Management of Cancer Patients using Radiopharmaceutical Therapy

D. Rajapaksha, P. Rathnayake and S. R. D. Rosa
Sri Lanka Atomic Energy Board

Cancer is the major cause of morbidity and mortality around the globe. Cancer shows a significant annual increase, approximately 30,000 new cases were recorded in 2021. It has become one of the major health burdens in Sri Lanka. The death rate due to cancer has doubled over the last 25 years and this has become the second commonest cause of hospital mortality in Sri Lanka. Female breast cancer has surpassed oral cancer as the most commonly diagnosed cancer type. There were an estimated 29,604 new cases and 16,691 cancer deaths in Sri Lanka in 2020. This figure is expected to increase by 23% every year till 2030. For cancer treatments and patient managements, Radiopharmaceuticals are widely used in the PET-CT scanning. 18F-fluorodeoxyglucose (FDG) PET/CT is a major imaging modality for cancer imaging, assisting diagnosis, staging of patients with newly diagnosed malignancy, restaging following therapy and surveillance.

Radionuclides, and the radiopharmaceuticals derived from them, are an established tool for key investigations in numerous disciplines of the life sciences and for diagnosis and treatment of many life-threatening diseases. Radiopharmaceuticals are produced by specialized machine called Cyclotron. A key component of the successful operation of a PET(Positron Emission Tomography) center is the on-demand availability of radiotracers (radiopharmaceuticals) labelled with suitable positron emitting radioisotopes. Out of the hundreds of positrons emiting labelled radiotracers, 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) is the most successful and widely used imaging agent in PET today. FDG is a glucose analog, and it tends to accumulate in the tissue with high glucose demand like tumors and inflammatory cells.

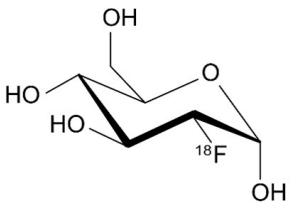


Figure 1: Molecule of 2-[18F]-fluoro-2-deoxy-D-glucose (FDG)

Whole body PET imaging with FDG measures glucose metabolism in all organ systems with a single examination, thus improving detection and staging of cancer, selection of therapy, and assessment of therapeutic response. Although it begins within a specific organ, cancer is a systemic disease, the most devastating consequences of which result from metastases. The FDG–PET method often allows for the early detection and quantification of metastasis; thus FDG–PET has found applications in the diagnosis, staging, and restaging of several clinical conditions including lung cancer, colorectal cancer, lymphoma, melanoma, head and neck cancer, and oesophageal cancer. Similarly, clinical applications in the fields of neurology, cardiology as well as inflammation/infection are on the rise. These radiopharmaceuticals have very short half-life radioisotopes, so they cannot be imported and stored in advance.

What is a Radiopharmaceutical?

Radiopharmaceutical is a radioactive compound for diagnosis and therapeutic treatment. They are injectable drugs. 95% of the radiopharmaceuticals are used for diagnostic purposes. Radiopharmaceutical is consisting with two Components a Radionuclide and a Pharmaceutical. PET is a nuclear medicine imaging technology that provides moderate-resolution, sensitive images of the biodistribution of a radiotracer in vivo. Hence, PET imaging with a suitable radiopharmaceutical can provide interpretation of a biological function. In addition to applications for diagnosis of diseases, PET imaging can provide important insights for both drug discovery and development and for potentially limiting side effects due to off-target binding. PET is based on the simultaneous detection of photons that are linearly traveling in opposite directions. Coincidence detection is used to determine the annihilation.

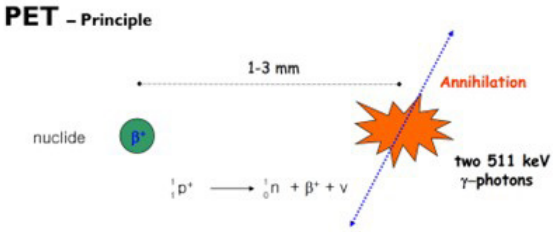


Figure 2: Principal of Positron emission tomography (PET) Scanning

Positron-emitting radiopharmaceuticals labeled with the short half-life positron emitting radionuclide fluorine-18 (t1/2=110min) are being increasingly used in clinical diagnosis. Fluorine-18 has relatively long half-life of 110 min compare with other radionuclides.

Table 1: Half Life of Radionuclides

radionuclide	half-life (min)	energy (keV)
C-11	20.4	511
N-13	10	511
O-15	2.07	511
F-18	110	511
Ga-68	68	511
Cu-64	12.7 h	511

^{18}F has the most ideal half-life for labeling of radiopharmaceuticals (small organic molecules, peptides, aptamers, and proteins) and has a unique and diverse chemistry for introduction into various molecules. In medicinal chemistry, fluorine is a favorable atom in drug development due to its physical properties including small van der Waals radius (1.47 Å), high electronegativity, and ability to form a strong bond with carbon (C–F energy bond of 112 kcal/mol), which in comparison to a carbon–hydrogen bond (C–H = 98 kcal/mol) is more thermally stable and oxidation resistant. Fluorine can act as a bioisostere with hydrogen (size and valence electrons) and oxygen (size and electronegativity). As a result of its significance in the pharmaceutical field, several selective fluorination reagents for nucleophilic (F^-) and electrophilic (F^+) incorporation have been developed and have become commercially available.

Cyclotron and F-18 Production

Medical Cyclotron technology started new era in Nuclear Medicine diagnosis. In the Cyclotron, particles such as protons, deuterons are accelerated and made to bombard to a suitable target material to produce positron-emitting radioisotopes. A charged particles can be accelerated during circular motion by combining magnetic and electric field. The positron emitters are produced using stable, non-radioactive isotopes by the (p, α), (p, n) or (d, n) reactions. The neutron activation of the surrounding medium draws the major attention in radiation safety. After irradiation, radioactive gases and liquids produced in the target is normally transferred out of the cyclotron vault into the hot laboratory through tubing.

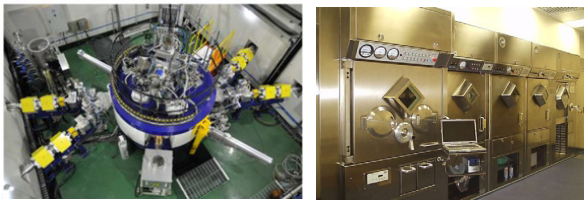


Figure 3: Cyclotron Facility and radiopharmaceutical synthesis in hot cells

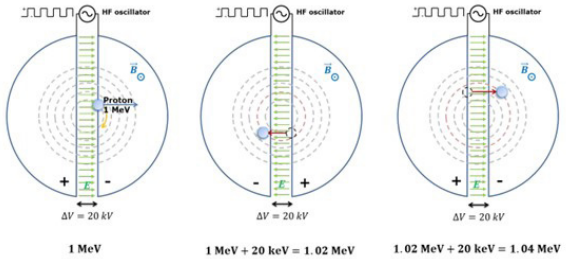


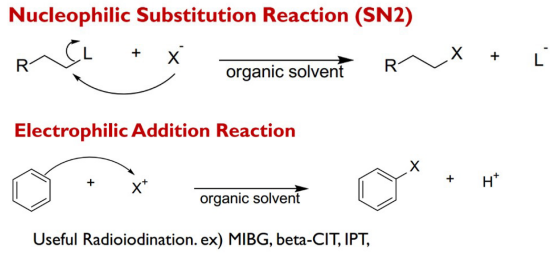
Figure 4: Electric field for accelerating (electric potential)

Cyclotron produced radioisotopes are incorporated or tagged with chemicals to produce radiopharmaceuticals. Chemical processing is carried out in specific units built for the purpose. A chemical synthesis module is use to prepare radiopharmaceutical from the positron emitting radioisotopes produced in a cyclotron. The cyclotron vault is the area with the highest amount of radioactivity, when the cyclotron beam is 'ON' for irradiation of the targets. After irradiation produced radioactive materials are transferred to the hot-cells. Fluorine-18 is produced primarily by proton (^{1}H) irradiation of ^{18}O, a stable naturally occurring isotope of oxygen. When the target is liquid $H_2{}^{18}O$, an aqueous solution of ^{18}F-fluoride ion is obtained.

$$^{18}_{8}O + ^{1}_{1}H \rightarrow ^{18}_{9}F + ^{1}_{0}n$$

Figure 5: The nuclear reaction for the production of ^{18}F.

The production method used is depend on the desired subsequent chemical reactions; ^{18}F-fluoride is produced for use as a nucleophile, while ^{18}F-fluorine is produced for use in electrophilic methods.



The specific activity (SA = radioactivity/mol) is the key differences between these two chemical forms synthesis ^{18}F isotope. Nucleophilic ^{18}F-fluoride is produced by the efficient nuclear reaction ^{18}O(p, n)^{18}F to give a high amount of radioactivity (>370 GBq/batch). Fluorine can replace hydrogen with minimal steric interference: maintaining favorable interaction with the target. Fluorine is also often used as a substituent in pharmaceuticals because it can increase the activity, potency, and stability of biologically active compounds.

How to Introduce Single Fluorine Atom into Aliphatic Organic Compound?

Although fluoride ion is a strong nucleophile, it is non-reactive for nucleophilic substitution in aqueous solution as it has bonds with the surrounding hydrogen in water molecules. To achieve nucleophilic fluorination, the ^{18}F-fluoride must be substantially dehydrated by evaporation of the water and subsequent displacement reactions conducted in polar aprotic organic solvents. The solubility and nucleophilicity of fluoride ion in organic solvents is enhanced by the addition of a phase transfer catalyst (PTC) (such that the cryptand Kryptofix 2.2.2 complexes potassium) or by the addition of bulky tetrabutylammonium cation.

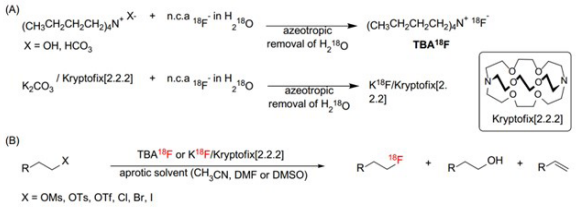


Figure 6: Synthetic routes of known radiotracers by 18F-aliphatic nucleophilic mechanism.

Common anionic leaving groups are halides such as Cl^-, Br^-, and I^-, and sulfonate esters tosylate (TsO-), mesylates(OMs), triflate(OTf).

Quality Control of Radiopharmaceuticals

With diagnostic radiopharmaceuticals, it is important to have a product with acceptable quality control (QC) parameters in order for the nuclear medicine study to be effective yet not to deliver unnecessary radiation exposure to the patient. However, with therapeutic radiopharmaceuticals it is mandatory to satisfy the guidelines for quality control because otherwise, the results could be life threatening to the patient. Radiochemical purity (RCP) of a radiopharmaceutical is defined as the percent of the total radioactivity present in the desired chemical form in a radioactive pharmaceutical. Without acceptable RCP in a diagnostic radiopharmaceutical, image interpretation can be compromised which can result in a delay of an accurate diagnosis and unnecessary radiation exposure since the nuclear medicine study must be repeated. Unlike the conventional pharmaceuticals, radiopharmaceuticals are often not heat sterilized prior to patient use. Application of aseptic processing is, therefore, of primary importance for microbiological purity of the radiopharmaceutical preparation. This is achieved through production in clean room environment where airborne particles are controlled to reduce the possibility of contaminant particles entering the product, and ultimately the patient.

Since synthetic methods are utilized in the preparation of these PET compounds, analysis of chemical purity is also necessary. To characterize and determine the quantity of potential chemical contaminants in the final product several methods maybe used, including Gas chromatography, HPLC,

spectrophotometry, ion exchange and solvent extractions. Using the example of ^{18}F-FDG, a colorimetric test for the detection of Kryptofix 2.2.2 has been developed to streamline the clinical production of this product. With this test, one can interpret whether the level of Kryptofix 2.2.2 is within the acceptable regulatory limits in the USP monograph for ^{18}F-Fluorodeoxyglucose. Half-life determinations for routine identity testing of PET radiopharmaceuticals of fluorine F-18 fludeoxyglucose (18F-FDG) are commonly performed using a dose calibrator and linear regression analysis. In the example of ^{18}F, the allowable physical half-life is 109.7 minutes, and the acceptable range is 105 to 155 minutes.

Figure 7: Quality Control Laboratory in Radiopharmaceuticals production facility

Establishing Radiopharmaceuticals production facility in Sri Lanka

PET-CT referrals are currently low in Sri Lanka as clinicians have to consider patient's financial status and the limited resources available for such health care services due to lack of cyclotron facilities and the costly ^{18}F-FDG transport. FDG is currently imported from India since the Cyclotron facility has not been established in the country, since over 97% of it decays while being transporting from India due to short half-life. The objective of the establishing a facility is to produce radiopharmaceuticals including ^{18}F-FDG use in PET-CT Scanners needed to improve health care services in Sri Lanka. By establishing such a facility, the country can manufacture and supply ^{18}F-FDG for PET-CT scanners efficiently while saving foreign exchange spent on importation of radiopharmaceuticals and on obtaining the necessary health-care services from abroad. Since the Sri Lanka Atomic Energy Board (SLAEB) is mandated by its Act No 40 of 2014 to utilize peaceful applications of nuclear science and technology for the socio-economic development of Sri Lanka, one of SLAEB's key functions is to build and operate the facility for the production and distribution of radioisotopes. A project to establishment of a Cyclotron in Sri Lanka has started by SLAEB under the technical support of International Atomic Energy Agency (IAEA). The project is now at the awarding stage. Once the project is successfully completed, the life expectancy of cancer patients would be increased while reducing the cost per scan incurred in such patients' management by the government.

Prof. S. R. D. Rosa *is currently serving as the chairman of the Atomic Energy Board, Sri Lanka. Prof. Rosa is an excellent Physics Lecturer and an educator. Professor Rosa obtained his B.Sc. In Physics (Special-First Class) University of Colombo in 1979, M. Sc. in Physics, University of Pittsburgh, Pennsylvania, USA in 1982 and his Ph.D.in Nuclear Physics; University of Pittsburgh in 1987. He has been very instrumental in setting up a medical cyclotron facility and X ray irradiation facility in Sri Lanka.*