body of healthcare data provides a wealth of knowledge that offers chances for personalised and precision therapy. We need advanced AI systems to make use of all this data since the sheer volume is daunting for doctors. Having enough training data is essential for creating these AI systems. As a result, the medical business is under a lot of pressure as a result of the growing amount of healthcare data, but there is also a chance for a revolution in health care. To improve picture quality, acquisition speed, and cut expenses, AI may be used during the capture and reconstruction of images.

1. **Definition**

Nuclear medicine is a branch of medicine that evaluates body functioning and diagnoses and treats diseases using radioactive tracers (radiopharmaceuticals) (Hamilton, 1942). Depending on the goal of the scan, these carrier molecules vary substantially. The carrier molecules that make up radioactive tracers are firmly bound to a radioactive atom. Some tracer molecules use the patient's own cells or molecules that interact with a certain protein or sugar in the body Doctors may follow the route of these radioactive tracers using cameras with specialized lenses. The two most popular imaging techniques used in nuclear medicine are SPECT (Single Photon Emission Computed Tomography) and PET (Positron Emission Tomography) examinations.

When a radioisotope is employed as a tracer, the radiation's energy activates the counting device, which then measures the precise amount of energy released by each atom during its disintegration, which distinguishes the compound from other naturally occurring materials. It is hard to distinguish one element's atom from another, with one obvious exception. For instance, once regular salt enters the blood stream, it often lacks any characteristics that would allow one to infer its origin or distinguish between sodium atoms that were added to the blood and those that were already there. The exception to this rule is when a few of the atoms are "tagged" with radioactive properties. The radioactive atoms can thus be easily found and diagnose. The tracers used to detect sickness or incorrect bodily function are only present in very tiny amounts and are thus generally safe. Their effects are comparable to those of the radiation that every one of us is constantly exposed to from both inside and outside the body due to natural sources. Therapeutic dosages, in contrast to those used for medical therapy, are administered to individuals who have a condition that has to be controlled, meaning the doctor wants to specifically remove any aberrant cells or tissues (WHO, 2013). Therefore, in these situations, the attending physician's competence and knowledge must be used to keep the effects to the targeted outcomes and prevent harm to healthy organs.

1. **Radioisotopes in Medicines**

The Pattern nuclear reactor in the Netherlands and the Chalk River Laboratories in Ontario, Canada, respectively, supply around one third and one third of the medical isotopes used globally, respectively. The Canadian Nuclear Safety Commission shut down the National Research Universal reactor in Canada on November 18, 2007, so that safety measures may be brought up to date. The upgrading took longer than anticipated, and in December 2007 there was a severe scarcity of medical isotopes. Therefore, in order to restart the reactor on December 16th, 2007, the Canadian government issued emergency legislation. This allowed for the continued production of medicinal isotopes.

The neutrons that are created in huge quantities as a result of the fission of U-235 are used to irradiate materials in the Chalk River reactor (National Research Council 2019). These neutrons alter the irradiated material's nuclei by either adding another neutron or by splitting it through nuclear fission. Molybdenum-99 is one of the fission products of uranium that is produced in reactors and is sent to radiopharmaceutical facilities all around North America. With a half-life of 2.7 days, the Mo-99 radioactive beta decays into Tc-99m, which is subsequently extracted. When ingested by a patient, the Tc-99m further degrades and emits a gamma photon that may be detected by a gamma camera. It eventually decays to Tc-99, which has a lower radioactivity level than Tc-99m. Another radioisotope that is frequently used in PET, F-18, is generated in a cyclotron, a circular accelerator rather than a nuclear reactor. The stable heavy oxygen isotope O-18 is bombarded by protons that have been accelerated by the cyclotron. Then, FDG is often produced with the F-18.

Recently, sustainability of radioisotope generation is the crucial issues that receives a lot of attention (IAEI). More than 160 distinct radioisotopes created in particle accelerators or medium- or high-flux research reactors are commonly employed in medical and various other industries (Wang wt al., 2022). The Table I lists a few of the radioisotopes generated by the reactor and particle accelerators along with some of their uses.

Table-I

|  |  |  |
| --- | --- | --- |
| Name of Radioisotope | Half-life | Use |
| Radioisotopes produced by reactors |
| Bismuth-213 | 45.59 min | It is an alpha emitter (8.4 MeV) used in the targeted alpha therapy (TAT) for the treatment of cancer. |
| Cesium-131 | 9.7 days | It produces X-ray photons in the 29.5 and 33.5 keV energy range and used in the brachytherapy for cancerous tumors. |
| Cesium-137 | 30 years | It is used in gauges and medical instruments for sterilization. |
| Chromium-51 | 28 days | It is used to label platelets and diagnose gastrointestinal haemorrhage. |
| Cobalt-60 | 5.27 years | It is used to limit the growth of malignant cells.  |
| Dysprosium-165 | 2 h | It is used to treat arthritis with synovectomy. |
| Erbium-169 | 9.4 days | It is used to treat synovial joints' arthritic discomfort. |
| Holmium-166 | 26 h | It is used liver tumour diagnosis and therapy. |
| Iodine-125 | 60 days | It is used in radioimmunoassay and brachytherapy of cancer. |
| Iodine-131 | 8 days | It is generally used in imaging of thyroid, diagnosing conditions, and monitoring renal blood flow. |
| Iridium-192 | 74 days | It is used as a source for internal radiation in the treatment of cancer.  |
| Iron-59 | 46 days | It is used in research on the spleen's iron metabolism (1095 keV) |
| Lead-212 | 10.6 h | It is used in TAT (239 keV) for malignancies |
| Palladium-103 | 17 days | It is used to create permanent implant seeds for brachytherapy treatment of early-stage prostate cancer. |
| Potassium-42 | 12.36 h | It is used to recognize brain tumors and determine the distribution of potassium in physiological fluids. |
| Radium-223 | 11.4 days | It is used to treat bone metastases from prostate cancer |
| Rhenium-186 | 3.71 days | It is used as therapeutically to treat the discomfort of bone cancer.  |
| Samarium-153 | 47 h | Selling as Quadra met, this drug is effective in reducing the pain caused by bone-localized secondary tumours.  |
| Selenium-75 | 120 days | It is used for research on the synthesis of digestive enzymes. |
| Sodium-24 | 15 h | It is used to study the body's electrolytes. |
| Ytterbium-169 | 32 days | It is used to study brain's cerebrospinal fluid. |
| Radioisotopes produced by accelerators |
| Cobalt-57 | 272 days | Used as a marker for in vitro diagnostic tests and to quantify organ size. |
| Copper-64 | 13 h | It is used for cancer treatment (511 keV) as well as PET imaging examinations of tumours. |
| Gallium-67 | 78 h | It is used to find inflammatory lesions (infections) and image tumours  |
| Indium-111 | 2.8 days | It is used in studies of the brain infections and colon transit. |
| Iodine-123 | 13 h | It is used to determine thyroid function. |
| Thallium-201 | 73 h | used to identify low-grade lymphomas |

* 1. **How we use Radioisotopes in medicines**

Radioactive materials are typically regarded as harmful to human health. Radioactivity occasionally causes serious health problems. Although this is true in excess, radioactivity may often be beneficial to human health. Radioisotopes are useful tools for medical diagnostic and therapeutic purposes.

**3.2.1 Diagnostic Uses of Radioisotopes**

The use of radioisotopes in diagnostic techniques in medicine is crucial. Medical experts can investigate the dynamic processes occurring in various bodily sections in conjunction with imaging equipment. The use of radioisotopes enables common medical procedures including SPECT, MRI, and PET. Patients are administered a material containing radiolabeled chemicals as part of these diagnostic procedures. The diagnostic equipment then tracks the radioactive tracers' gamma ray emissions and creates a picture using the radiation. The picture is used by medical practitioners to identify aberrant circumstances and diagnose health issues.

**3.2.2 Therapeutic Uses of Radioisotopes**

The ability of radioisotopes to treat medical disorders is a key component of their use in medicine. Although therapeutic radioisotope applications are less common than diagnostic applications, they are still just as significant. Therapeutic applications usually aim to eliminate a specific cell population, such as cancer cells or other aberrant tissue development. Radioactive isotopes are injected into the body to accomplish this. The radioactive material then breaks apart and destroys the undesirable cells when harmful cells ingest it. Thyroid cancer (Mansi et al., 2004), hyperthyroidism (Mariani et al, 2021) and non-Hodgkin lymphoma (Bischof et al., 2003) are a few of the illnesses that are commonly treated using radioisotopes. The usage of radioisotopes in the medical industry is one of their many crucial applications, which spans numerous industries. Although there are many more applications for radioisotopes than those covered above, today's medical industry uses them most frequently for diagnostic and therapeutic purposes.

**3.3 Advantages of the Radioisotope Technique:**

* Advanced treatment options

The choices for treating a variety of medical disorders have been improved digitally and technically by nuclear medicine. Cancer is one of these illnesses. Radiation and chemotherapy are used to treat cancer. Nuclear medicine has been a gift to patients in dire situations when they had lost hope for survival.

* Early detection of ailments

Nuclear medicine has a very high sensitivity for detecting very serious medical disorders. What inspires individuals to trust in its strength is their accuracy. Many doctors and other medical professionals have used it to identify challenging possibilities at an early stage of treatment.

* Accuracy is the key

The greatest benefit of nuclear medicine is this. Due to its precision, several challenging medical operations have become easier. Due of its precision, it may also be thoroughly examined and analysed. When it comes to treatments, the exact processes don't cut any corners. Patients have historically been required to endure challenging operations and procedures to obtain a thorough diagnosis. Nuclear medicine has greatly simplified this.

**Nuclear diagnostic techniques**

* 1. **Single Photon Emission Computed Tomography (SPECT)**

Single photon emission computed tomography (SPECT), a three-dimensional nuclear medicine imaging technique, combines scintigraphy and computed tomography data. This enables the distribution of the radionuclide to be shown in three dimensions as opposed to planar nuclear imaging alone, providing improved detail, contrast, and spatial information.

**Design**

In SPECT machines, which combine a number of gamma cameras (ranging from one to four cameras), a gantry spins around the patient. Attenuation correction and anatomical localization are the main uses of single photon emission computed tomography-computerized tomography (SPECT-CT), a sort of hybrid imaging that combines SPECT with a separate CT scanner.

**Principle**

Gamma cameras encircle the person and provide spatial information on the distribution of radionuclides within tissues. The use of many gamma cameras increases the detectors' effectiveness and spatial resolution. Three-dimensional images are frequently produced when the projection data from the cameras is gathered, generally in axial slices 1–3. With SPECT-CT 1, attenuation modification and improved resolution anatomical localization are both achievable.

**Uses**

* Tc-99m sestamibi myocardial perfusion study
* brain imaging (perfusion and receptor-binding radiotracers)
* Tc-99m sestamibi parathyroid scan
* white cell scan
* bone scan
	1. **Positron Emission Tomography (PET)**

 A contemporary non-invasive imaging approach for measuring radioactivity in vivo is positron emission tomography (PET). A positron-emitting radiopharmaceutical is injected intravenously, allowed to spread throughout the body, and then scanned to identify and measure patterns of radiopharmaceutical accumulation throughout the body. Data from a PET scan may be rebuilt and shown as a three-dimensional picture, much like with SPECT imaging. Scintigraphy, in contrast, only produces planar data that may be utilised to produce a two-dimensional image.

**Principle**

A radiolabelled biological compound such as F-18 fluorodeoxyglucose (FDG) is injected intravenously. Uptake of this compound followed by further breakdown occurs in the cells. Tumor cells have a high metabolic rate, and hence this compound is also metabolized by tumor cells. FDG is metabolized to FDG-6-phosphate which cannot be further metabolized by tumor cells, and hence it accumulates and concentrates in tumor cells. This accumulation is detected and quantified.

**Radiopharmaceutical detection**

The positron-emitting isotope given to the patient experiences + decay in the body, where a proton is changed into a neutron, a positron (also known as a positron particle), and a neutrino. After a brief journey, the positron collides with an electron to form an annihilation. Two high energy photons that are travelling in completely opposite directions are produced by the annihilation process. The energy of each photon is 511 keV. These two photons are detected by two detectors facing each other at opposite ends, and the radioactivity is localised somewhere along the line between the two detectors. The line of reaction is what we refer to as here.

**Uses**

* oncologic
* detection, staging, response to treatment
* differentiation between radiation necrosis and recurrence
* neurologic
* early diagnosis of Alzheimer disease
* localization of seizure focus in interictal phase
* localizing eloquent areas (e.g. speech, motor function)
* cardiac
* identification of hibernating myocardium
* infection/inflammation
* pyrexia of unknown origin (PUO)
* vasculitisoor spatial resolution.
1. **Limitations and challenges**
* High operating costs

As much as it is effective, it is expensive! Equipment cost, purchase cost, setting up cost, operations and maintaining, everything come with heavy expenditure. It is one of the biggest advantages of nuclear medicine.

* Health risks

Nuclear medicine sadly causes several major health problems when exposure is high or sustained. These processes and tools emit dangerous radiation, which is particularly dangerous for pregnant patients and older individuals. Some examples have also shown irreversible negative consequences.

* No guaranteed assurance

Nuclear medicine can't always guarantee a patient will recover despite its accuracy and established benefits. Still, there remains uncertainty. In the world of medicine, there are also a lot of predictions, chances, and failures.

* Shortage of Trained Nuclear Medicine Scientists

All fields of nuclear medicine are severely lacking in clinical and research staff. Due to a lack of university faculty in nuclear chemistry and radiochemistry, the training of radiopharmaceutical chemists in particular has not kept up with current needs at universities, medical facilities, and industry. There is a critical need for more training programmes, more doctorate students, and post-doctoral fellowship opportunities with the necessary infrastructure to facilitate multidisciplinary work.

* Inadequate Domestic Supply of Medical Radionuclides for Research

The majority of the medicinal radionuclides utilised in routine nuclear medicine procedures have no domestic sources. The creation and assessment of novel radiopharmaceuticals is hampered by the absence of a dedicated home accelerator and reactor facility for year-round uninterrupted production of medicinal radionuclides for research.

* Cumbersome Regulatory Requirements

The research points out regulatory limitations that obstruct the speedy introduction of innovative radiopharmaceuticals into clinical feasibility studies. Nuclear medicine research cannot easily be used in practise because to the complexity of U.S. Food and Drug Administration (FDA) toxicologic and other regulatory criteria, as well as the absence of standards for the production of nuclear imaging devices and radiopharmaceuticals. Additionally, it is difficult to harmonise methods for multi-institutional clinical studies since there is no widespread agreement on standardised image capture in nuclear medicine imaging processes.

* Need for Technology Development and Transfer

For nuclear medicine to advance, technical advancements from the lab must be applied in the clinic. For effective translation into the clinic, research should be conducted in areas such as detector technology, image reconstruction methods, better data processing techniques, and the development of reduced cost radionuclide manufacturing technologies.

**Conclusion**

In the near future, the discipline of nuclear medicine will undoubtedly become more important for diagnostic and therapeutic purposes. It is anticipated to display an ever-increasing relevance and usefulness in the fields of medication development and drug delivery systems research as well. By (1) offering more effective and affordable methods for bringing new medications to market, (2) creating new and more efficient treatments for cancer and cardiovascular disease, (3) enhancing our comprehension of abnormal physiological conditions, and (4) creating new, powerful anticancer drugs, further advancements in the field are likely to significantly advance the development of personalised medicine. During the development and regulatory phases of the research and marketing authorization process, more thorough and efficient in vivo studies will be required due to the introduction of new and more complicated medications as well as more inventive and technical delivery methods. In addition, recent advances in accelerator engineering, computer science, materials science, chemistry, and nanotechnology promise that a new generation of radiopharmaceuticals and nuclear medicine devices will soon be produced that will be more affordable, accessible, and accurate. Despite the difficulties that lie ahead, if we invest in the infrastructure for radionuclide production, dedicate ourselves to training and supporting the upcoming generation of nuclear medicine researchers, technicians, and clinicians, and create a programme that will support nuclear medicine research, we will all benefit from better nuclear medicine.

**References**:

1. W.J. MEREDITH., J.B. MASSEY., THE EFFECTS OF X-RAYS, Fundamental Physics of Radiology (Third Edition), 1977.
2. Johannes Czernin, Ida Sonni, Aria Razmaria and Jeremie Calais, The Future of Nuclear Medicine as an Independent Specialty, Journal of Nuclear Medicine September 2019, 60 (Supplement 2) 3S-12S; DOI: <https://doi.org/10.2967/jnumed.118.220558>.
3. Turner JH. Recent advances in theranostics and challenges for the future. Br J Radiol. 2018 Nov;91(1091):20170893. doi: 10.1259/bjr.20170893. Epub 2018 Mar 29. PMID: 29565650; PMCID: PMC6475948.
4. Capobianco E, Deng J. Radiomics at a Glance: A Few Lessons Learned from Learning Approaches. Cancers (Basel); 2020.
5. Guiot J, Vaidyanathan A, Deprez L, et al,. A review in radiomics: Making personalized medicine a reality via routine imaging. Med. Res. Rev; 2021.
6. Kocak B, Durmaz ES, Ates E, Kilickesmez O. Radiomics with artificial intelligence: a practical guide for beginners. Diagn Interv. Radiol. 25(6):485-95; 2019.
7. Nensa, F., Demircioglu, A., and Rischpler, C., Artificial Intelligence in Nuclear Medicine, J Nucl Med 2019; 60:29S–37S
8. Hatt M, Le Rest CC, Antonorsi N, Tixier F, Tankyevych O, Jaouen V, et al. Radiomics in PET/CT: Current Status and Future Ai-Based Evolutions. In: Seminars in Nuclear Medicine. WB Saunders Seminars in Nuclear Medicine (2020). doi: 10.1053/j.semnuclmed.2020.09.002
9. JOSEPH G. HAMILTON, The Use of Radioactive Tracers in Biology and Medicine, RADIOLOGY, Vol. 39, No. 3, Pages 541-572, November, 1942.
10. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses. 2nd edition. Geneva: World Health Organization; 2013. ANNEX 2, Drug dosages and regimens. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK154444/>
11. National Research Council (US) Committee on Medical Isotope Production Without Highly Enriched Uranium. Medical Isotope Production without Highly Enriched Uranium. Washington (DC): National Academies Press (US); 2009. 2, Molybdenum-99/Technetium-99m Production and Use. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK215133/>
12. <http://www-naweb.iaea.org/na/news-na/na-gc-medical-isotopes.html>
13. Wang Y, Chen D, Augusto RDS, Liang J, Qin Z, Liu J, Liu Z. Production Review of Accelerator-Based Medical Isotopes. Molecules. 2022 Aug 19;27(16):5294. doi: 10.3390/molecules27165294. PMID: 36014532; PMCID: PMC9415084.
14. Mansi L, Moncayo R, Cuccurullo V, Dottorini ME, Rambaldi PF. Nuclear medicine in diagnosis, staging and follow-up of thyroid cancer. Q J Nucl Med Mol Imaging. 2004 Jun;48(2):82-95. PMID: 15243406.
15. Mariani G, Tonacchera M, Grosso M, Orsolini F, Vitti P, Strauss HW. The Role of Nuclear Medicine in the Clinical Management of Benign Thyroid Disorders, Part 1: Hyperthyroidism. J Nucl Med. 2021 Mar;62(3):304-312. doi: 10.2967/jnumed.120.243170. Epub 2020 Oct 2. PMID: 33008929.
16. Bischof Delaloye A. The role of nuclear medicine in the treatment of non-Hodgkin's lymphoma (NHL). Leuk Lymphoma. 2003;44 Suppl 4:S29-36. doi: 10.1080/10428140310001616935. PMID: 15154740.