APPLICATIONS OF RADIOISOTOPES IN MEDICINE

TAPAS DAS*

'Nuclear medicine' is the medical specialty, which utilizes the nuclear properties of radioactive substances in diagnosis, therapy and research to evaluate metabolic, physiologic and pathologic conditions of human body. As an integral part of patient care, nuclear medicine is presently used in the diagnosis, treatment and prevention of many serious ailments. Now-a-days, nuclear medicine offers procedures that are immensely helpful to a broad spectrum of medical sciences ranging from oncology to cardiology to psychiatry. Today physicians are equipped with a wide variety of nuclear imaging procedures and these uniquely provide information about the function of virtually every major organ/tissue of the human body. Nuclear medicine imaging procedures often identify abnormalities at the very early stage of the progression of the disease, long before it could be detected by other alternative diagnostic modalities and this allows the disease to be treated early in its course. However, the actual strength of nuclear medicine lies in its ability to monitor both anatomical and physiological functions *in-vivo*, which is not possible by the other contemporary imaging modalities, such as, computed tomography (CT) scanning, nuclear magnetic resonance imaging (MRI) and ultrasound imaging[1]. Though, these imaging modalities are able to delineate anatomical features with a much superior resolution, they provide only limited information on the physiological functions[1]. Although the field of nuclear medicine is dominated by the diagnostic procedures, it also has valuable therapeutic applications, which include treatment of hyperthyroidism, rheumatoid arthritis, Hodgkin's disease and a wide range of cancers, like cancers in breast, ovary, prostate, liver, colon, lung and endocrine glands. Nuclear medicine has also been extensively used to treat various heart ailments, leukemia and for providing pain relief to the patients suffering from metastatic bone cancer. Nuclear medicine has always been perhaps the most exciting area of investigation in medicine[2]. Today, it is considered as one of the important diagnostic and therapeutic specialty in the armamentarium of medical sciences in spite of its modest beginning less than a century ago.

Nuclides having fixed number of protons but variable numbers of neutrons are known as isotopes. There are 2500 known isotopes; however, only 280 of them are stable. The rest of the nuclides are unstable. Radioisotopes are these unstable nuclides, which emit some kinds of energetic rays and/or particles in the process of becoming a more stable isotope. Although there are a few naturally occurring radioisotopes, including ^{40}K, ^{87}Rb, ^{113}Cd, ^{115}In, ^{124}Sn, ^{144}Nd and ^{147}Sm, there half-lives are generally so long or their abundances so low, or both; that they are unsatisfactory for nuclear medicine applications[3]. Hence, the radionuclides used in nuclear medicine are mostly artificial and produced either in a cyclotron or in a nuclear reactor. For the 20-25 years, which followed the 1939-1945 war, radionuclide production for biomedical applications was mostly centered on major nuclear reactor installations[4,5]. However, soon after, particle accelerators, mainly cyclotrons also started playing a crucial role for this purpose owing to the favorable characteristics of accelerator-produced neutron deficient radionuclides in these applications[6,7]. The type of radionuclides produced in a cyclotron or a nuclear reactor depend on many factors, such as, nature of the target materials used, nature of the bombarding particles, its energy etc. Apart from these, medically useful short-lived radionuclides can conveniently and readily be obtained at the desired site by using the radionuclide generator systems[8].

* Radiopharmaceuticals Chemistry Section, Radiochemistry and Isotope Group, Bhabha Atomic Research Centre, Trombay, Mumbai-400085, Email: tdas@barc.gov.in

Particle accelerators, mainly cyclotron is a major source for the production of neutron-deficient radionuclides, which decay either by electron capture or by positron emission. In a cyclotron, a high energy beam of accelerated particles are generated by circulating the charged particles, such as, protons, deuterons, α-particles, tritium and so forth under vacuum by means of an electromagnetic field and the targets of stable elements are bombarded with this particle beam. By varying the type of target and its position in the cyclotron, several types of conditions can be established which make the machine adaptable for production of a wide variety of radionuclides[9]. As radionuclides produced by cyclotron are not isotopic with the target material, post-irradiation chemical separation usually yields a high specific activity (activity per unit mass) product. Cyclotron produced radionuclides, such as, ^{67}Ga, ^{111}In, ^{123}I and ^{201}Tl decays by electron capture and used in diagnostic nuclear medicine while short-lived radioisotopes such as, ^{11}C, ^{13}N, ^{15}O and ^{18}F are useful in PET (positron emission tomography) imaging.

A large number of radionuclides used in nuclear medicine are also produced in nuclear reactors. Nuclear reactor is a device in which the nuclear fission chain reaction takes place, in a controlled manner, for the production of energy and neutrons. Most of the reactor produced radionuclides available for biomedical usages are produced either through the recovery of fission products or by neutron activation of the specific targets. In nuclear fission several radioisotopes and stable isotopes of different elements are produced and very elaborate and extensive processing facilities are required to ensure the production of a particular radioisotope with high radionuclidic purity. The most important advantage of this method is that, several medically useful radionuclides can be obtained with higher specific activity than that obtainable from corresponding neutron activation method. However, the need of highly sophisticated processing facilities with remote handling equipments and good infrastructure for highly active and long-lived waste disposal increases the cost of the radionuclide. In the neutron activation method, the target nucleus first absorbs a neutron and then emits either a gamma photon or a charged particle depending upon the energetics of the reaction. In some cases, multistage neutron capture process involving successive neutron capture also takes place, though this route is of limited utility owing to the production of radionuclide with very low specific activity. On the other hand, neutron capture followed by particle emission type reactions has the advantage of involving transmutations thereby providing radionuclides with very high specific activity. However, the most common route employed for the production of radionuclides used in radiopharmaceuticals is the (n,γ) reaction. The advantage of this method is its inherent simplicity and almost all the elements undergo this reaction, though with varying probabilities. However, specific activity of the radioisotopes obtained by this method is relatively low as the target and product are the isotopes of same element and hence, cannot be separated by any easy means. Many bio-medically important radionuclides, such as, ^{24}Na, ^{99}Mo, ^{153}Sm, ^{165}Dy, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{192}Ir and ^{198}Au are produced by using the (n,γ) reaction[10].

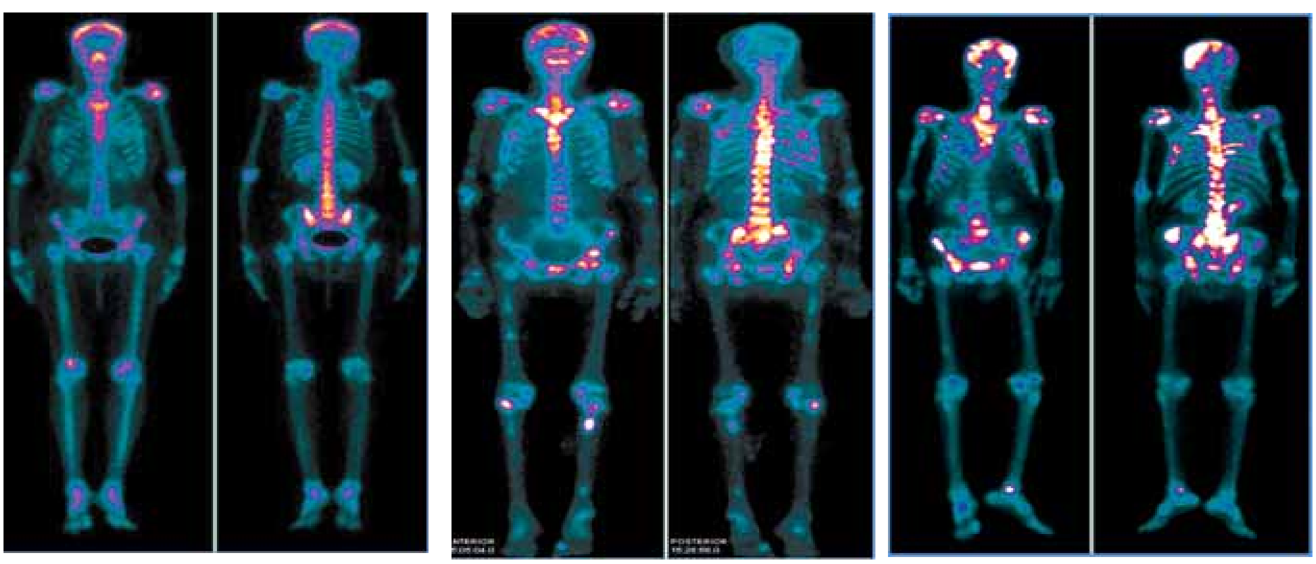
Use of radionuclide generator system is also a popular route for obtaining some of the short-lived radionuclides at the hospital radiopharmacies. Radionuclide generators may be defined as a device containing a longer-lived parent nuclide in equilibrium with its daughter nuclide from which the daughter nuclide with a shorter half-life can be obtained at regular intervals. The radionuclide generator is the most convenient method of making short-lived radionuclides available at long distances from the production site[8]. In a longer-lived parent - shorter-lived daughter chain, a fraction of the daughter atoms that undergo radioactive decay is replaced by new daughter atoms formed from the radioactive decay of the parent. The net result of this combination of continual growth and decay on the part of the daughter is that the activity of the daughter, while in the presence of the regenerating parent, decreases at a slower rate than in the absence of the parent. Therefore, the apparent half-life of the shorter-lived daughter is increased and in equilibrium mixture equals that of the parent. This provides more time for shipment, permits a longer shelf-life and results in a continuous source of the daughter radionoelide within the user's laboratory[8].

Applications of radioisotopes in human health care are extensively wide-spread and cover both the diagnostic and therapeutic domains. The diagnostic procedures could be performed either by *in-vivo* use of radiopharmaceuticals or by *in-vitro* use of radioimmunoassay. On the other hand, therapeutic procedures could be effected either by using the sealed sources or by the systematic administration of radiopharmaceuticals.

'Radiopharmaceuticals' are a special class of radiochemical formulations having high purity and safety for human administration and used for either diagnosis or therapy. Radiopharmaceuticals take the advantage of both the nuclear properties of the radionuclides and the pharmacological properties of the pharmaceuticals. Radiopharmaceuticals usually have no pharmacologic effect as in most of the cases they are injected in tracer quantities. They do not show any dose-response relationship and thus differ from conventional drugs. In majority of cases, a radiopharmaceutical has two components, namely, a radionuclide and ligating moiety, usually known as carrier molecule. The usefulness of a radiopharmaceutical is dictated by the characteristics of these two components[11]. The carrier molecule, which is often, although not always, is an organic moiety; governs the preferential localization of the radiopharmaceutical in the organ of interest or its participation in the physiologic function of a particular organ/tissue while the tagged radionuclide is responsible for bringing the imaging or therapeutic efficacy of the radiopharmaceuticals.

Diagnostic radiopharmaceuticals may be defined as radiolabeled molecules designed to produce images of the specific disease sites. Present day nuclear medicine physicians are equipped with more than one hundred nuclear medicine imaging procedures and these uniquely provide information about the function of virtually every major organ system of the human body. It is estimated that 30-50 million diagnostic nuclear medicine investigations are performed annually world-over. As the main objective of using a diagnostic radiopharmaceutical is to image the organ of interest or to know its physiologic function, the radioisotope must be a pure gamma emitter and hence, should decay by electron capture or isomeric transition without any internal conversion. ^{99m}Tc is the most commonly used diagnostic radionuclide as more than 70% of the nuclear medicine procedures are based on this radionuclide. The emission of suitable energy gamma photons (140 keV) with high abundance, optimum half-life (6 h), availability from a ^{99}Mo-^{99m}Tc generator and versatile chemistry of Tc has made ^{99m}Tc the 'Work-horse of Nuclear Medicine'[10]. In fact, nuclear medicine physicians are equipped to image any organ system of human body using the ^{99m}Tc-labeled radiopharmaceuticals. Apart from ^{99m}Tc, several other radionuclides such as, ^{123}I, ^{67}Ga, ^{111}In, ^{201}Tl find regular use in nuclear medicine imaging, which is termed as Single Photon Emission Computed Tomography (SPECT). Table-1 lists some of the commonly used diagnostic radiopharmaceuticals employed for SPECT studies along with their applications.

In a comparatively newly developed imaging modality, known as 'Positron Emission Tomography' (PET), radionuclides which emit positrons are used for imaging the organ of interest. The two 511 keV photons, which come out due to the annihilation of positron when it meets with an electron, are detected in coincidence in this modality to record the image[10]. PET is rapidly becoming a major diagnostic imaging modality in nuclear medicine owing to its ability to record images with much superior sensitivity and better resolution. Currently PET imaging is reported to contribute 10-15% of all imaging applications in nuclear medicine. As the radioisotopes used for this modality is usually short-lived, presence of a medical cyclotron is needed either in the hospital premises or nearby regions. In India, although the first medical cyclotron was established in 2002 at the 'Radiation Medicine Centre', Mumbai, the field saw a rapid growth since then. ^{18}F is the radionuclide of choice for most of the PET imaging and [^{18}F]-2-Fluoro-2-Deoxy-Glucose (^{18}F-FDG) has been termed as the 'Molecule of the Millennium' owing to its extensive applications in various medical fields such as, oncology, neurology, cardiology and psychiatry[12]. A list of some of the PET radiopharmaceuticals along with their applications is provided in Table-2.



(a) (b) (c)

Figure 1: Typical whole-body images recorded using ^{99m}Tc-MDP, a bone imaging agent. (a) Normal human, (b) breast cancer patient with multiple metastases and (c) prostate cancer patient with extensive metastases

Typical whole-body images of cancer patients having multiple metastases along with the images of a normal human being obtained with ^{99m}Tc-MDP (^{99m}Tc-labeled methylene diphosphonic acid), a commonly used agent for skeletal imaging, are shown in Figure 1 (a) to (c). The additional uptakes observable in the whole-body scans of breast and prostate cancer patients (Figure b and c) clearly indicate the extensive spreading (metastases) of the disease.

The development of SPECT-CT and PET-CT in the recent past has really brought a revolution in the field of diagnostic nuclear medicine. These hybrid imaging modalities, which provide the advantages of monitoring physiological functions along with very accurate anatomical visualization, has made a very significant impact in the management of cancer and various other ailments.

On the other hand, 'Radioimmunoassay' (RIA) is a versatile radioanalytical technique which is used to measure minute (nanomolar) quantities of an analyte of clinical interest in biological specimens. This Noble prize winning technology, where ^{125}I is used as the radiotracer, is very helpful in diagnosing diseases related to hormones. A variety of radiometric assay kits have now become indispensable in pathology laboratories and regularly used for measuring various types of hormones, tumor-specific antigens, viral antigens and tumor markers.

TABLE 1: Some of the commonly used diagnostic radiopharmaceuticals for SPECT studies along with their applications

Radiopharmaceuticals	**Applications**
^{99m}Tc-based Radiopharmaceuticals	
^{99m}Tc-L,L-ECD *(ECD: L,L-ethylenedicysteine diethyl ester)*	Brain imaging
^{99m}Tc-d,l-HMPAO *(HMPAO: Hexamethyl propylene amine oxime)*	Brain imaging
^{99m}Tc-Pertechnetate	Thyroid imaging
^{99m}Tc(V)-DMSA *(DMSA: Dimercapto succinic acid)*	Imaging of medullary carcinoma of thyroid
^{99m}Tc-SestaMIBI	Myocardial imaging
^{99m}Tc-Tetrofosmin	Myocardial imaging
^{99m}Tc-Mebrofenin	Hepatobiliary imaging
^{99m}Tc-HSA Microspheres *(HSA: Human serum albumin)*	Lung imaging
^{99m}Tc-Aerosol	Lung imaging
^{99m}Tc-MDP *(MDP: Methylene diphosphonic acid)*	Bone imaging
^{99m}Tc-Sulphur colloid	Reticuloendothelial system imaging
^{99m}Tc-EC *(EC: L,L-Ethylene dicysteine)*	Renal function imaging
^{99m}Tc-MAG_3 *(MAG_3: Mercapto acetyl triglycine)*	Renal function imaging
^{99m}Tc(III)-DTPA *(DTPA: Diethylenetriamine penta acetic acid)*	Renal function imaging
^{99m}Tc(III)-DMSA *(DMSA: Dimercapto succinic acid)*	Kidney imaging
^{99m}Tc(III)-GHA *(GHA: Gluocoheptanoic acid)*	Kidney imaging
^{99m}Tc-HYNIC-TOC *(HYNIC: Hydrazinonicotinamide)* *(HYNIC-TOC: HYNIC coupled-Tyr^3-Octreotide)*	Imaging of neuroendocrine cancers
^{99m}Tc-HYNIC-TATE *(HYNIC-TATE: HYNIC coupled-Tyr^3-Octreotate)*	Imaging of neuroendocrine cancers
Other than ^{99m}Tc-based Radiopharmaceuticals	
^{67}Ga-Citrate	Soft tissue tumor imaging
^{111}In-labeled peptides	Imaging of tumors
^{111}In-labeled monoclonal antibodies	Imaging of tumors
^{123}I-MIBG *(MIBG: meta-Iodobenzylguanidine)*	Myocardial imaging Imaging of neuroendocrine cancers
^{201}Tl-thallous chloride	Myocardial imaging
Radioactive noble gas ^{133}Xe	Lung imaging

TABLE 2: Some of the PET radiopharmaceuticals along with their applications

Radiopharmaceuticals	Applications
$[^{18}F]$FDG (2-fluoro-2-deoxyglucose)	Imaging of tumor based on glucose metabolism
$[^{18}F]$NaF (Sodium fluoride)	Bone imaging
$[^{18}F]$FMISO (Fluoromisonidazole)	Imaging of hypoxic tumors
$[^{18}F]$FDOPA	Monitoring Perkinson's disease
$[^{18}F]$FFAZA (Fluoroazomycinarabinose)	Imaging of hypoxic tumors
$[^{18}F]$FES (Fluoroestradiol)	Breast cancer imaging
^{68}Ga-DOTA-NOC *(DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)* *(DOTA-TOC: DOTA coupled Nal^{3}-Octreotide)*	Imaging of neuroendocrine cancers
$[^{13}N]$-NH_3 (ammonia)	Heart imaging

Therapeutic applications of radionuclides are based on the well-known factor that the ionizing radiations, especially the particulate emissions, have the ability to destroy cells by depositing their energy. Therapeutic efficacy of radionuclides is accomplished by effectively manipulating the cytotoxic effects of radiation to arrest and annihilate the proliferation of cells, most often tumor/cancer cells without causing any serious damage to the surrounding normal cells. Therapeutic doses of ionizing radiation can be delivered to the sites of disease in three different ways, viz. external beam irradiation or 'Teletherapy', implantation of radioactive needles / wires / seeds or 'Brachytherapy' and systematic administration of therapeutic radiopharmaceutical or 'Radionuclide therapy'.

External beam irradiation or 'Teletherapy' is traditionally carried out with high intensity gamma radiation sources, such as, those from ^{60}Co (E_γ = 1.33 and 1.17 MeV) housed in heavily shielded teletherapy units. Indigenously developed 'Bhabhatron' teletherapy units are used extensively for this purpose. More than 1,00,000 patients undergo external beam radiotherapy every year in India during the course of their treatment.

'Brachytherapy' involves the implantation of a source of radiation, usually in the form of a wire or seed or needle, in close proximity to the tumor/diseased tissue. Although brachytherapy started with the implantation of the radium needles nearly a century ago, currently radioisotopes such as, ^{103}Pd, ^{125}I, ^{137}Cs, ^{192}Ir, ^{198}Au etc. are used. This treatment modality is used for the management of various types of carcinoma such as eye, breast cervical, prostate etc.

Radionuclide therapy or *in-vivo* targeted radiotherapy involves administration of therapeutic radiopharmaceuticals in the body. Therapeutic radiopharmaceuticals may be defined as radiolabeled molecules designed to deliver therapeutic dose of ionizing radiation to specific disease sites with high specificity in the body. Over the past 70 years, the most widely used radionuclide for therapy is ^{131}I which finds extensive applications in the treatment of some forms of hyperthyroidism, for ablation of remnant thyroid tissue after thyroidectomy and for treating the metastatic lesions from well-differentiated thyroid carcinoma. Apart from the management of thyroid related diseases, therapeutic radiopharmaceuticals find extensive applications in providing the palliative care to the cancer patients suffering from excruciating pain arising due to skeletal metastases. Although the conventional treatment modalities such as, administration of analgesics and external beam radiotherapy are prevalent practices for controlling the bone pain, these modalities have multiple side effects.

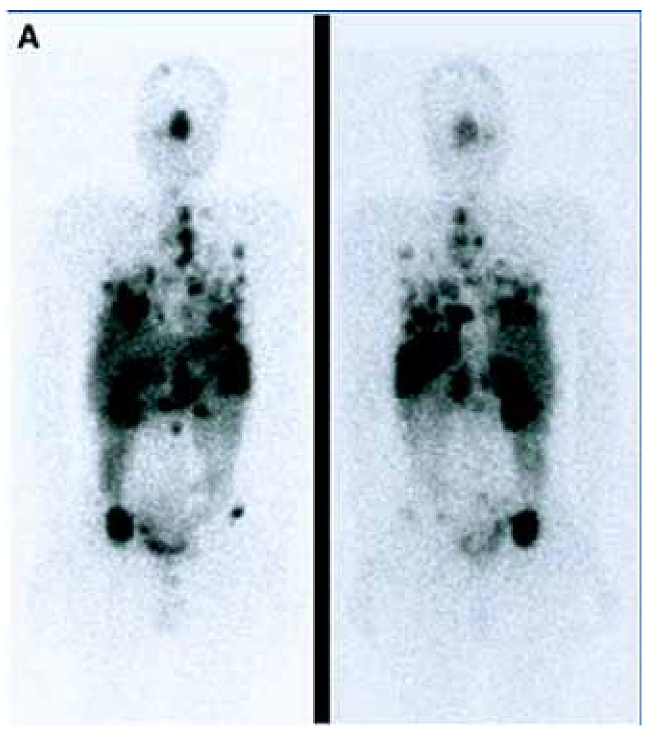


Figure 2: Typical whole-body post-therapy images of a patient with neuroendocrine originated tumors recorded after administration of ^{177}Lu-DOTA-TATE.

Radionuclide therapy employing the suitable radiopharmaceuticals (such as, ^{32}P-Orthophosphate, $^{89}SrCl_2$, ^{153}Sm-EDTMP, ^{186}Re-HEDP/^{188}Re-HEDP, ^{177}Lu-EDTMP) are presently considered to be the most effective method for providing pain relief to the patients suffering from multiple skeletal metastases[13].

In the recent years, targeted radionuclide therapy involving molecular carriers such as, peptides, hormones and antibodies have also gained popularity and being used for the treatment for various kinds of cancers. Peptide Receptor Radionuclide Therapy (PRRT) employing radiolabeled peptides, particularly using ^{177}Lu-DOTA-TATE (^{177}Lu-labeled DOTA coupled Tyr^{3}-Octrotate), is now an established therapeutic modality for the treatment of patients suffering from a wide variety of inoperable neuroendocrine cancers over-expressing somatostatin receptors. In the last decade, PRRT has gained momentum and at present is being routinely used as a therapeutic regimen in a limited number of countries including India[14]. Figure 2 shows the whole-body scintigraphic images of a neuroendocrine cancer patient treated with ^{177}Lu-DOTA-TATE[15].

Radioimmunotherapy (RIT) based on radiolabeled monoclonal antibodies (MoAbs) has also emerged as an important and useful procedure to treat various types of cancers. MoAbs designed against various antigens or receptors associated with specific tumor types serve as targeted carriers of radionuclides towards the malignant tumors over-expressing either antigens or receptors. Use of two radiolabeled MoAbs based on anti-CD20 antibody namely, Zevalin® (^{90}Y-labeled) and Bexxar® (^{131}I-labeled) has been approved by US FDA (Food and Drug Administration of United States of America) for RIT and both these agents have demonstrated significant anti-tumor response following treatment in patients with B-cell lymphomas. At present, a host of other radiolabeled MoAbs are being evaluated for RIT applications and these agents are in different stages of clinical evaluation.

Radionuclides are also used in 'Radiation Synovectomy' or 'Radiosynoviorthesis', where the radiolabeled preparations are used to control and counteract excessive proliferation of synovial membrane in arthritis affected joints. This methodology has the advantage over other treatment modalities such as, chemical synovectomy and surgical intervention in terms of cost, side effects and need for hospitalization[16]. Table-3 lists some of the commonly used therapeutic radiopharmaceuticals along with their applications. Targeted radionuclide therapy in combination with other treatment modalities such as, chemotherapy and surgical intervention have now become an integral part in the management of a wide variety of cancers such as, prostate, colon, breast, ovary.

TABLE 3: List of some of the commonly used therapeutic radiopharmaceuticals

Radiopharmaceuticals	Used for the treatment of
^{131}I-Sodium iodide *(solution and capsules)*	Hyperthyroidism Thyroid carcinoma
^{131}I-MIBG	Neuroblastoma
^{153}Sm-EDTMP *(EDTMP: Ethylenediaminetetramethylene phosphonic acid)*	Bone pain palliation
$^{89}SrCl_2$	Bone pain palliation
^{186}Re-HEDP *(HEDP: 1-hydroxyethylidene-1,1-diphosphonic Acid)*	Bone pain palliation
^{188}Re-HEDP	Bone pain palliation
^{32}P-Orthophosphate	Bone pain palliation Polycythemia rubra vera
^{90}Y-DOTA-TOC *(DOTA-TOC: DOTA coupled-Tyr^{3}-Octreotide)*	Neuroendocrine cancers
^{90}Y-DOTA-TATE *(DOTA-TATE: DOTA coupled-Tyr^{3}-Octreotate)*	Neuroendocrine cancers
^{177}Lu-DOTA-TATE	Neuroendocrine cancers
^{90}Y-Microspheres	Hepatocellular carcinoma
^{131}I-Tositumomab	Non-Hodgkin's lymphoma
^{90}Y-Ibritumomab-tiuxetan	Non-Hodgkin's lymphoma

In the recent past, the concept of theranostic applications of radiopharmaceuticals is gaining momentum with an aim to obtain so called 'Personalized Medicine'. 'Theranostic' refers to a combination of two interdependent applications namely therapy and diagnosis, using the same agent[17]. Since both diagnosis and therapy can be effected using this concept of theranosis, the treatment regime can be individualized for a specific patient which forms the basis of personalized medicine. In actual practice, theranosis can be effected by replacing a diagnostic radioisotope in a radiopharmaceutical with a therapeutic radioisotope usually with same chemical properties (i.e. ^{186}Re/^{188}Re for ^{99m}Tc), while using the same molecular vector, or by using the same radiopharmaceutical for both diagnosis and therapy, albeit with different doses[18]. Presently several radiopharmaceuticals are being investigated for determining their suitability for theranostic applications.

It is evident from the above discussion that radionuclides are routinely used for diagnosis, treatment and management of a wide variety of ailments all over the world. Radionuclides play a pivotal role in human health care and are an important tool in improving the quality of human life. ❐

References

1. S. Jurisson, D. Berning, W. Jia and D. Ma. Coordination compounds in nuclear medicine. *Chem. Rev.* **93**, 1137-1156 (1993).
2. V.R. McCready. Milestones in nuclear medicine. *Eur. J. Nucl. Med. Mol. Imaging* **27**, S49-S79 (2000).
3. P.S. Baker. Reactor-produced radionuclides. In: (G.A. Andrews, Ed.), *Radioactive pharmaceuticals*. U.S. A.E.C. Symposium Series, Oak-Ridge, Tennessee, U.S.A. (1965) 129-142.
4. J.K. Poggenburg. The nuclear reactor and its products. *Semin. Nucl. Med.* **4**, 229-243 (1974).
5. T.J. Ruth, B.D. Pate, R. Robertson and J.K. Porter. Radionuclide production for the biosciences. *Nucl. Med. Biol.* 16, 323-336 (1989).
6. S.M. Qaim. Nuclear data relevant to cyclotron-produced short-lived medical isotopes. *Radiochim. Acta* **30**, 147-162 (1982).
7. A.P. Wolf and W.B. Jones. Cyclotrons for biomedical radioisotope production. *Radiochim. Acta* **34**, 1-7 (1983).
8. F.F. Knapp and S. Mirzadeh. The continuing important role of radionuclide generator systems in nuclear medicine. *Eur. J. Nucl. Med. Mol. Imaging* **21**, 1151-1165 (1994).
9. Cyclotron produced radionuclides: Principles and practice. Technical Report Series No. 456. International Atomic Energy Agency, Vienna (2008)
10. G.B. Saha. Production of radinuclides. In: *Fundamentals of nuclear pharmacy*. 3rd edition, Springer-Verlag, New York (2000) 46-64.
11. S. Liu and D.S. Edwards. Bifunctional chelators for therapeutic lanthanide radiopharmaceuticals. *Bioconj. Chem.* **12**, 7-34 (2001).
12. IANCAS Bulletin. Positron emission tomography: Products and application (Edited by N. Ramamoorthy and M.G.R. Rajan). 12, 199-260, (2014).
13. T. Das, H.D. Sarma, A. Shinto, K.K. Kamaleshwaran and S. Banerjee. Formulation, pre-clinical evaluation and preliminary clinical investigation of an in-house freeze-dried EDTMP kit suitable for the preparation of ^{177}Lu-EDTMP. *Cancer Biother. Radiopharm.* **29**, 412-421 (2014).
14. T. Das and S. Banerjee. Formulation of patient dose of ^{177}Lu-DOTA-TATE in hospital radiopharmacy in India: Preparation using *in-situ* methodology vis-a-vis freeze dried kit. *Cancer Biother. Radiopharm* **29**, 301-302 (2014).
15. T. Das, S. Chakraborty, K.G. Kallur, M. Venkatesh and S.Banerjee. Preparation of patient doses of ^{177}Lu-DOTA-TATE using indigenously produced ^{177}Lu : The Indian experience. *Cancer Biother. Radiopharm*. **26**, 395-400. (2011).
16. E. Deutsch, J.W. Brodack and K.F. Deutsch. Radiation synovectomey revisited. *Eur. J. Nucl. Med. Mol. Imaging* 20, 1113-1127 (1993).
17. G.L. DeNardo and S.J. DeNardo. Concept, consequences, and implications of theranosis. *Semin. Nucl. Med*. **42**, 151-163. (2012).
18. R.P. Baum and H.R. Kulkarni. Theranostics: From molecular imaging using Ga-68 labeled tracers and PET/CT to personalized radionuclide therapy - the Bad Berka experience. *Theranostics* **2**, 437-447 (2012).