Radioisotopes for diagnosis and treatment: Recent trends and path forward

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I INTRODUCTION

Nuclear energy can light up the country by providing electricity. But also be used in a variety of other field including health care to prevent, diagnose and treat disease. Application of radioisotopes (RI) in health care constitutes one of the most important peaceful uses of atomic energy. To day, over 8,00,000 patient investigations are carried out annually in India spanning over 500 centers using radiopharmaceuticals. As far as radiation therapy is concerned, there are more than 300 radionuclidic therapy units operating in over 220 radiotherapy centers in India.

II RADIOISOTOPES

(a) Why radioisotopes - Radioisotopes are used because of the penetrating and ionizing characteristics of the radiations emitted from decaying atoms. Radiopharmaceuticals are substances that are localize in specific organs or tissues. They emit gamma rays that can pass through tissue and can be detected externally by special types of cameras: gamma or PET cameras. For therapy, radiopharmaceuticals delivered a high dose of radiations, specifically to the targeted tumor. A therapeutic radiopharmaceutical emits particulate radiation that typically travels short distances in body tissues, where it either destroys or damages the surrounding cells in the area to which it has distributed.

(b) Classifications - Medical application of radioisotopes and radiation can be broadly classified into two categories including radiopharmaceutical and radiation therapy. A radiopharmaceutical is a radioactive compound which, when administered for the purposes of diagnosis or therapy, elicits no physiological response from the patient. Radiation therapy involves the use of ionizing radiation to destroy cancer cells. The aim of radiation therapy is to impart specific amounts of the radiation at tumors or parts of the body where there is/was disease. Since cancers can occur anywhere in the body, a wide range of equipment is necessary for optimum management.

III RADIOPHARMACEUTICALS

(a) Characteristics - Radiopharmaceuticals, as mentioned above are radiolabelled molecule that exhibit desired biological behavior, either for diagnosis or therapy. If brief they can be considered to be composed of

- a radionuclide
- a carrier molecule (proteins, antibodies, inorganic, organic compounds).

In diagnosis, a radiopharmaceutical containing a radionuclide is administered to a patient and the radiopharmaceutical accumulates in a biological tissue or organ that it is selectively targeted. The organic or biological substrate to which this radionuclide is attached is designed to favor the accumulation of the administered radiopharmaceutical in the targeted cell, tissue, or organ. The radiation emitted from the accumulated radioactivity will then be detected by external measuring devices such as a gamma camera or positron emission tomography to reconstruct to images for diagnostic purposes. For therapy, a cytotoxic level of radiation dose is delivered to disease site by the decaying radionuclides in the radiopharmaceuticals accumulated in the disease site. The diagnostic imaging technique, also called scintigraphy, is performed with radiopharmaceuticals labeled with γ-emitting radionuclides. The physicochemical properties of certain radionuclides allow their use for a therapeutic purpose, based on the ability to deliver cytotoxic level of radiation dose due to the ionizing radiation emitted by the labeled substance. When these vectors are used in association with therapeutic radionuclides, essentially β- or α-emitters, this is described as vectorized or metabolic radiotherapy.

The ideal radiopharmaceutical should:

(i) Emit radiation at a desirable energy level.
(ii) Have a short half-life
(iii) Have high location selectivity.
(iv) Be easy to prepare.
(v) Be inexpensive.
(vi) Exhibit no toxicity.

(b) Mechanisms of localization of radiopharmaceuticals- The mechanism of localization of a radiopharmaceutical in a particular target involves one of the following:

(i) Active Transport: This is the metabolic pathway in the body for moving a radiopharmaceutical across a cell membrane and into the cell. $Na^{123}I$ for thyroid imaging.

(ii) Phagocytosis: This involves physical entrapment of colloidal particles by Kupffer cells in the RE System. Example: ^{99m} Tc- sulfur colloid for liver/spleen imaging.

(iii) Capillary blockade: This involves the intentional microembolization of a capillary bed with particles which offer the scope for external visualization of the perfusion of this capillary bed. Example: ^{99m} Tc-MAA for pulmonary perfusion imaging.

(iv) Cell Sequestration: Injection of damaged RBC's to produce a spleen scan with no visualization of the liver. Example: heat damaged autologous ^{99m}Tc-RBC's.

(v) Simple/exchange diffusion: a mechanism whereby a radiotracer diffuses across cell membranes and then binds/attaches to a cell component. Example: $Na^{18}F$ for bone imaging.

(vi) Compartmental Localization: placement of a radiotracer in a fluid space and imaging of that fluid space. Example: ^{99m}Tc-HSA for MUGA's, ^{111}In-DTPA for cisternograms, ^{133}Xe gas for pulmonary perfusion.

(vii) Chemisorption: surface binding of radiopharmaceutical to a solid structure, e.g., ^{111}In-platelets bound to surface of an active thrombus.

(viii) Antigen/antibody reaction: uptake at tumor site due to specific binding of radiolabeled antibody to surface antigens on tumors.

(ix) Receptor-binding: binding of radiopharmaceutical to high-affinity receptor sites. Example: ^{68}Ga-octreotide for localization of neuroendocrine and other tumors based on binding of a somatostatin analog to receptor sites in tumors.

IV DIAGNOSTIC RADIOPHARMACEUTICAL

(a) Role- Diagnostic radiopharmaceuticals provide information about the functioning of a person's specific organs to make a quick, accurate diagnosis of the patient's illness. The thyroid, bones, heart, liver and many other organs can be easily imaged, and disorders in their function revealed. They play a critical role throughout every phase of disease, including:

(i) Diagnosis and staging
(ii) Treatment planning
(iii) Monitoring response to therapy
(iv) Monitoring for recurrent/residual disease

(b) Properties of the ideal diagnostic radiopharmaceutical

(i) Pure gamma emitter:The radioisotope should be a pure gamma ray emitter, decaying by either electron capture or isomeric transition.

(ii) Energy of Gamma Rays: 100 < gamma energy < 250 keV.

(iii) Effective half-life: Ideally, a radiopharmaceutical's effective half life equals approximately 1.5 times the duration of the diagnostic procedure.

(iv) Photon Abundance: As high as possible.

(v) High Target to non-target ratio: 5:1 minimum for planar imaging, about 2:1 for SPECT imaging.

(vi) Easy Availability and inexpensive.

(vii) Patient safety: The radiopharmaceutical should exhibit no toxicity to the patient.

(viii) Simple preparation and Quality Control

Most radiopharmaceuticals used in diagnostic nuclear medicine procedures emit gamma radiation and have relatively long physical half-lives. The amount of activity required for the formulation of radiopharmaceutical used is carefully chosen to provide the least amount of radiation exposure to the patients, but at the same time ensure an accurate test. Localization of gamma rays emitted by single photon-emitting radiotracers is accomplished by an Anger scintillation camera (gamma camera), which converts the gamma rays to light photons via sodium iodide scintillation detectors. Images of the bio- distribution of injected diagnostic radiopharmaceutical in the body can be acquired using a gamma camera to obtain information about the function of tissues. There are several techniques of diagnostic nuclear medicine. The word "Scintigraphy" ("scint") refers to all the two-dimensional nuclear medicine imaging techniques. Such 2D images, known as planar scintigrams, are degraded by the superposition of non-target activity from the 3D body which restricts the measurement of organ function and prohibits accurate quantification of that function. Computer processing of scintigrams can increase the accuracy with which the image approximates the activity distribution, selectively enhance normal or abnormal structures of interest and optimize the use of the display system presenting the image. "SPECT" is a 3D

tomographic technique that uses gamma camera data from many projections and can be reconstructed in different planes. "Positron emission tomography" (PET) uses coincidence detection to image functional processes.

For medical diagnosis applications the workhorse isotope is ^{99m}Tc which is is obtained from radionuclide generator containing ^{99}Mo owing to its suitable half life (~ six hours), readily available in the form of ^{99}Mo/^{99m}Tc generator; extremely convenient for use in hospitals, gamma ray energy 140keV which can be detected with high efficiency, decay by "isomeric transition" with emission of single gamma rays and low energy electrons and have versatile chemistry. Some of the technetium labelled compounds and their clinical uses manufactured and supplied by BRIT are shown in Table:1.

Table-1
Technetium labelled compounds and their clinical uses

Radiopharmaceutical	BRIT Kit Code	Short form	Clinical Use
^{99m}Tc-Phytate	TCK-16	^{99m} Tc-Phy	Liver imaging
^{99m}Tc Sulphur Colloid	TCK-5	^{99m}TcS/C	Liver and spleen imaging
^{99m}Tc Mebrofenin	TCK-39	^{99m} Tc-mebro	Hepatobilliary function
^{99m}Tc Methylene di Phosphonate	TCK-30	^{99m}Tc-MDP	Bone Scan
^{99m}Tc Red Blood Cells	TCK-38	^{99m}Tc-RBC	Cardiac Function and Blood Pool Scans
^{99m}Tc Mibi	TCK-50	^{99m}Tc-MIBI	Myocardial Perfusion (Heart Muscle Blood Flow)
^{99m}Tc Diethylene Triamine PentaAcetic Acid	TCK-7	^{99m}Tc-DTPA	Renal Function
^{99m}Tc Ethylene di cysteine	TCK-43	^{99m}Tc-EC	Renal tubular function
^{99m}Tc Glucoheptonate	TCK-15	^{99m} Tc-GHA	Kidney imaging
^{99m}Tc Ethyl cystienate dimer	TCK-42	^{99m}Tc- ECD	Brain Scan and Scans for Infection

Table 2
Principal radionuclides used in diagnostic radiopharmaceuticals

Radionuclide	*Symbol*	*Half-life*	*Mode of decay*	*Energy of gamma(s) (keV)*
Technetium-99m	^{99m}Tc	6.01 h	isomeric transition	141
Iodine-123	^{123}I	13.27 h	electron capture	159
Indium-111	^{111}In	67.31 h	electron capture	171, 245
Gallium-67	^{67}Ga	78.27 h	electron capture	91, 93, 185, 209, 300

Positron Emission Tomography (PET) is a specialised nuclear medicine procedure that uses positron emitting radiolabeled tracer molecules to measure biological activity. The more commonly used positron-emitting radionuclides are listed in table 2, and it can be seen that many of them are either directly biogenic or can be easily incorporated into naturally occurring biological substances. To date, the most widely used PET tracer has been ^{18}F-fluoro-deoxyglucose (FDG). This substance is taken up into cells using the same mechanism as normal glucose, but once in the cell, it cannot be further metabolized and remains trapped there. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is used to determine abnormal glucose metabolism in tumours and other sites. It has general applications in all areas where abnormal glucose metabolism may be present including in circumstances such as differentiating the tumour from scar tissue; evaluating the presence of the tumour in light of rising tumour markers and normal morphological imaging techniques; and assessing response to therapy where other techniques are deemed to be unhelpful. PET images of physiology can also be used to detect pathological changes well in advance of other diagnostic imaging procedures, or a combination of other test.

Table: 3
Positron-emitting radionuclides using in PET imaging.

Radionuclide	Half-life(min)	Maximum positron energy (MeV)
^{11}C	20.3	0.96
^{13}N	9.97	1.19
^{15}O	2.03	1.70
^{18}F	109.8	0.64

BARC along with BRIT operates the 16.5 MeV Medical Cyclotron recently set up in Radiation Medicine Centre (RMC), Parel, Mumbai producing special radiopharmaceuticals like ^{18}FDG for Positron Emission Tomography (PET) studies and supplies are already being made to Hinduja Hospital and Bombay Hospital apart from in-house requirement of RMC.

(c) Therapeutic radiopharmaceutical- Therapeutic radiopharmaceutical is designed to deliver therapeutic doses of ionizing radiation to specific disease sites for cure, disease control or pain palliation. The ionizing radiation induces irreversible damage to the DNA molecule inside the cell, thereby stopping these cells from continuing to grow and divide. In radionuclide therapy, the biological effect is obtained by energy absorbed from the radiation emitted by the radionuclide. Therefore, a radionuclide used for targeted therapy must emit particulate radiations which have relatively short path length thereby depositing the radiation energy in a small volume of cells.

Radionuclides used for targeted therapy should decay by alpha, beta or Auger electron emission. Within each category of these radionuclides, there are multiple radionuclides with a variety of tissue ranges, half-lives, and chemistries which offer the attractive possibility of optimizing targeted radionuclide therapy to the needs of an individual situation. Unlike tumor-directed drugs and toxins, which kill only the directly targeted cells, a unique feature of radionuclides is that they can exert a 'bystander' or 'crossfire' effect, potentially destroying adjacent tumor cells even if they are not targeted by the radiopharmaceutical. A systemically administered targeted radiotherapeutic agent has the potential to eliminate primary tumor site as well as metastasis and other malignant cell populations undetectable by diagnostic imaging.

(d) Properties of the ideal therapeutic radiopharmaceutical

(i) Particle emitter such as β or α with a small γ component for dosimetric purpose.
(ii) Medium/high energy (>1 MeV).
(iii) Half life in days.
(iv) High target: non target ratio.
(v) Minimal radiation dose to non target organ in patient and Nuclear Medicine personnel
(vi) Safety for administration & non toxicity.
(vii) Inexpensive, readily available radiopharmaceutical.
(viii) Simple preparation and quality control requirement if manufactured in house

(e) Types- The efficacy of a therapeutic radiopharmaceutical depends on the radiotoxic nature of the radionuclide and the targeting ability of the vector used for carrying the radionuclide to the proliferating sites. Therapeutic radiopharmaceuticals currently used for treatment of various types of diseases are as follows.

(i) **Thyroid cancer:** Use of iodine-131 for the treatment of thyroid cancer patients is a key example of the early and most successful radionuclide therapy. It is far too quickly forgotten that the successful therapy of thyroid cancers is inconceivable without the use of iodine-131. More than 90% of cases of this cancer are treated and definitively cured with this nuclear medicine method, and this has been the case for the past fifty years.

(ii) **Neuroendocrine Tumors (NETs) using ^{131}I-mIBG:** Metaiodobenzylguanidine (mIBG) is a catecholamine analogue similar to noradrenalin, which accounts for the uptake of this radiopharmaceutical in catecholamine storage vesicles. Use of mIBG labeled with ^{131}I is useful to image as well as treat sympatomaticmedulla neoplasms, such as neuroblastoma and pheochromocytoma.

(iii) **Bone pain palliation therapy:** Bone metastasis is a common complication in cancer patients who endure severe bone pain. Bone metastases may occur in almost all tumors at different frequencies, however, prostate, lung, and breast cancer have maximum chance for metastasis. Radiopharmaceutical treatment of metastatic bone pain has emerged as an effective modality that provides palliation

of pain to multiple areas of the skeleton simultaneously without the significant soft-tissue toxicity. The radionculides used and proposed for bone pain palliation have wide ranging nuclear characteristics such as half life, decay energy, availability of imageable photons etc.

(iv) **Radiosynovectomy:** Radiosynovectomy or radiosynoviorthesis is defined as the restoration of inflamed and damaged synovial membrane of the joints after intra articular injection of radionuclide based preparations. In this procedure, a beta-emitting radionuclide in colloidal or particulate form is injected into the articular cavity in which they are phagocytized by the outermost cellular layer of the synovial membrane and deliver radiation dose to the synovium without excessive irradiation of surrounding tissue.

V TREATMENTS

(a) Treatment of hepatocellular carcinoma (HCC) and hepatic malignancies: Hepatocellular carcinoma (HCC) is a malignant tumor of the liver hepatocyte. It may present either as primary liver cancer or as secondary liver tumors. Radioembolization is one of the intriguing therapies for the treatment of liver malignancies for administering radiotherapy internally to provide the cytotoxic radiation dose. The technique of trans-arterial radio-embolization exploits HCC preferential blood supply from the hepatic artery to deliver the radioactive particles which end up in hepatic end-arterioles, allowing localized delivery of therapeutic doses, while sparing the surrounding liver parenchyma. Thus, it is essentially a flow-directed mode of treatment that is dependent on neoangiogenesis. In this modality, ^{131}I or ^{188}Re labeled lipiodol, ^{90}Y or ^{166}Ho labeled microspheres/particles are some of the radiopharmaceuticals that have been extensively studied.

(b) Peptide receptor radionuclide therapy (PRRT): Neuroendocrine tumors (NETs) are relatively rare tumors, mainly originating from the digestive system, able to produce bioactive amines and hormones. These cells are able to synthesize, accumulate and secrete numerous bio-active molecules acting like neurohormones, neurotransmitters and neuromodulators. NETs tend to be slow growing and are often diagnosed when metastatic. Peptide receptor radionuclide therapy is an effective treatment option for patients with well-differentiated somatostatin receptor-expressing neuroendocrine tumors. NETs usually over-express somatostatin receptors, thus enabling the therapeutic use of somatostatin analogues, one of the basic tools, able to reduce signs and symptoms of hormone hypersecretion, improve quality of life, and slow tumor growth. The peptides 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), Tyr3-octreotate (DOTATATE) and DOTA, Tyr3-octreotide (DOTATOC) (brand name Onalta), predominantly targeting sst2, have been granted Orphan Drug status by the European Medicines Agency and the US Food and Drug Administration for application in PRRT. Peptide receptor radionuclide therapy (PRRT) with somatostatin analogues ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE has emerged as the effective modality of treatment which demonstrated impressive results on tumor response, overall survival, and quality of life in patients with gastroenteropancreatic neuroendocrine tumors. Besides somatostatin receptor-targeting peptides, multiple other radio peptide analogs were developed targeting several other receptors overexpressed on various tumors. Some of these peptide analogs, including cholecystokinin, gastrin, gastrin-releasing peptide, arginine-glycine-aspartate (RGD)-peptides, and glucagon-like peptide analogs appeared very promising in preclinical and clinical imaging and PRRT studies.

(c) Radioimmunotherapy (RIT): Radioimmunotherapy (RIT) uses monoclonal antibodies as the vector for transport of the radioactivity to cancer cells. The radiolabeled antibodies are directed against various antigens overexpressed on tumor cells or blood vessels formed during angiogenesis. RIT combines the synergistic effects of both radiation and immunotherapy with manageable local and systemic side effects. Beta decay radionuclides have been extensively used for radionuclide treatments and offer better radiopharmaceutical characteristics for design and therapy administration. The unique characteristics of cross fire effect, adequacy of delivery to cell surface added to the ease of labeling, and availability led to widespread use of beta particle radioimmunoconjugates. The improved effectiveness of antibodies labeled with beta emitting radionuclides relates to the phenomenon of "cross fire" or "by-stander" effect, where in the tumor cells within close range of the targeted cell are also, killed secondary to beta ionizing radiation irrespective of the antigen expression.

BRIT produces and supplies a wide range of radiopharmaceuticals to hospitals and medical institutions to enable various diagnostic and therapeutic studies on patients. These products undergo strict, analytical and quality control tests, including sterility pyrogen tests and biodistribution.

VI RADIATION THERAPY

"Radiation therapy" (or "radiotherapy") is the medicine/medical use of ionizing radiation for the treatment of malignant and benign disease. Radiation therapy is used to treat cancer and a few non-cancerous diseases.

(a) Classification- Radiation treatments can be called:

(i) Definitive-to cure,
(ii) Palliative-to treat symptoms, but not cure.

More than half of all cancer patients are treated with radiation therapy sometime during the course of their illness. About half of these are treated for cure, and half for palliation.

(b) The factors, which determine radiation therapy, include

(i) The sensitivity of the tumor to RT,
(ii) the volume of tumor cells to be eradicated and
(iii) The tolerance of the most radiation sensitive vital tissues in the area.

(c) Radiation can be used at different stages of cancer treatment including:

(i) Early stages in an attempt to cure or control the cancer.
(ii) Before surgery to shrink the cancer.
(iii) After surgery to prevent cancer from recurring.
(iv) With surgery or chemotherapy for advanced cancer as an adjunct mode of therapy.

The radiation used for cancer treatment comes either from special machines or from radioactive substances. There are two basic types of radiation therapy. They are external beam radiation therapy (EBRT) or *teletherapy* and internal beam therapy or *brachytherapy.*

(d) External beam radiation therapy (Teletherapy):- With external beam radiation therapy, a machine is used to direct the electromagnetic radiation to the cancer site through the skin. The source of electromagnetic radiation comes from either an electron accelerator (LINAC) or radiation emitted from radioactive elements of isotopes. Majorities of the patients who are treated with radiation therapy are treated with external beam irradiation.

Since cancers can occur anywhere in the body, a wide range of equipment is necessary for optimum management. The treatment machines include linear accelerators, cobalt-60 teletherapy unit, and superficial x-ray machine. External beam therapy can be used to treat the following diseases as well as many others:

(i) Breast Cancer
(ii) Colorectal Cancer (Bowel Cancer)
(iii) Head and Neck Cancer
(iv) Lung Cancer

The radiation therapist brings the patient into the treatment room and places him/her on the treatment couch of the teletherapy machine in exactly the same position that was used for simulation using the same immobilization devices. The therapist carefully positions the patient using the alignment lasers and the marks that had been placed on the patient during simulation. Beams from one or more directions may be used and the beam may be on for as long as several minutes for each field. The treatment process can take 10 to 30 minutes each day and in each sitting normally radiation doses of 2 Gy is given. Patients usually receive radiation treatments once a day, five days a week for a total of two to nine weeks. The total cumulative dose given to the patient will be about 40 -60 Gy. The patient's diagnosis determines the total dose and duration of treatment.

(e) New Evolutions- First developed 85 years ago in England (First teletherapy machine containing 2.5g of Radium was installed at the Middlesex Hospital, London in 1919), advances in technology and a better understanding of its effects on the body have made external beam therapy more refined. As a result, wide varieties of treatments using geometrical shaping and intensity modulation of beams have evolved.

Some of the recent developments are:

(i) Gamma Knife.
(ii) Conformal Therapy.
(iii) Intensity modulated radiation therapy (IMRT).
(iv) Intraoperative radiation therapy.
(v) Postoperative radiation therapy
(vi) Total Body Irradiation (TBI).

BRIT plays a major role in the battle against cancer by supplying cobalt tele-therapy sources to cancer hospitals in the country. To meet the growing demand of teletherapy machines, DRHR of the BARC has developed a computerized telecobalt machine Bhabhatron with the TMC.

(f) Brachythyerapy - Brachytherapy is a word derived from the ancient Greek words for short distance or close (*brachy*) and treatment (*therapy*). The term is generally used to describe the use of radioactive isotopes in the treatment of cancer and benign diseases. This allows for a very high dose of radiation to be given to the cancer while reducing side effects. Brachytherapy implants can be either temporary or permanent, depending on the site being treated and the isotope being used. Patients can also be treated by different strengths of isotopes, where either a low dose of radiation is delivered over several days to months, or a very high does of radiation is delivered in a matter of minutes via a temporary catheter.

A variety of different radioactive sources have been used in brachytherapy. Table.4 gives a summary of their characteristics.

Brachytherapy can be used to treat cancer in different part of the body including breast, lungs, eye, prostate, cervix using wide varieties of apparatus and applicators.

Table 4
Characteristics of radionuclides used for brachytherapy

Radionuclide	Typical form	Typical application	Half life
^{60}Co	pellets	HDR remote after loading	5.27 years
^{125}I	seeds	Permanent or temporary volume implants	60 days
^{137}Cs	needles, pellets, tubes	LDR remote afterloading	30 years
^{192}Ir	hairpin, wires, HDR sources	Interstitial implants, HDR and LDR remote afterloading	74 days
^{198}Au	seeds	Permanent volume implants	2.7 days
^{226}Ra	needles	Not commonly used any more	1600 years

VII CONCLUSION

Radioisotopes play a significant and indispensable role in studying and understanding biological processes, viewing internal biological structures and processes for diagnosis of abnormal conditions, and in cure and alleviation of sufferings of cancer patients. With the availability of large number of diagnostic agents, SPECT and PET are matured technologies and is the mainstay of functional diagnostic imaging. Treatment of cancer with radioisotopes provides effective cure and the palliation of intractable symptoms. In a country like India, where more than 70% patients present in advanced and inoperable stages, radiation therapy plays an important role. While PET has seen the maximum growth in the last 15 years, next phase of growth of nuclear medicine is expected to be in radionuclide therapy. The new imaging modalities that appeared on the market at this very beginning of the new century and the new molecules and therapeutic technologies associated to the radioactivity open a very encouraging window that fascinates experts from other medical disciplines, and more particularly the oncologists, the hematologists and the neurologists. Cancer treatment remains at the forefront of any new therapeutic modality.