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Review Article

Nuclear Medicine, Molecular Imaging, and Radiopharmaceuticals: Benefits in Diagnosis, Treatment Outcomes, and Public Health

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Abstract

Although the term "nuclear medicine" sounds contemporary, its exact history and study of uses date to the late 19th century. Nuclear medicine is a noninvasive, multi-disciplinary technique involving radiopharmaceuticals and instrumentation to examine physiological functions and diagnose, stage, and treat diseases. The World Health Organization designates nuclear medicine as a medical specialty that employs radioactive materials to diagnose or treat a patient's condition. Nuclear medicine is also used in medical research. The application of nuclear medicine is typically conducted as an outpatient procedure for assessing or treating functional disorders.

Nuclear medicine comprises molecular imaging, such as molecular magnetic resonance spectroscopy, magnetic resonance imaging, targeted ultrasound, optical bioluminescence, optical fluorescence, positron emission tomography, and single-photon emission computerized tomography.

Radiopharmaceuticals are radioactive agents used in therapeutic and diagnostic procedures—and are organized into four categories: radiopharmaceutical preparations (a ready-to-use formulation suitable for human consumption), radionuclide generator ("offspring" radionuclide separated from the parent radionuclide in developing radiopharmaceutical preparations), radiopharmaceutical precursor (a radionuclide designed for radio-labeling procedures using a radiopharmaceutical preparation), and a radiopharmaceutical preparation kit (a multidose vial that may need further processing, such as heating, boiling, filtering, and buffering to create a radiopharmaceutical preparation, and must be used within 12h). Nuclear medicine techniques include PET, PET-CT, SPECT, micro-PET, and micro-CAT.

Nearly 10,000 hospitals worldwide use radionuclides (about 90% of their use is for diagnostic purposes). The most frequently used radionucleotide in diagnostics is ^{99m}Tc, comprising about 40 million examinations per year and accounting for 80% of all examinations in nuclear medicine worldwide.

The application of nuclear medicine has upgraded patient care and medical research in numerous ways. Nuclear imaging allows physicians to cost-effectively obtain medical data that would be otherwise unobtainable or need more invasive and costly procedures. Nuclear medicine in telediagnosis is currently well-regarded concerning the digitization of images, image compression, the transmission of images, and data interpretation. Teleradiology systems are widely accepted in clinical practice.

Nuclear medicine plays an essential role in specific medical specialties, including oncology, cardiology, neurology, and psychiatry. Training for nuclear medicine includes a radiation medicine diploma program, a 1-year diploma course in medical physics and techniques, a diplomate program in medical radioisotope techniques; more expanded specialty programs are being developed and introduced. Nuclear medicine and radiopharmaceutical procedures are vital to medicine and specific medical procedures.

Keywords: *Nuclear Medicine (NM); Molecular Imaging (MI); Radiopharmaceuticals (Rphs)*

Abbreviations

2-DG: 2-deoxy-D-glucose; 18F-FEAU: 18F-fluoro-5-ethyl-1beta-D-arabinofuranosyluracil; 32P: phosphorus-32; 89Sr: strontium-89; 99mTc: technetium-99m; AMP: antimicrobial peptide; CMS: Center for Medicare and Medicaid Services; COPD: chronic obstructive pulmonary disease; DMRIT: Diploma in Medical Radioisotope Techniques; DNB: Diploma of the National Board; DRM: Diploma in Radiation Medicine; FDA: US Food and Drug Administraiton; GEP-NET: gastroenteropancreatic neuroendocrine tumor; HN: head and neck; IPEN: Nuclear and Energy Research Institute; MD: medical doctor; MI: molecular imaging; MRI: magnetic resonance imaging; MMP: matrix metalloprotease; MRS: magnetic resonance spectroscopy; NM: nuclear medicine; NSCLC: non-small cell lung cancer; OI: optical imaging; PET: positron emission tomography; Rph: radiopharmaceutical; SPECT: single photon-emission computed tomography; UBI: ubiquitin; US: ultrasound imaging; WHO: World Health Organization

Introduction

Nuclear medicine (NM) is a noninvasive, multi-disciplinary technique involving the use of radiopharmaceuticals (Rphs) and instrumentation to explore physiological functions and diagnose, stage, and treat diseases. Once inhaled or injected, the Rphs accumulate in the organ or tissue of interest [1].

History and development

The history of discrete fields encompassing radiation sciences is interrelated. The discovery and use of x-rays and gamma-rays in diagnosis and treatment has had a profound influence on medicine. In 1896, French scientist Henri Becquerel discovered radioactivity when most attention was focused on x-rays and cathode tube rays. Becquerel observed that a photographic material was exposed (fogged) when placed near uranium [1].

Observations in radioactivity were less frequent than those for the x-ray. Roentgen's findings provided anecdotal evidence of other researchers; it was intuitive and immediately adopted. Becquerel**,** however, could not generate the same enthusiasm for his discovery. In 1898, the discovery of radium by Marie Curie and her husband Pierre spawned an interest in radioactivity worldwide. In industrial radiography, x-rays were promptly replaced by radium. Rutherford discovered alpha and beta particles in 1899, and Villard discovered gamma rays in 1900. In 1903, Alexander Graham Bell suggested the use of radioactive sources to treat tumors [1].

These findings were groundbreaking for NM, which involved the functional evaluation of biological and metabolic processes. In the 1920s, radioactive phosphorus was used to perform bone scans in animals to reveal metabolic processes [1].

Subsequently, phosphorus-32 (32P) was utilized to treat leukemia. 32P continues to be utilized as a general radionuclide for bone scans and treatment. In the late 1930s, radioactive iodine was applied to study the physiology of the thyroid, with its applications currently extending to imaging and therapy. In 1939, strontium-89 (89Sr) was introduced for clinical procedures and is now also used to palliate painful bone metastases.

Although beta emissions are therapeutically helpful, they are not appropriate for imaging. Thus, radionuclides with gamma emissions were adopted to advance NM. In 1939, NM witnessed a key breakthrough following the discovery of technetium-99m (^{99m}Tc) by Emilio Segre and Glenn Seaborg. In 1951, Cassen developed a rectilinear scanner [1].

Several key milestones in NM include the first annual meeting of the Society of Nuclear Medicine in 1954, the development of the scintillation camera in 1958, 99mTc's commercial availability in 1960, the emergence of emission tomography in 1962, and commercial availability of single photon-emission computed tomography (SPECT) cameras in 1976 [1]. The appearance of multiple detector cameras and

hybrid SPECT/CT devices, digital technology, reconstruction algorithms, and computer technology, combined with Rph developments, has improved NM's competencies while keeping the working principle constant since the late 1970s. The discovery of x-rays and radium diluted the stringency of radiation safety for both patients and health practitioners.

Misapplication of the x-ray is well described, but the mishandling of radium was more frequent in the early years. Radium was used in several products, such as tonics, toothpastes, cocktails, and contraceptives—for its supposed health benefits [2].

Discussion

Nuclear medicine definition

The World Health Organization (WHO) defines NM as a field that "incorporates all applications of radioactive materials in the diagnosis or treatment of the disease and medical research". Typically, NM is an outpatient-led process for assessing or treating functional disorders [3].

Molecular imaging

Molecular imaging (MI) is described as "the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems" [4]. MI comprises molecular magnetic resonance spectroscopy (MRS), magnetic resonance imaging (MRI), targeted ultrasound, optical bioluminescence, optical fluorescence, positron emission tomography (PET), and SPECT [5].

There is a need for problem-free knowledge transfer and molecular measurements among species to enable clinical translation. This fluid knowledge transfer can be realized by sustained progress and extensive accessibility to scanners dedicated to imaging studies in small animals, offering *in vivo* imaging abilities similar to humans in mice and primates [6,7].

Radiopharmaceuticals

Radiopharmaceuticals (Rphs) comprise radioactive agents used in therapeutic and diagnostic interventions. Although Rphs have a systemic route of administration, they accumulate in specific tissues due to their biomolecular properties. In a PET scan, this accumulation is indicated by hyperintensity areas, suggesting high tissue metabolic demand. Compounds emitting beta particles or gamma rays are used for diagnosis, whereas compounds emitting alpha particles are reserved for therapeutic interventions.

Radio imaging uses a considerably low concentration of radiotracers. This imaging technique is employed to analyze tissue physiology and disease, as well as monitor treatments. Radiation emitted from a radiotherapeutic agent's nuclide helps palliate or eradicate the target cells [8,9].

Rphs can be classified into four categories as follows:

- **Rph preparation:** Rph preparations are medicinal products in ready-to-use formulations suitable for human consumption. The inclusion of a radionuclide in the formulation is essential and must be appropriate for diagnostic or therapeutic applications.
- **Radionuclide generator:** In a radionuclide generator, a daughter radionuclide is separated from the parent radionuclide to develop an Rph preparation.
- **Rph precursor:** An Rph precursor is a radionuclide designed for radiolabeling procedures using an Rph preparation.

- **Kit for Rph preparation:** This kit is usually a multidose vial that may need further processing, such as heating, boiling, filtering, and buffering to create an Rph preparation, and must be used within 12h [10].

- **Radiopharmaceutical substances used in imaging, diagnosis, and treatment:** In NM, Rphs are applied in diagnostic imaging along with radiotherapy. They are well tolerated and help diagnose organ diseases and treat pathological conditions, such as cancer. Typically, Rphs are available as oral, intravenous, or inhalation formulations. They have specific radioactive tracers that localize to organs, such as the kidneys, thyroid, lungs, heart, bone, or blood. High-dose radiations are delivered to the cancerous lesion or hyperfunctioning thyroid through specific Rphs [11].

An Rph contains a radionuclide, which permits external scan, attached to a non-radioactive element, which acts as a carrier or ligand to direct the radionuclide to a specific organ [12].

NM cameras help detect radioactive particles. These cameras are specific for the type of radiation emitted by the radioactive particle. SPECT cameras perceive gamma-ray photons emitted by a radionuclide during decay. PET cameras sense a pair of gamma rays emitted following positron decay [13].

Nuclear medicine techniques

The NM techniques include PET, PET-CT, SPECT, micro-PET, and micro computerized axial tomography (micro-CAT). These techniques are practiced in the early disease stage to assess biochemical dysfunctions, mechanisms, and association with various conditions, such as cancers, cardiovascular diseases, and cognitive disorders [14,15].

ASPECT examination envisages blood flow through veins and arteries and allows a pre-surgical assessment of seizures. It also helps in the diagnosis of brain ischemia, spondylolysis, and tumors [13].

A PET imaging senses a pair of gamma rays generated by the interaction between a positron and an electron in the tissue. It perceives the electronic signal released by the scintillation crystals due to gamma rays [13].

Gamma cameras recognize radiations emitted by the radionucleotide ^{99m}Technetium, and PET imaging recognizes radiations emitted by ^{18}fluorine.

Although the PET and SPECT images have high sensitivity, they have a low spatial resolution. On the contrary, MRI and CT have low sensitivity and high spatial resolution. To overcome the limitations of the individual procedures, these imaging techniques are commonly combined, increasing sensitivity and obtaining higher-quality images [13].

X-ray CT is a three-dimensional imaging technique used to obtain high-resolution images with detailed information of the visceral structures [13].

Radiopharmaceuticals for diagnosis in the human body

Specific radiations destroy cancer cells. A radionuclide producing specific radiation can be localized to the desired organ to kill cancer cells. Techniques of using a radionuclide for diagnostics and treatment are similar. Often, beta radiation also destroys cancer cells. ^{90}Yttrium, which emits beta radiation, is used to treat cancers, particularly non-Hodgkin lymphoma and liver tumor. Other nuclides useful in radiotherapy are ^{131}cesium, ^{153}samarium, ^{32}phosphorus, ^{223}radium, ^{131}Iodine, and ^{103}palladium [16].

Radionuclides in medicine

Nearly 10,000 hospitals worldwide use radionuclides, and about 90% of their use is for diagnostic purposes. The most frequently used radionucleotide in diagnostics is ^{99m}Tc, with about 40 million examinations per year, accounting for 80% of all examinations in NM worldwide [16].

In the United States and Europe, more than 20 and 10 million medical procedures are performed annually, respectively. The Nuclear and Energy Research Institute (IPEN) of Brazil reported 360 diagnostic clinics and NM hospitals and 72 PET installations in 2017. Further, in 2017, of the 70% of institutions in Brazil's South and Southeast regions with a license to practice, 33 hospitals had specialized rooms for this therapy [16].

NM value matrix

NM-RPh delivers "unique value" in metastatic thyroid cancer treatment by radio-iodine. It offers significant value addition in myocardial imaging. The rapidly developing NM-RPh for neurology is expected to gain entry to the "significant value addition" list soon. Additionally, it adds value to renal studies.

Judicious use of the NM-RPh combination ensures enhanced patient management by utilizing already known benefits in several areas and developing the opportunity for further research. The NM value matrix of utility grading versus patient volume can be drawn by including all established and emerging indications for an NM procedure, along with the corresponding RPh product in use. These data could be updated intermittently. Moreover, professional societies related to NM perform advisory roles and responsibilities.

A consensus-based NM value matrix obtained by the method mentioned above will represent to investors and medical policy-makers, unambiguously, the advantages and limitations of NM-RPh options for serving deserving patients. The NM value matrix has been captured by *The Indian Journal of NM* (*IJNM*) publication as an Annex. In the future, it is necessary to occupy unique value and significant value addition columns in the NM value matrix with widely available and maintainable RPh products. It is crucial to persuade the referral sources and practitioners to study NM-RPh as the first line of procedure in as many areas as appropriate (unique value list indications) and a definitive and significant value process [17].

Radiopharmaceuticals in imaging systems

SPECT

Unlike PET, SPECT immediately detects gamma-ray photons emitted by a radionuclide during decay and is economical and extensively used in the clinical setting [18]. However, the spatial resolution of small-animal SPECT (micro-SPECT) is higher than PET due to advances in imaging tools. Micro-SPECT is more useful in preclinical evaluations in animal studies and transformation research, such as neurology, cardiovascular disease, oncology, and drug development [19].

X-Ray-CT imaging

High-resolution small-animal CT (micro-CT) has modernized CT imaging from organ or tissue to the molecular level, and plays a central role in preclinical research. The advantages of CT include high spatial resolution, relative simplicity, rapid acquisition time, excellent hard-tissue imaging, and availability. Due to restrictions, such as limited soft-tissue resolution, ionizing radiation, and poor sensitivity, CT is usually combined with other imaging techniques, such as SPECT and PET, to obtain anatomical parameters for physiological and biochemical analyses [20].

The advancement of CT contrast agents has renewed confidence in CT molecular imaging. For example, Hyafil., *et al*. (2007) reported cellular imaging of macrophages in the rat model of atherosclerotic plaques through CT with iodinated nanoparticles [21].

Pan., *et al*. (2009) reported that contrast agents of polymeric nanoparticles consisted of radiopaque organically soluble elements or organometallics that can further improve CT imaging sensitivity [22].

Li., *et al*. (2010) conjugated 2-deoxy-D-glucose (2-DG) to a gold nanoparticle to prepare a CT molecular imaging agent (AuNP-2-DG) that could be used for CT imaging to obtain high-resolution anatomic structure and metabolic information of the tumor. *In vitro* experiments revealed that AuNP-2-DG could be employed as a functional CT contrast agent [23].

Multimodality imaging

Multimodality imaging can offer synergistic advantages compared to a single modality. It recompenses for individual imaging system limitations while taking advantage of their strengths. This modality has become the recent developmental trend in modern medicine [24]. Multimodality imaging (PET/SPECT, PET/CT, and PET/MRI) are used to obtain adequate anatomical and molecular information for clinical diagnosis.

Abgral., *et al*. (2018) evaluated 18F-FDG PET/CT's diagnostic capabilities in 91 patients with head and neck (HN) cancer who had been cured without clinical evidence of recurrence [25]. The sensitivity, specificity, and accuracy of 18F-FDG PET/CT for diagnosing recurrence were 100%, 85%, and 90%, respectively. The positive and negative predictive values were 77% and 100%, respectively.

MRI has apparent advantages over CT, such as excellent soft-tissue contrast, high spatial resolution, and absence of ionizing radiation.

Lee., *et al*. (2012) used PET/MRI to assess the presence of monocytes in the non-ischemic remote zone after myocardial infarction. They revealed that inflammatory cells in infarct and distant non-infarct areas could be detected by PET/MRI imaging. Currently, PET/MRI is also being adopted in clinics [26].

Kjær., *et al*. (2012) conducted a PET/MRI examination on a female patient with cervical cancer for restaging following radiotherapy and compared the results with PET/CT [27]. They found that PET/MRI was better than PET/CT imaging regarding the precise definition of the primary tumor. However, PET and MRI in a single gantry devoted to simultaneous PET/MRI are theoretically risky. Other multimodality imaging techniques that have been reported are optical imaging (OI)/ultrasound imaging (US), OI/CT, OI/MRI, and US/MRI. OI is a versatile technique in preclinical research.

Cost-effectiveness

There has been continuous pressure on NM physicians to keep the cost of NM procedures low and to generate productive results for the money spent. A procedure is considered cost-effective when its benefits are of value to the applied additional costs (money and radiation dose). The paybacks of diagnostic procedures are assessed by the test performance, which depends on a specific task. Outcome efficacy (efficacy O) is an amount of the success attained through therapeutic procedures. Costs related to NM procedures comprise money, discomfort, time, possible drug reactions, and hypothetical risk associated with cancer and radiation dose. The public's insight of these concluding risks, or costs, is high. Decision trees are helpful to determine viable strategies, benefits, costs, and outcomes, estimating the cost-effectiveness of each strategy [28].

The use of NM has upgraded patient care in numerous ways. Nuclear imaging permits physicians to cost-effectively obtain medical data that would be unobtainable or need more invasive procedures. For instance, FDG-PET imaging has been evaluated to save almost US $400,000 for 100 patients when compared to surgery to evaluate the presence of malignancy in indeterminate lung lesions as observed on CT [29].

Cost savings in cancer patient management

An extensively accepted application of MI is PET/CT for preoperative staging of non-small cell lung cancer (NSCLC) and solitary pulmonary nodules. Clinical trials and cost-effectiveness analyses together have demonstrated that PET/CT provides accurate preoperative staging of lung cancer [30], resulting in a decrease in unnecessary surgeries and treatment costs [31]. For example, cost-effectiveness analyses performed together with a randomized clinical trial demonstrated that preoperative staging with PET/CT decreased the number of futile thoracotomies by nearly 20% for patients with suspected NSCLC, saving approximately EUR 19,314 per failed thoracotomy that was ducked and improving patients' quality of life [32]. Additionally, PET and PET/CT use for diagnosing solitary pulmonary nodules clinched was reported to be economical, especially for patients with a low or high probability of malignancy, with each additional quality-adjusted life-year costing only USD 20,000 or 16,000, respectively [33].

Nuclear medicine in telediagnosis

Tele-NM is currently well received. Techniques have been advanced to acquire and digitize images, image compression, transmission, and interpretation. Teleradiology systems are widely accepted in clinical practice. Applications comprise offering services from large to small institutions, focusing on outpatient clinics, imaging centers, and nursing homes. Teleradiology has also gained entry into international applications. Several states and medical boards have established regulations and policies to prevent non-licensed physicians in the respective state from delivering telemedicine services. National and international communication networks are being built to enable information and knowledge dissemination remotely [34].

Indications

Table 1 (below) details some of the US Food and Drug Administration (FDA)-approved Rphs and their indications [35].

Radiopharmaceutical	Indications
Carbon-11 choline	PET imaging of patients with suspected prostate cancer recurrence. CT or MRI may also be used to recognize the possible sites of prostate cancer recurrence following histologic validation.
Carbon-14 urea	Diagnosis of *Helicobacter pylori* infection in the stomach.
Fluorine-18 florbetaben.	PET imaging of the brain to determine cognitive decline in Alzheimer's disease.
Fluorine-18 flortaucipir	PET imaging for Alzheimer's disease.
Fluorine-18 flucicovine	PET imaging in men with suspected prostate cancer recurrence.
Fluorine-18 sodium fluoride	PET bone imaging in osteogenesis.
Fluorine-18 fludeoxyglucose	PET imaging to evaluate irregular glucose metabolism in oncological conditions, determine myocardial hibernation, and categorize areas of abnormal glucose metabolism linked with foci of epileptic seizures.
Fluorine-18 fluoroestradiol	PET imaging patients with recurrent or metastatic breast cancer.
Fluorine-18 flutemetamol	PET imaging of the brain to determine cognitive decline in Alzheimer's disease or other cognitive conditions.
Gallium-67 citrate	Diagnosis of Hodgkin disease, lymphoma, and bronchogenic carcinoma.
Gallium-68 dotatate	PET imaging for neuroendocrine tumors (NETs).
Indium-111 chloride	Radiolabeling.
Indium-111 oxyquinoline	Radiolabeling autologous leukocytes.
Indium-111 pentetreotide	Scintigraphic localization of primary and metastatic neuroendocrine tumors possessing somatostatin receptors.
Iodine I-123 iobenguane	Detection of primary or metastatic neuroblastoma or pheochromocytoma.
Iodine I-123 sodium iodide capsules	Evaluating thyroid function and morphology.
Iodine I-125 human serum albumin	Determining plasma volume and total blood.
Iodine I-125 iothalamate	Evaluation of glomerular filtration.
Iodine I-131 human serum albumin	Determining cerebral neoplasms, cardiac output, localization of the placenta, protein turnover, total blood or plasma volumes, heart or great vessel delineation, cardiac or pulmonary blood volumes, and circulation times.
Iodine I-131 sodium iodide	Diagnostic: performance of the radioactive iodide and localizing metastases associated with thyroid malignancies. Therapeutic: Treatment of thyroid carcinoma and hyperthyroidism.
Lutetium Lu-177 Donate	Treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Molybdenum Mo-99 generator	Rph preparation is indicated in vesicoureteral imaging, salivary gland imaging, thyroid imaging, and nasolacrimal drainage system imaging.
Nitrogen-13 ammonia	Diagnostic PET imaging of the myocardium under rest or pharmacologic stress conditions.
Radium-223 dichloride	Treatment of castration-resistant prostate cancer, symptomatic bone metastases, and unknown visceral metastatic disease.
Rubidium-82 chloride	PET imaging for myocardial perfusion.
Samarium-153 lexidronam	Pain relief in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan.
Strontium-89 chloride	Pain relief in patients with painful skeletal metastases.
Technetium-99m mebrofenin	Hepatobiliary imaging.
Technetium-99m medronate	Bone imaging to delineate areas of altered osteogenesis.
Technetium-99m mertiatide	To develop renogram curves for the whole kidney and renal cortex, split function, renal failure, urinary tract obstruction and calculi, and congenital and acquired abnormalities.
Technetium-99m oxidronate	Bone imaging to delineate areas of altered osteogenesis.
Technetium-99m pentetate	Imaging of the kidneys and lungs.
Yttrium-90 chloride	Radiolabeling.

Table 1 : *FDA-approved radiopharmaceuticals and their indications.*

Conditions treated by nuclear medicine and radiopharmaceuticals

Conditions effectively treated with NM comprise neural crest tumors, neuroendocrine tumors, and non-Hodgkin lymphoma. NM also offers effective palliation of bone metastasis pain.

Rphs are the foundation of NM, allowing for a progressively specific yet sensitive description of clinical pathophysiology. High-technology nuclear imaging, along with therapy, is an asset in healthcare. It decreases the pain of examination by presenting from the outside what is inside. It measures how the inside works from the outside. It permits objective outcome analysis. It symbolizes the pathological condition of the tissue and, at the same time, depends on quality assurance at all levels for software and hardware [36].

Contraindications

NM is contraindicated in pregnancy and allergic reactions [37].

Nuclear medicine in specific conditions

- Investigations to demonstrate specific diagnosis, such as thyroid disease.
- Investigations to eliminate specific diagnosis, such as renography.
- Follow-up investigations, such as myocardial perfusion imaging after angioplasty or coronary bypass surgery [36].

Medical specialties utilizing nuclear medicine

According to the Center for Medicare and Medicaid Services (CMS) data, NM plays a vital role in medical specialties, including oncology, cardiology, neurology, and psychiatry, accounting for about US $1.7 billion. Per the Society of NM, nearly 20 million NM procedures are accomplished annually in the United States alone, of which 12 million are procedures approved for and reimbursed through the CMS.

Further, the use of PET is progressing rapidly compared to other imaging modalities. Between 2000 and 2005, the estimated average annual growth rate in PET and PET/CT procedures was 80% compared to 9% for non-PET NM procedures, 11% for CT, and 13% for MRI. The use of NM procedures is expected to increase considerably in the future [36,38].

Evidence-based research in NM

Antimicrobial peptides (AMPs) labeled with PET radiotracers or SPECT are advancing considerably. The use of ^{99m}Tc-ubiquitin (UBI) has been assessed in animal and human studies [39,40]. The new probe ^{99m}Tc-fluconazole has been projected to recognize fungal infections. SPECT/CT scintigraphy and ^{99m}Tc-ethambutol planar have high specificity and sensitivity and are valuable in detecting pulmonary and extrapulmonary diseases, especially tuberculosis [41].

Viral infections can be detected using new Rphs, such as ^{18}F-fluoro-5-ethyl-1beta-D-arabinofuranosyluracil (^{18}F-FEAU), in PET/CT studies. The ^{18}F-FEAU identifies an enzyme generated by the herpes simplex virus [42]. Several new PET Rphs for infection imaging have been verified in preclinical trials, potentially translating to humans [43].

Multiple molecular probes, such as fibroblast targeting somatostatin receptor agents (111In-octreotide), and several PET agents, such as 64Cu- and 68Ga labeled, have been developed for diagnosing fibrosis [44,45].

Existing techniques can sense established fibrosis, but there is a need to develop tools to detect early disease and monitor progression. For example, an ongoing clinical trial assesses the capability of the 68Ga-CBP8 probe to perceive type I collagen deposition in radiation-induced fibrosis and early IPF [46,47].

Molecular imaging techniques in ischemia-reperfusion injury are being considered principally for assessing primary graft dysfunction in lung transplants. Dimastromatteo., *et al*. in a murine model, have described positive results using ^{99m}Tc-cFLFLF SPECT imaging [48].

Matrix metalloproteases (MMPs) secreted by inflammatory cells have been examined in asthma and chronic obstructive pulmonary disease (COPD). PET and SPECT tracers have been established with an objective for early detection and monitoring of the disease activity [49].

Training for nuclear medicine

Training in NM is a mandatory requirement for specialist doctors, nurses, technologists, technicians, and physicists. The International Atomic Energy Agency (IAEA) has a hoary custom of conducting regional training programs and additional training classes for individuals staying abroad to ensure NM's safe practice in its customer countries. Training programs respective to different job categories in NM include Diploma in Radiation Medicine (DRM), Diploma of the National Board (DNB), and Doctor of Medicine (MD) degrees in NM for physicians and a 1-year diploma course in medical physics or techniques (Diploma in Medical Radioisotope Techniques [DMRIT]) for NM technologists.

Successful trainees are awarded a final certificate (degree or diploma), recognized by the local health authority, hospital, and government, to represent the specialist aptitude in NM [36].

The future of nuclear medicine in healthcare

The therapeutic use of NM is rapidly advancing and is considered an alternative for cancer treatment. In addition to its traditional applications in rheumatology and endocrinology, therapeutic radionuclides have now expanded focus to tumor-targeting therapy. In the therapy, radionuclides are localized in the tumor site using the appropriate route of administration and mechanism of action of the drug. The therapy is an excellent alternative for managing benign and malignant lesions due to its non-invasiveness and lower toxicity than con-

ventional chemotherapy and external beam radiotherapy. However, limitations include inadequate therapeutic efficacy in solid tumors than hematological tumors, low target-to-non-target rate, and absence of radionuclide generators. The therapeutic efficacy of NM can be improved following advancements in administration and grouping of multiple treatment modalities.

Conclusion

Nuclear medicine incorporates molecular imaging, such as molecular magnetic resonance spectroscopy, magnetic resonance imaging, targeted ultrasound, optical bioluminescence, optical fluorescence, positron emission tomography, and single-photon emission computerized tomography.

Approximately 10,000 hospitals globally use radionuclides (about 90% of their use for diagnostic purposes). The most often used radionucleotide in diagnostics is ^{99m}Tc, involving about 40 million examinations per year and accounting for 80% of all nuclear medicine studies worldwide.

Nuclear medicine plays an indispensable role in specific medical specialties, including oncology, cardiology, neurology, and psychiatry. Education for nuclear medicine includes a radiation medicine diploma program, a 1-year diploma curriculum in medical physics or techniques, a diplomate program in medical radioisotope techniques—and more specialty programs being advanced and proposed. Nuclear medicine and radiopharmaceutical procedures are necessary and indispensable medical procedures.

Radiopharmaceuticals are radioactive agents used in therapeutic and diagnostic procedures—and are arranged into four categories: radiopharmaceutical preparations (a ready-to-use formulation suitable for human consumption), radionuclide generator ("offspring" radionuclide separated from the parent radionuclide in developing radiopharmaceutical preparations), radiopharmaceutical precursor (a radionuclide designed for radio-labeling procedures using a radiopharmaceutical preparation), and a radiopharmaceutical preparation kit (a multidose vial that may need further processing, such as heating, boiling, filtering, and buffering to create a radiopharmaceutical preparation, and must be used within 12h). Nuclear medicine techniques include PET, PET-CT, SPECT, micro-PET, and micro-CAT.

"Nuclear medicine" is a modern term; however, its original history and investigation of applications date to the late 19th century. Nuclear medicine is a noninvasive, multi-disciplinary technique involving radiopharmaceuticals and instrumentation to investigate physiological functions and diagnose, stage, and treat disorders. The World Health Organization describes nuclear medicine as a medical specialty that applies radioactive materials to diagnose or treat patients' medical conditions. Nuclear medicine is also utilized in medical research. Nuclear medicine procedures are typically performed on an outpatient basis for evaluating or managing functional disorders.

The utilization of nuclear medicine has enhanced patient care and medical research. Nuclear imaging enables physicians to cost-effectively collect medical data that would be otherwise unavailable or require more invasive and expensive procedures. Currently, nuclear medicine in telediagnosis is well-regarded in digitizing images, image compression, the transmission of images, and data interpretation. Teleradiology systems are widely trusted in clinical practice.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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