NUCLEAR MEDICINE FOR THE DIAGNOSIS AND THERAPY OF CANCER

M.R.A. Pillai Ph.D.; D.Sc

Molecular Cyclotrons, Puthuvype, Ernakulam, Kerala 682 508

Email: pillai.m.r.a@gmail.com

Abstract

Nuclear medicine is a medical faculty used for the diagnosis of a large number of diseases. It also has a niche in the treatment of certain type of cancers. There are two imaging modalities available in nuclear medicine, SPECT and PET. Radiopharmaceuticals made using a gamma emitting isotope called ^{99m}Tc is used for SPECT imaging. PET uses radiopharmaceuticals labelled with radioisotopes decaying by positron emission tomography. Radiopharmaceuticals made of both α and β- emitting radioisotopes are used for targeted therapy. India is one of the early entrant in nuclear medicine and that leadership position continues.

Introduction

The quest to use radioactivity for disease management is as old as the discovery of radium by Marie Curie and Pierre Curie in the year 1898. Radium-226 was tried as a medicine to treat a variety of diseases but miserably failed. The treatment resulted in unwanted radiation exposure without any commensurate benefits and thus abandoned. The use of atomic bombs in Hiroshima and Nagasaki in August 1945 brought the widespread awareness of the damages of radiation making the people scary of the use of radioactivity. However, once the war ended scientists started working towards the beneficial uses of radiation and radioisotopes in medicine which were the bye products of the reactors made for making nuclear weapon materials. The result was the emergence of two important medical fields namely radiotherapy and nuclear medicine.

Nuclear Medicine

Nuclear medicine is a faculty of medicine in which radioactive formulations called ‘radiopharmaceuticals’ are administered to the patients. Radioisotopes decaying by β- or alpha

particles emission are used for therapy. Radioisotopes decaying by emission of β+ particles or emitting gamma photons are used for diagnostic imaging.

Diagnostic Nuclear Medicine

There are two imaging modalities, single photon emission computed tomography (SPECT) and positron emission tomography (PET). SPECT most commonly uses a radioisotope called technetium-99m having a half-life of 6 hours. Technetium-99m emits low energy (140 keV) gamma photons and is ideal for imaging. It gives low radiation dose to the patient as well as the attenuation of the 140 keV gamma photons in the body is minimal. Technetium-99m is eluted from ^{99}Mo/^{99m}Tc generator as and when needed in the nuclear medicine department. The generator can be used for a week as the half-life of ^{99}Mo is 67 hours. Molybdenum-99 used in the generator is produced in nuclear reactors.

Technetium-99m is part of the formulation of different radiopharmaceuticals which are used for imaging organs such as heart, liver, kidney and brain. It also has a major role in cancer management. or e.g. a bone scan using ^{99m}Tc-MDP (methylene diphosphonate) is used for imaging cancer patients suspected to have bone metastasis.

Patients needing investigations are injected with the specific radiopharmaceutical. After a predefined time, the radioactivity distribution within the body is measured using an instrument called gamma camera. A gamma camera contains a large NaI(Tl) crystals and the radioactivity emitting from the body of the patients is measured and processed to images. Modern gamma cameras have multiple heads containing the NaI(Tl) crystals which can move around the patient to collect tomographic images (Fig.1). A rough estimate is that over 20 million SPECT studies are done annually the world over using ^{99m}Tc radiopharmaceuticals.

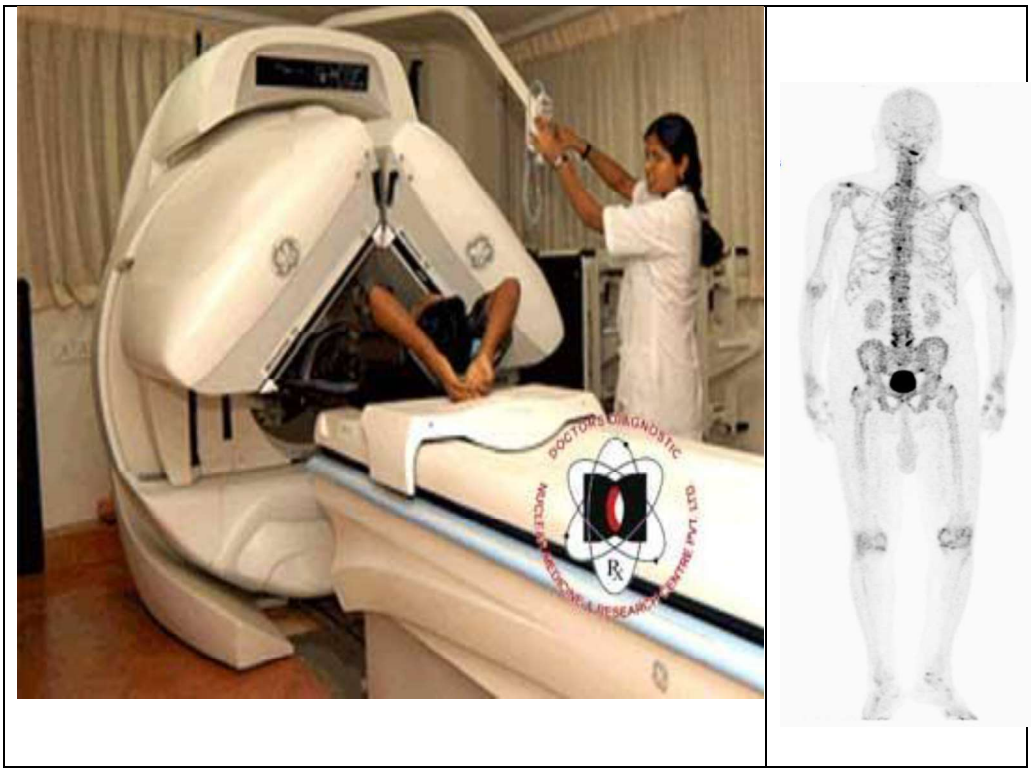

Fig.1. A patient undergoing SPECT imaging. The planar image on the right is of a patient injected with ^{99m}Tc-MDP (methylene diphosphontate). Abnormal uptakes seen in certain parts of the bone correspond to bone metastasis.

Positron emission tomography (PET)

PET imaging uses radioisotopes decaying by emission β+ particles or positrons. This mode of decay is common in neutron deficient isotopes. Neutron deficient isotopes are produced in cyclotron. A typical example is the use of fluoirine-18 having a half-life of 110 min. The positrons emitted by the decaying radionuclide after losing its kinetic energy annihilates with an electron and in this process emits two gamma photons in the opposite directions. A PET camera having scintillation crystals arranged in 360 degree is used to measure the radioactivity. A coincidence counting technique is used in which the two gamma photons are simultaneously measured and reconstructed to images. PET imaging has better resolution as compared to SPECT imaging.

The present trend is to use fusion imaging in which both PET and SPECT are fused with computed tomography (CT). PET-CT imaging is an essential part of cancer management and

used for staging, therapy response assessment and recurrence evaluation. The most common radiopharmaceutical used for this purpose is [^{18}F]fluoro-2-deoxy-2-D-glucose (FDG) which is a proliferation tracer and taken up by most fast growing cancers. There are other PET radiopharmaceuticals using both ^{18}F and ^{68}Ga radioisotopes. All PET radioisotopes with a few exception are produced in cyclotrons. A PET imaging study in a nuclear medicine department is shown in Fig.2.

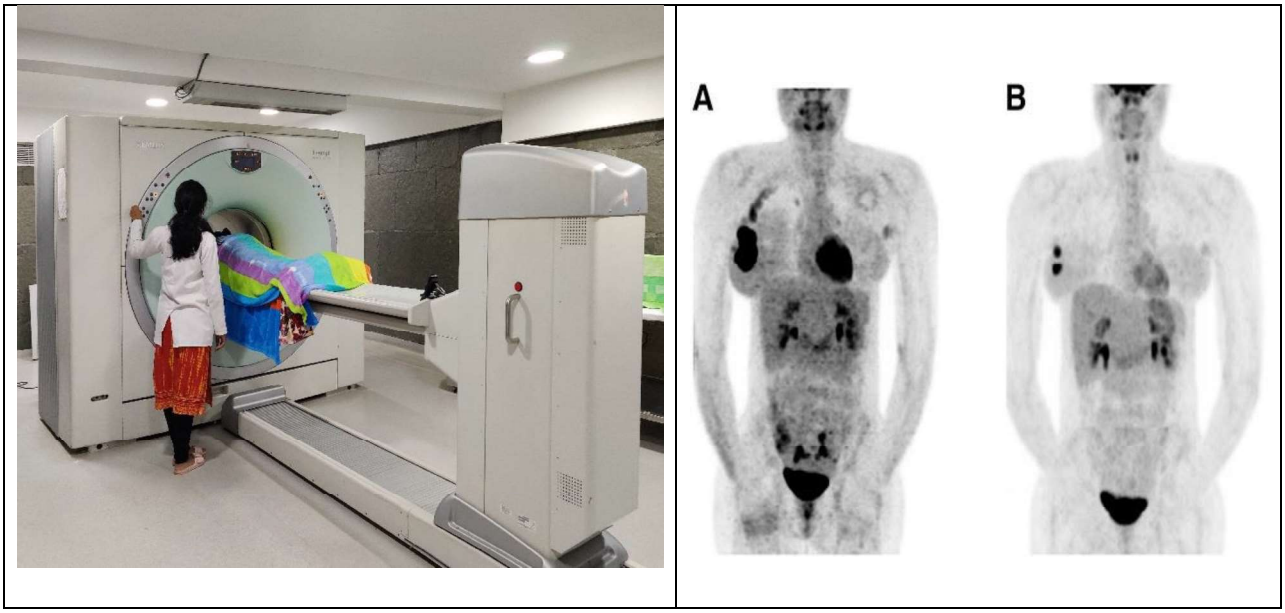

Fig.2: A patient undergoes a PET-CT imaging study (Left). The patient was injected with FDG and the images are acquired after an hour. The figure on the right shows the PET images of a patient before and after treatment. Significant reduction in the uptake of radioactivity is seen in the image on the right indicating that the tumour load has significantly reduced, an indication that the treatment is in the right direction.

Targeted radiotherapy of cancer

Targeted therapy is the delivery of radioactivity directly to the cancer cells where it decays and deposits the energy in the vicinity to kill them. Targeted therapy is known for more than eighty years and used for the treatment of thyroid cancer. A patient suffering from thyroid cancer undergoes a total removal of the gland and a large dose of iodine-131 is given orally to destroy the remnant cancer cells. Papillary and follicular thyroid carcinoma which are the major cancers of the thyroid are completely curable. This therapy is in practice since 1946. Unfortunately there were no other similar success stories for targeted therapy for a very long time.

Bone pain palliatives

Bone metastasis is a major problem during the final stages of cancer especially that of the breast and prostate cancer. The major manifestation is pain which reduces the quality of the life of the patients. Radiopharmaceuticals labelled with β- emitting radioisotopes are used as pain palliatives. These include, ^{153}Sm-EDTMP and ^{177}Lu-EDTMP. Radium-223, an alpha emitting radioisotope as $^{223}RaCl_2$ is also used as a bone pain palliation agent. These radiopharmaceuticals accumulate in metastatic bone and destroy the cancerous cells and reduce the pain.

Theranostic nuclear medicine

'Theranosis' is a term used for a combination of diagnosis and therapy of diseases. Though this term was never used, diagnosis and treatment of thyroid cancer using radioiodine (^{131}I) is the best example of theranostic medicine. The amount of activity to be injected in each patient is decided based on the diagnostic image obtained from the patient. Hence, this is also a 'personalized medicine'. Off late the radiopharmaceutical scientists have succeeded in developing a few theranostic pairs of radiopharmaceuticals. These radiopharmaceuticals use either peptides or enzyme inhibitors as carrier molecules to deliver particle emitting radionuclides to the cancer sites. These small molecules have the advantage that they accumulate in the tumour fast and the rest of the radiopharmaceuticals get excreted. Hence, the tumour to back ground ratio is very high.

These peptides or inhibitor molecules are labelled with diagnostic radioisotopes such as ^{18}F, ^{68}Ga or ^{99m}Tc. PET or SPECT imaging studies are done to visualize the tumours which is followed with the administration of high dose of β- or alpha particle emitting radioisotopes tagged with the same peptide or inhibitor molecules. Lutetium-177 is one of the most commonly used radioisotope for targeted β- therapy whereas ^{225}Ac is used for targeted alpha therapy. Lutetium-177 has a half-life of 6.73 days and emits medium energy β- particles. Actinium-225 has a half-life of 10 days and decays by emission of four alpha particles thereby delivering a large quantum of energy within the tumour cell.

Patients suffering from a rare cancer called neuroendocrine tumour (NETs) are one of the major beneficiaries of this innovative therapy. A peptide called DOTATATE is used for carrying the radioisotope to the tumour site. DOTATATE is an analogue of the somatostatin hormone.

Somatostatin receptors are overexpressed in patients suffering from neuroendocrine tumours. Hence, DOTATATE is an ideal vector to carry the radioisotopes to the tumour. ^{68}Ga-DOTATATE is used for PET imaging of NETs patients.

Therapy using ^{177}Lu-DOTATATE is done if the tumour load is high, distributed and inoperable. 200-250 mCi of ^{177}Lu-DOTATATE is used for each cycle of therapy. Part of the ^{177}Lu-DOTATATE accumulates in the tumour and the remaining gets excreted in a few hours. The radiopharmaceutical accumulated in the tumour is not redistributed and decays completely in the tumour cells thereby killing them. 4-5 cycles of therapy are done which provide relief to the patients. Likewise, ^{68}Ga-PSMA (prostate specific antigen inhibitor) is used for imaging and ^{177}Lu-PSMA is used for the treatment of inoperable prostate cancer. Very little side effects are exhibited in these sort of therapies. The treatment is done in an outpatient ward and the patient is released on the same day.

Status of Nuclear Medicine in India

Thanks to the visionary leadership of Homi Jehangir Bhabha, the first nuclear reactor in Asia, Apsara became critical on 4th August 1956. Nuclear medicine in India started immediately thereafter with the setting up of an isotope program. The commissioning of the CIRUS reactor in 1960 and Dhruva reactor in 1985 increased the capacity of production of radiosiotopes significantly.

The Radiation Medicine Centre (RMC) was established adjacent to the Tata Memorial Hospital in Parel, Mumbai. RMC was in the forefront to establish nuclear medicine and also provided trained manpower for running nuclear medicine departments not only in India but also in many other countries. The first medical cyclotron was set up in RMC in 2002 starting PET imaging in India.

Nuclear medicine is well-established in India with 415 nuclear medicine departments operating in major hospitals and as independent units. Most of these centres operate SPECT, PET and therapy. As of today, there are more than 330 PET-CTs as well as four PET-MR machines. There are 100 SPECT-CT and 206 SPECT/planar cameras. The training of nuclear medicine physicians and technologists is now done by many of the major Institutes and Hospitals.

India has 23 cyclotrons making PET radiopharmaceuticals. But these cyclotrons are distributed in 11 states. On a conservative estimate, India needs about 100 cyclotrons to cover the supply of PET radiopharmaceuticals in the country. At least half of the present cyclotrons are run by private entrepreneurs and this trend will continue in future. There is a good business potential in radiopharmaceuticals production and PET-CT imaging.

Dhruva is the only research reactor available for radioisotope production in India. This reactor is in the 40^{th} year of operation and will be due for decommissioning in a few years. Hence, building a high flux ($>5x10^{14} n.cm^{-2}.s^{-1}$) reactor is an essential need to sustain the continued growth of nuclear medicine in India. The efforts by the Department of Atomic Energy to build the new reactor in the public-private-partnership (PPP) mode need to be accelerated, the fruition of which will put India as major player in radioisotope and radiopharmaceuticals field in the World.

About the Author

Dr. M.R.A. Pillai Ph.D.; D.Sc. is a radiopharmaceutical scientist with over forty-five years of active academic and research experience. He held positions in BARC; BRIT; University of Missouri Columbia (UMC), International Atomic Energy Agency (IAEA) and at the Homi Bhabha National Institute. He published over 250 journal papers, three books and edited 14 books for the IAEA. He is currently working as Group Director, Molecular Group at Cochin and supporting cyclotron and nuclear medicine programs of the group. He travelled to 55 countries mostly to extent technical support to their programs related to isotope production and radiopharmaceuticals.