PRODUCTION AND APPLICATIONS OF RADIOPHARMACEUTICALS

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Abstract:
Application of radioisotopes in healthcare for diagnosis and therapy is gaining popularity due to its high sensitivity, therapeutic efficacy and cost-effectiveness. This chapter briefly describes the necessity of artificial radioisotopes and the methods followed for the production of radioisotopes in nuclear reactor and cyclotron. It briefly touches upon the general design of radiopharmaceuticals that forms the mainstay of clinical nuclear medicine. It will also give the reader a brief idea on some of the important radiopharmaceuticals currently being used in clinical nuclear medicine practice.
Key words: *Radioisotopes, Radioactivity, Radiopharmaceuticals, Nuclear medicine, SPECT, PET*

Introduction:
While use of nuclear energy for production of electricity is well-known, its potential role in human healthcare is less obvious. In the present day healthcare system, man-made radioisotopes find immense applications in diagnosis of a variety of diseases such as cardiovascular disorders, kidney, thyroid and liver dysfunctions, Alzheimer's and Parkinson disease, etc. including cancer.[1] Not only for diagnosis, radioisotopes also play an important role in the treatment of various types of diseases, particularly cancers. 'Nuclear medicine' employs the nuclear properties of the radioisotopes in diagnosis and therapy to study the metabolic, physiologic and pathologic conditions of human body.[2] It is important to note that radioisotopes as such are rarely used in radio-diagnosis and targeted radionuclide therapy of various clinical conditions. Generally, radioisotopes are chemically tagged to biologically active molecules to obtain a 'Radiopharmaceutical', which is safe to administer in human

body to obtain diagnostic information or to deliver therapy in a non-invasive manner. This Chapter will take the reader on a short, but fascinating, journey providing glimpses on the production of radioisotopes, design and preparation of radiopharmaceuticals and their applications in routine clinical practice.

Radioisotopes

Radioisotopes have unstable nuclei that undergo spontaneous change with concomitant emission of particulate or electromagnetic radiation such as alpha, beta, Auger electrons or gamma photons. Alpha (α) particles are mono-energetic helium nuclei whereas beta particles are electrons which can be either positively or negatively charged. While electrons with unit negative charge (β^-) are well-known, electrons with a positive charge are called positrons (β^+). While the energy spectrum of beta particles emitted from the nucleus is continuous, Auger electrons are mono-energetic and are of atomic origin. Gamma (γ) rays are electromagnetic radiation of fixed energy with very high penetrating properties. The conventional unit of radioactivity is Curie (Ci), which is defined as the quantity of any radioactive material which undergoes 3.7×10^{10} disintegrations per second. The SI unit of radioactivity is Becquerel (Bq), which is defined as one disintegration per second (dps). Every radioisotope has its characteristic half-life ($T_{1/2}$), which is defined as the time taken to reduce the radioactivity to half of its initial value. It is interesting to note that half-lives of radioisotopes vary over a very wide range.

Radioisotopes can be broadly divided into two categories based on their clinical applications viz. diagnostic radioisotopes or therapeutic radioisotopes. Diagnostic radioisotopes emit tissue penetrating γ-radiations of energy, preferably in the range of 100-250 keV, suitable for efficient detection with NaI(Tl) detectors generally employed in gamma camera or SPECT (Single Photon Emission Computed Tomography) imaging system. Positron emitting radioisotopes also falls under the category of diagnostic radioisotopes. The positrons undergo a phenomenon called 'annihilation'. In this process, the β^+ emitted from the nucleus of the radioisotope combines with an electron from the surroundings to produce two 511 keV γ photons. These two γ-photons of equal energy moving in opposite directions can be used for obtaining high resolution diagnostic images using PET (Positron Emission Tomography) camera.

It is preferable that a diagnostic radioisotope is a pure gamma emitter since concomitant particulate emissions, if present, does not contribute to any diagnostic information, but give unnecessary radiation dose to the patient. This is following the guiding principle of human radiation exposure, 'ALARA' (As Low As Reasonably Achievable), which recommends avoiding radiation dose, however small it is, that does not bring any benefit to the patient. However, it is important to note certain unique exemptions to this rule such as, use of Iodine-131 (^{131}I) for both diagnosis as well as therapy, despite being a beta-gamma emitter. Therapeutic radioisotopes, on the other hand, are characterized by particulate emissions, α, β^- or Auger electrons, with or without concomitant emission of γ-radiation. These particulate emissions with high LET (Linear Energy Transfer, which indicates the amount of energy transferred by these particles per unit path length travelled) are suitable for therapeutic

applications. The co-emission of gamma radiations are considered to be a boon for therapeutic applications since it permits monitoring the distribution of the radiotracer *in-vivo*.

It is natural for any reader of this subject to question the necessity of producing artificial radioisotopes when several radioisotopes such as Tritium (^{3}H), Carbon-14 (^{14}C), Potassium-40 (^{40}K) etc. are available in nature. It should be noted that naturally available radioisotopes are generally less abundant and their isolation is challenging. More importantly, the choice of radioisotope for a given application is based on a host of factors including the half-life of the radioisotope, energy of particulate radiation, availability and most importantly, the chemistry it follows. These factors necessitate the artificial production of radioisotopes with nuclear characteristics suitable for intended application.

Production of Radioisotopes:

All radioisotopes used for the preparation of radiopharmaceuticals are man-made and produced using either a nuclear reactor[3] or a particle accelerator, predominantly cyclotron.[4] Stable and highly pure target materials are bombarded with thermal neutrons (neutrons having kinetic energy of 0.025 eV) in a nuclear reactor or with energetic beam of particles in a cyclotron, which disturbs the neutron to proton ratio of the stable elements thereby producing unstable radionuclides, which subsequently undergo nuclear decay by emission of various particles like α, β⁻, β⁺, Auger electrons along with γ-radiation (in majority of cases, but not always). The nature and quantity of the radioisotope produced from a particular irradiation process depends on many factors, such as, nature and energy of bombarding particle, quantity and purity of the target, time of irradiation and half-life of the radionuclide being produced.

A large number of radioisotopes used in nuclear medicine are produced in nuclear reactors. Reactor-produced radioisotopes are neutron rich and primarily decay by the emission of β⁻ particles along with or without the emission of γ-photons. Nuclear reactor is a device in which chain reaction of nuclear fission is carried out in a controlled way in order to produce energy and neutrons. Fission produced high-energy neutrons are thermalized using a suitable moderator and used for the production of radioisotopes. Most of the reactor-produced radioisotopes used for preparation of radiopharmaceuticals are obtained either through the separation of fission products or by neutron irradiation on the specific targets. In case of nuclear fission, a large number of radioisotopes are produced together and the desired radioisotopes for medical applications are separated through elaborate and extensive procedures inside specially designed lead-shielded radioisotope processing facility. The major advantage of this route is the availability of several useful radioisotopes with high specific activity (in no-carrier-added from) in huge quantities from a single irradiation. However, sophisticated processing chambers with remote handling gadgets and good facilities for handling and storing highly radioactive long-lived wastes are essential for producing radioisotopes employing this route. In the neutron activation route, stable target, preferably in the oxide/carbonate/nitrate/metallic form, is bombarded with the thermal neutrons, which produce the desired radionuclide along with the emission of gamma photons. In some cases, formation of the desired radionuclide is accompanied with the emission of charged particles. Neutron activation route is the most commonly and widely used route for

the production of medically useful radionuclides. In the former process, radioisotopes are obtained with comparatively lower specific activity (activity per unit mass), as in this case both target and final product are the isotopes of the same element and hence, cannot be separated by simple chemical procedures. However, neutron bombardment followed by the emission of charged particles produces high specific activity radioisotopes as in this case it is possible to chemically separate the desired radionuclide from the irradiated target. Table-1 lists some of the important reactor-produced radionuclides used for the preparation of radiopharmaceuticals along with their nuclear decay characteristics and common production route.

Table-1: Some important reactor-produced radionuclides used for the preparation of radiopharmaceuticals

Radionuclide	Half-life	Mode of Decay[*]	Common Production Route
^{32}P	14.26 d	β^-	^{32}S (n,p) ^{32}P
^{67}Cu	2.40 d	β^- & γ	^{67}Zn (n,p) ^{67}Cu
^{89}Sr	50.53 d	β^-	^{88}Sr (n,γ) ^{89}Sr
^{90}Y	64.00 h	β^-	^{235}U (n,f) ^{90}Y
^{99}Mo	67.00 h	β^- & γ	^{98}Mo (n,γ) ^{99}Mo ^{235}U (n,f) ^{99}Mo
^{131}I	8.02 d	β^- & γ	^{130}Te (n,γ,β^-) ^{131}I
^{153}Sm	46.27 h	β^- & γ	^{152}Sm (n,γ) ^{153}Sm
^{166}Ho	26.83 h	β^- & γ	^{165}Ho (n,γ) ^{166}Ho
^{177}Lu	6.73 d	β^- & γ	^{176}Lu (n,γ) ^{177}Lu
^{186}Re	90.64 h	β^- & γ	^{185}Re (n,γ) ^{186}Re

[*]*Only principal decay mode is mentioned*

Table-2: Some important cyclotron-produced radionuclides used for the preparation of radiopharmaceuticals

Radionuclide	Half-life	Mode of Decay[*]	Common Production Route[#]
^{11}C	20.39 min	β^+	^{14}N (p,α) ^{11}C
^{13}N	9.97 min	β^+	^{16}O (p,α) ^{13}N
^{15}O	122.24 s	β^+	^{14}N (d,n) / ^{15}N (p,n) ^{15}O
^{18}F	109.77 min	β^+	^{18}O (p,n) ^{18}F
^{47}Sc	3.345 d	β^- & γ	^{48}Ti (p,2p) ^{47}Sc
^{67}Cu	61.83 h	β^- & γ	^{68}Zn (p,2p) ^{67}Cu
^{67}Ga	3.261 d	EC	^{68}Zn (p,2n) ^{67}Ga
^{111}In	2.805 d	EC	^{111}Cd (p,n) ^{111}In
^{201}Tl	72.912 h	EC	^{203}Tl (p,3n) ^{201}Tl

[*]*Only principal decay mode is mentioned.*
[#]*Other route for production also exists.*
EC indicates decay by electron capture

Several medically important radionuclides are produced in particle accelerators, mainly cyclotrons.[4] Cyclotron produced radionuclides are neutron-deficient and decays either by electron capture or by positron emission. In a cyclotron, a highly energetic beam of accelerated particles, like protons, deuterons, α-particles, tritium are generated under vacuum by circulating the charged particles using an electromagnetic field. The targets of stable elements are bombarded with these highly energized particles which produces the desired radioisotopes. Cyclotron produced radionuclides are available in no-carrier-added form and thus having very high specific activity. Table-2 lists some of the important cyclotron-produced radionuclides used for the preparation of radiopharmaceuticals along with their nuclear decay characteristics and common production route.

Radioisotopes produced either in a reactor or a cyclotron is radiochemically processed to make it chemically suitable for the formulation of radiopharmaceuticals. This is usually done in specially designed laboratories using heavily lead-shielded radioisotope processing facilities equipped with remote handling machineries. The low amount of materials which need to be chemically processed and high radiation emanating from such materials make the chemical processing of radioisotopes quite challenging. Additionally, as majority of radioisotopes used for the radiopharmaceutical applications are short-lived, radiochemical processing of irradiated targets required to be completed in minimum possible time, which makes the process further challenging.

Radionuclide Generator	Parent		Daughter		Decay Mode of Daughter Radionuclide[*]
	Radionuclide	Half-life	Radio-nuclide	Half-life	
^{68}Ge-^{68}Ga[#]	^{68}Ge	270.82 d	^{68}Ga	67.63 min	β^+
^{82}Sr-^{82}Rb[#]	^{82}Sr	25.55 d	^{82}Rb	1.27 min	β^+
^{90}Sr-^{90}Y[#]	^{90}Sr	28.78 y	^{90}Y	64.10 h	β^- & γ
^{99}Mo-^{99m}Tc[*]	^{99}Mo	65.94 h	^{99m}Tc	6.02 h	IT
^{188}W-^{188}Re[#]	^{188}W	69.40 d	^{188}Re	16.98 h	β^- & γ
^{229}Th-^{229}Ac[#]	^{229}Th	7430.0 y	^{225}Ac	10.00 d	α & γ

[*]*Only principal decay mode is mentioned.*   [#]*Based on secular equilibrium*
IT indicates decay by isomeric transition   [*]*Based on transient equilibrium*

Medically useful short-lived radionuclides can also be obtained from the radionuclide generator systems.[5] Radionuclide generators may be defined as a device which contains a longer-lived parent radionuclide in equilibrium with its comparatively shorter-lived daughter radionuclide, from which the daughter radionuclide can be obtained at a regular interval. Radionuclide generators are the most convenient method of obtaining short-lived

radioisotopes for the formulation of radiopharmaceuticals at hospitals/laboratories, which are far-away from the radioisotope production site. The radioactive equilibrium established between the parent radionuclide and daughter radionuclide may be either transient (half-life of the daughter is not negligible compared to parent's half-life) or secular (half-life of the daughter is negligible compared to parent's half-life) in nature. Table-3 lists some of the important radionuclide generator systems used for the formulation of radiopharmaceuticals at the nuclear medicine centers.

Radiopharmaceuticals:

Radiopharmaceuticals may be defined as radioactive drugs of adequate radiochemical purity and pharmaceutical safety, suitable for oral or intravenous administration in humans for diagnosis or monitoring the progress of a disease or to effect therapy of an ailment. A radiopharmaceutical generally consists of a target/carrier molecule (organic moiety) to which a suitable radioisotope is attached through a chemical bond. However, $Na^{131}I$ (for diagnosis and therapy of thyroid related disorders), $Na_3^{32}PO_4$ (for bone pain palliation), $Na^{18}F$ (for bone imaging) etc. are few inorganic chemicals, which do not fit into the general definition of radiopharmaceuticals, but used as radiopharmaceuticals in routine clinical practice. Such radiopharmaceuticals are inherently capable of tracing biological processes in our body to provide diagnostic information. If necessary, the same mechanism can also be used to deliver therapeutic dose of radiation for disease control.

Modern radiopharmaceuticals, however, have well-defined structural features. Schematic diagram of a typical radiopharmaceutical is shown in Figure-1. The function of the biomolecule, also known as carrier molecule, is to target the organ/tissue of interest along with the attached radioisotope, which is responsible for the diagnostic or therapeutic efficacy of the formulation. It is sometimes difficult to attach radioisotope directly to the carrier molecule, either because the carrier molecule does not possess the right functional group(s) to form a stable bond with the radioisotope or by doing so the carrier molecule loses its ability to effectively target the disease site. In such cases, radioisotope is attached with the carrier moiety by using a suitable linker and a bifunctional chelating agent (BFCA).
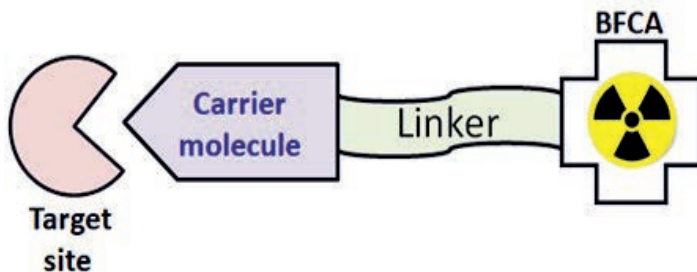

Figure-1: Schematic diagram of a typical radiopharmaceutical

Classification of radiopharmaceuticals

Based on chemical nature, radiopharmaceuticals can be classified into following categories: (a) Simple radiochemicals [^{131}I as sodium iodide ($Na^{131}I$), ^{32}P as sodium orthophosphate ($Na_3^{32}PO_4$), ^{89}Sr as strontium chloride ($^{89}SrCl_2$), ^{201}Tl as thallium chloride ($^{201}TlCl$), etc.]; (b) Compounds with non-metallic radioisotope [Compounds labeled with ^{131}I such as

metaiodobenzyl guanidiene (mIBG), ^{11}C compounds such as ^{11}C-acetate, ^{11}C-palmitate, ^{18}F-compounds such as 2-fluoro-2-deoxy glucose (FDG)]; (c) Compounds with metallic radioisotope or coordination complexes [complexes of transition metals such as ^{99m}Tc, $^{186/188}$Re, ^{64}Cu, ^{90}Y; lanthanides such as ^{177}Lu, ^{153}Sm, ^{166}Ho and p-block radiometals such as, ^{111}In, ^{68}Ga; and (d) particulate formulations such as colloids and macro-aggregates of radiometals like ^{198}Au-gold colloid, ^{32}P-chromic phosphate, ^{99m}Tc-labeled macro-aggregated albumin, hydroxyapatite (HA) particles labeled with ^{166}Ho, ^{177}Lu, etc.

Like radioisotopes, based on their applications, radiopharmaceuticals can also be classified as (a) Diagnostic radiopharmaceuticals, and (b) Therapeutic radiopharmaceuticals. Additionally, in the recent time the concept of 'Theranostic radiopharmaceuticals' is also gaining momentum.

Diagnostic radiopharmaceuticals:

Diagnostic radiopharmaceuticals are used for diagnosis of a disease, to monitor progression or regression of the disease or to assess the function of an organ such as liver, lung or kidneys. Diagnostic radiopharmaceutical acts as a tracer to provide patho-physiological information of the patient in the form of a scan. This requires a tracer that can produce signals which can penetrate the body so that they can be detected and recorded by some instruments placed outside the human body. Gamma rays, because of their high penetrative strength can be used for this purpose. Therefore, most of the diagnostic radiopharmaceuticals contain a gamma-emitting radioisotope. Diagnostic radiopharmaceuticals are radiolabeled molecules, generally possessing structural features shown in Figure-1, which are used to produce images of the morphologic structure, evaluation of physiological functions of specific organs/tissue or any abnormalities in the body of the patient. As mentioned earlier, diagnostic radiopharmaceutical uses either a γ-emitter or a β$^+$-emitter. In the former case, the radiopharmaceutical is used for SPECT imaging, while when the latter is used, the radiopharmaceutical is employed for PET scanning. Technetium-99m (^{99m}Tc) is the radioisotope most commonly used in the diagnostic nuclear medicine.[6] Suitable nuclear decay characteristics (decays by emission of 140 keV gamma photons with a half-life of 6 h), amenable chemistry and easy availability from a ^{99}Mo-^{99m}Tc generator has made ^{99m}Tc 'Work-horse of Nuclear Medicine', as 75-80 % of all radiopharmaceuticals are based on this radioisotope. Table-4 lists some of the important radiopharmaceuticals routinely used for diagnosing various human ailments.

Table-4: List of important diagnostic radiopharmaceuticals routinely used in clinical nuclear medicine practice

Radiopharmaceutical	Application
^{99m}Tc-ECD, ^{99m}Tc-TRODAT, ^{99m}Tc-HMPAO	Brain imaging
^{99m}Tc-Sestamibi, ^{99m}Tc-Tetrofosmin, ^{201}TlCl	Cardiac imaging
^{99m}Tc-Sulphur colloid	Liver imaging
^{99m}Tc-Mebrofenin	Hepatobiliary function
^{99m}Tc-MAA, ^{68}Ga-MAA	Lung imaging
^{99m}Tc-MDP, ^{68}Ga-BPAMD, Na^{18}F	Bone imaging

^{99m}Tc-GHA, ^{99m}Tc(III)-DMSA, ^{99m}Tc-DTPA, ^{99m}Tc-EC, ^{99m}Tc-MAG$_3$	Kidney imaging
^{99m}Tc-Leuocytes, ^{99m}Tc-Ciprofloxacin, ^{99m}Tc-UBI	Infection/Inflammation imaging
^{18}F-FDG	Cancer diagnosis
^{99m}Tc-HYNIC-TOC/TATE, ^{68}Ga-DOTA-TOC/TATE	Diagnosis of NETs
^{68}Ga-PSMA	Diagnosis of prostate cancer

A good diagnostic radiopharmaceutical should have high target-specificity, excellent radionuclidic and radiochemical purity, adequate *in-vivo* stability, fast accumulation in target organs and rapid clearance from non-target organs. Additionally, the radiopharmaceutical should produce images with high target-to-non-target ratio to clearly distinguish the disease site from normal tissue. Availability and cost may be considered as other factors that determine the utility of a diagnostic radiopharmaceutical in clinical nuclear medicine practice.

A typical diagnostic procedure involves administration of a diagnostic radiopharmaceutical, which has passed all quality control tests and declared suitable for administration into patients.[7] There are two main routes for administration of radiopharmaceuticals, oral or intravenous. As the name suggests, in oral administration, the patient swallows capsules containing the radiopharmaceutical or drink liquid radiopharmaceutical formulation through mouth. In intravenous route, the radiopharmaceutical is administered into the patient through intravenous route using a syringe. It is worth noting that orally administered radiopharmaceuticals are very few in clinical uses today and Na^{131}I is one of them. After administration of the radiopharmaceutical, the patient is scanned under a gamma camera. Gamma camera or 'Anger camera' is a device with a sufficiently big NaI(Tl) detector with automated arrangement to scan the patient from head-to-toe. By this process, the detector records the distribution of radioactivity in patient's body and presents it as a 2-D scan or planar image. It could be noted that 2-D images does not provide depth information about the cancerous lesions in patient's body.

Tomography is a technique of constructing 3-D images from gamma emissions acquired at different angles from the patient's body. A SPECT camera is equipped with a NaI(Tl) detector and associated electronics to detect and record γ-radiations emitted by the radiopharmaceuticals administered into the patient's body. Gamma camera's with single head (one detector), double head or triple head detectors are commercially available. In this technique, 2-D images of the patient acquired at different angles, based on the γ-emission from the single photon-emitting radioisotope in the administered radiopharmaceutical, were used to reconstruct the 3-D image of the distribution of activity within the patient's body. Though the 3-D images obtained by this procedure provide depth information of the activity distribution, resolutions of such images are low. In PET camera, the BGO (Bismuth germanium oxide) detector operating in coincidence detection mode records the γ-emissions consequent to the annihilation of positrons and calculate the precise location of annihilation event thereby constructing high-resolution images.

Though PET as well as SPECT provides 3-D images of activity distribution in patients, uncertainty in exact anatomical location of the lesions is a problem to take surgical decisions based on the these scans. To circumvent this problem, hybrid imaging or fusion imaging is

introduced. This technique involves fusion of images obtained from two distinct techniques. Computed tomography (CT) is an imaging modality which uses X-rays to provide anatomical details of the patient. SPECT or PET image is fused with corresponding CT image to obtain SPECT/CT or PET/CT image, which provides exact details of the location of the lesions in the anatomical structures.

It is very important to note that diagnostic radiopharmaceuticals play a very important role in deciding the therapeutic course of action to be taken for the patient. It not only provides the diagnosis, it can very well-assist in evaluating the effectiveness of therapy helping the nuclear medicine physicians to take corrective measures to ensure best clinical outcome for the patient.

Therapeutic radiopharmaceuticals:
Therapeutic radiopharmaceuticals may be defined as radiolabeled agents capable to deliver cytotoxic doses of ionizing radiation to the disease sites with high target-specificity in order to control and/or cure the disease. Although the use of unsealed sources of radiation for human health-care has been reported almost seven decades ago, application of therapeutic radiopharmaceuticals has gained momentum in the last two and half decades owing to the development of sophisticated target-specific molecular carriers and availability of radionuclides suitable for targeted radionuclide therapy in high radionuclidic purity and adequate specific activity. For therapy involving radiopharmaceuticals, particulate emitters i.e. the radionuclides which decay by the emission of α/β^-/Auger electrons are used, as the high-LET radiations are more useful in delivering lethal doses of cytotoxic radiation to the diseased sites. The β^--emitting radionuclides are most commonly used in therapeutic radiopharmaceuticals. Due to its high LET, β^--emitters are capable of delivering significant cytotoxic radiation dose to the cells. At the same time, they are far more controllable than α-emitting radionuclides from the standpoint of distribution in tissue since, an almost perfect distribution is required for effective therapy with α-emitters, whereas a less-than-perfect tissue distribution is not critical for effective therapy with β^--emitters. This is due to the difference in the range in tissue of these two particles, as α-emitters have a range of only several micrometers, while β^--emitters can penetrate several mm to cm. In the recent time, use of α-emitters has been reported for the treatment of prostate and neuroendocrine cancers.[8]

Iodine-131 is one of the most extensively used radionuclide, which finds application in the treatment of thyroid disorders. Iodine accumulates in the thyroid gland due to some physiological process as it is utilized for the synthesis of thyroid hormones, namely triiodothyronine (T3) and thyroxine (T4). Radioiodine is administered in the form of an inorganic salt, $Na^{131}I$ and used for destroying the overactive thyroid tissue in Hyperthyroidism, shrinking the over-sized thyroid glands in Goiter and to obliterate the cancerous lesions in ca. thyroid. Among different radiotracers used for radionuclide therapy, use of ^{131}I is unique as it is administered orally - either mixing it with water/juices or ingested in the form of capsules. Apart from these, ^{131}I-labeled meta-iodobenzylguanidine (^{131}I-mIBG) is used for the treatment of neuroendocrine cancers.

In the last two decades, peptide receptor radionuclide therapy (PPRT) has emerged as an important treatment modality for the treatment of various types of cancers, particularly

neuroendocrine cancers and prostate cancer.[9] Cancerous cells often over-express a variety of receptors. Many such receptors can specifically be targeted by using regulatory peptides and thus radiolabeled peptides can be used to deliver the lethal doses of ionizing radiation to the cancerous lesions. Metastatic neuroendocrine cancers, over-expressing somatostatin receptors, are regularly treated with ^{177}Lu/^{90}Y-labeled somatostatin analogs, like DOTA-TATE (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid coupled Tyr^3-Octreotate, a peptide containing eight amino acids in a specific sequence). These radiopharmaceuticals are injected through intravenous route and usually multiple administrations are required at specific time intervals to cure or at least control the disease. Another PRRT agent, namely ^{177}Lu-labeled PSMA-617 (Prostate Specific Membrane Antigen) has shown encouraging results in the treatment of metastatic prostate cancer and presently considered as one of the primary treatment modalities for controlling the disease. Radiolabeled RGD-peptides (Arginine-Glycine-Aspartic acid) have shown considerable promise in the treatment of solid tumors over-expressing integrin $\alpha_v\beta_3$ receptors. Many other radiolabeled peptides are presently in different phases of clinical trials and are expected to be available for the treatment of various types of cancers in the coming years.

Trans-arterial radio-embolization (TARE) using suitable β^--emitting radionuclide has emerged as a promising alternative to combat liver cancer and liver metastases.[10] The radiopharmaceuticals used in this therapeutic modality are administered through the hepatic artery either in the form of radiolabeled particulates of well-defined size or by incorporating them into a highly lipophilic and viscous liquid medium e.g. lipiodol (iodinated ethyl esters of fatty acids of poppy seed oil). ^{90}Y-labeled glass microspheres, known as TheraSphere$^{™}$, which consists of insoluble glass microspheres with ^{90}Y as an integral constituent of the glass, is the most commonly used agent for the treatment of liver cancer. BhabhaSphere, a similar radiolabeled prepartion has recently been developed in India for the treatment of liver cancer. SIR-Spheres$^{®}$, another ^{90}Y-labeled prepartion involving resin microspheres, is also used for the treatment of metastatic liver carcinoma. Apart from these, ^{90}Y/^{131}I/^{188}Re-labeled lipiodol also finds use in treating liver cancer. In these preparations, lipiodol serves the dual purpose of embolizing medium (stopping the blood supply) as well as a vehicle to deliver the therapeutic radioisotope to the cancerous lesions. While ^{131}I is incorporated in the lipiodol through isotope exchange reaction, ^{90}Y/^{188}Re is dispersed in the lipiodol medium via the formation of highly lipophilic complexes of these radioisotopes.

Cancer patients often suffer from the excruciating bone pain at the advanced stage of the disease. Use of bone-seeking radiopharmaceuticals as metastatic bone pain palliation (MBPP) agent is well-documented in the literature.[11] Such agents are considered as best in the category as these agents offer effective pain palliation with minimum side effects. Phosphorus-32 in the form of sodium orthophosphate (Na$_3$^{32}PO$_4$) was the first agent to be used for bone pain palliation followed by ^{89}Sr in the form of strontium chloride (^{89}SrCl$_2$, known as Metastron$^{®}$). However, these agents are reported to cause significant bone marrow damage owing to the emission of higher energy β^- particles from ^{32}P/^{89}Sr. Sm-153-labeled EDTMP (ethylenediamine tetramethylene phosphonic acid), also known as Quadramet$^{®}$, is extensively used for MBPP application. In the recent time, ^{177}Lu-EDTMP has emerged as another important radiopharmaceutical for controlling metastatic bone pain of cancer patients.

The clinical use of ^{188}Re-HEDP (hydroxyethylidene-1,1-diphosphonate) for MBPP application has also been well-documented in the literature.

Cancerous cells often express different types of antigens. As the reaction of an antibody with its antigen is very specific, use of radiolabeled antibodies offer great potential to treat cancer.[12] This modality, termed as Radioimmunotherapy (RIT), has been used for the treatment of non-Hodgkin's lymphoma (NHL), a type of blood cancer. The use of two RIT agents, namely Bexxar® (^{131}I-tositumomab) and Zevalin® (^{90}Y-ibritumomab tiuxetan) has been approved for the RIT of NHL. The availability of humanized monoclonal antibodies has improved the potential of this modality to a great extent. In the recent time, clinical applications of ^{90}Y/^{131}I/^{177}Lu-labeled Rituximab and ^{90}Y/^{177}Lu-labeled Trastuzumab have been reported for the treatment of patients suffering from NHL and metastatic breast cancer, respectively. Presently efforts are underway to develop many other radiolabeled monoclonal antibodies for the RIT of various types of cancers.

Targeted alpha therapy (TAT) has emerged as an attractive therapeutic option in the present time for the patients suffering from multiple micro-metastases.[13] Xofigo® or Alpharadin® (^{223}RaCl$_2$) is the first α-emitting radiopharmaceutical, whose clinical use has been approved for MBPP application in May, 2013. Encouraging results have been reported in the contemporary literature in connection with the use ^{225}Ac-DOTA-TATE and ^{225}Ac-PSMA-617 for the treatment of neuroendocrine cancers and prostate cancer, respectively.

Radiation synovectomy (RSV), which refers to the treatment of arthritis employing radioisotopes, is an example of use of therapeutic radiopharmaceuticals for non-oncological application. RSV, which has emerged as cost-effective alternative of chemical and surgical synovectomy, involves local intra-arterial administration of suitable β⁻-emitting radionuclides in the form of either radiocolloids or radiolabeled particulates of specific size into the affected synovial joints to control and counteract excessive proliferation of synovial membrane in arthritis affected joints.[14] The choice of radionuclide for RSV application depends on the size of the joint being treated. Radionuclides emitting high energy β⁻-particles (^{90}Y, ^{166}Ho, ^{188}Re) are used for the treatment of large-size joints (shoulder, hip, knee etc.), medium energy β⁻-particles (^{153}Sm, ^{186}Re, ^{177}Lu, ^{175}Yb) for medium-size joints (elbow) and low energy β⁻-particles (^{169}Er) are used for the treatment of small-size joints (phalangeal joints). The use of several inorganic colloids or macro-aggregates incorporating therapeutic radionuclide, such as ^{90}Y/^{169}Er-Citrate, ^{90}Y-Silicate, ^{90}Y/^{165}Dy-FHMA (Ferric Hydroxide Macro Aggregate), ^{32}P-Chromic Phosphate Aggregate, ^{198}Au-Colloid has been reported for this purpose. However, preformed particulates of 5-20 μm size labeled with suitable radionuclides are preferred for RSV application due to their minimal leakage from the affected joint. Hydoxyapatite (HA) particles of appropriate size labeled with ^{90}Y, ^{177}Lu and ^{169}Er are used for the treatment of arthritis affected joints of large, medium and small sizes, respectively.

Theranostic radiopharmaceuticals:

The term 'Theranostic/Theranosis' refers to a combination of two interdependent applications namely therapy and diagnosis, using the same agent. Since both diagnosis and therapy can be effected by using the radiopharmaceuticals, the concept of 'theranostic radiopharmaceuticals'

is becoming popular. Theranosis helps in augmenting a diagnostic dose to a therapeutic one in order to tailor the therapy in a specific patient. There are three distinct possibilities, by which theranosis can be employed in radiopharmaceuticals[15]. In the first case, a matched radionuclide pair e.g. ^{99m}Tc (diagnostic) and ^{188}Re (therapeutic) can be used for formulation of radiopharmaceuticals using the same carrier moiety, as the complexation chemistries of Tc and Re closely resembles each other. Another way of achieving theranosis is using the radioisotopes of the same element such as, ^{123}I (diagnostic) and ^{131}I (therapeutic) for the formulation of radiopharmaceuticals. The third and perhaps the most desirable way of achieving theranosis is using the same radionuclide which decays by particulate emission along with imageable gamma photon(s), such as ^{177}Lu, ^{166}Ho. Due to obvious reasons, the last option is most attractive, as the radiopharmaceutical used for the diagnosis and therapy remains same in all respects, thereby assuring near-identical biological distribution and pharmacokinetics in patients.

Contributions of Department of Atomic Energy (DAE) to radioisotope program in India:

Considering DAE's role as the primary agency to cater to the radioisotope requirement in our country, this chapter will be incomplete without mentioning its contributions. DAE has always been at the forefront of radiopharmaceutical research ensuring a steady supply of radioisotopes and making available state-of-the-art clinical radiopharmaceuticals at an affordable cost. Using DHRUVA and APSARA-U reactors in BARC (Mumbai) and cyclotrons at RMC (BARC, Mumbai) and VECC (Kolkata), a plethora of medical radioisotopes such as, ^{18}F, ^{68}Ga, ^{99}Mo (for ^{99m}Tc), ^{131}I, ^{125}I, ^{177}Lu, ^{153}Sm, ^{201}Tl are produced and supplied to the hospitals for healthcare applications (through Board of Radiation and Isotope Technology, BRIT, Navi Mumbai). DAE is constantly improving and expanding its facilities to accommodate the growing demand of the radioisotopes. In addition, DAE also supplies ready-to-use radiopharmaceuticals and freeze-dried kits through BRIT. It is worthwhile to mention that most of the radiopharmaceuticals and allied products, such as freeze-dried kits supplied through BRIT are the result of relentless effort by scientists in BARC. The readers are recommended to visit official web-site of BRIT (www.britatom.gov.in) for the detailed and up-to-date information regarding radiochemicals, freeze-dried kits and radiopharmaceuticals supplied by DAE for healthcare applications.

Conclusions:

Radiopharmaceuticals are radioactive formulations suitable for human administration and usually consist of a pharmaceutical/drug moiety and a radionuclide having appropriate nuclear decay characteristics. Radiopharmaceuticals are routinely employed for the diagnosis of various kinds of human diseases and detection of bodily malfunctions. Such preparations also find extensive use in the management of cancers and palliative care. Radiopharmaceuticals play a pivotal role in human healthcare and worldwide around 40 million patients are benefitted annually from the usage of such radioactive formulations.

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