7

Nuclear Science and Health

Nuclear 101
Nuclear Science and Health

A Resource Material for Secondary Students and Science Teachers

TABLE OF CONTENTS

Hi there! I'm Radia! In this booklet, you will learn about:

1. *The history of radioactive materials used for medical purposes*

2. *The different uses of nuclear and radiation technology for diagnosis and treatment of various diseases*

INTRODUCTION

Medical applications account for majority of the procedures involving nuclear science. Around 10,000 hospitals worldwide use radionuclides/radioisotopes for the in vivo diagnosis and treatment of about 35 million patients every year [1]. The global radionuclides market was valued at $9.6 billion in 2016, with medical radionuclides accounting for about 80%, and it is projected to reach about $17 billion by 2021 [2]. Majority of the demand comes from technetium-99m which is the most common radionuclide used in nuclear medicine. Steady supply of technetium-99m heavily relies on nuclear reactors producing fission-based molybdenum-99 and neutron irradiation of natural molybdenum. With the increasing number of medical cyclotrons and emerging nuclear medicine technologies such as positron emission tomography (PET), clinical utilization of other radionuclides is anticipated in the future.
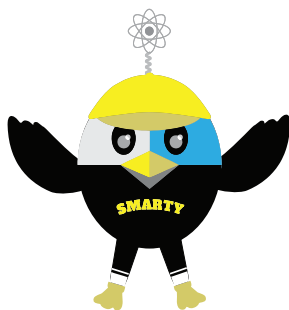
Marie Curie's tomb was enclosed in lead shield in Panthéon in Paris, France. Her belongings including clothes, furniture, cookbooks, and laboratory notes will remain radioactive for the next 1500 years due to the half-life of Radium-226 (1600 years).

HISTORY OF RADIONUCLIDES USED IN MEDICINE

In 1898, Drs. Marie and Pierre Curie (Fig. 1) discovered radium and polonium (named after Marie Curie's birthplace, Poland) in pitchblende or uraninite. Marie, together with her assistant Andre Debierne, refined tons of pitchblende to isolate one-tenth gram of pure radium chloride in 1902 and became successful in extracting pure metallic radium in 1910 [3]. During World War I, Marie became interested in potential medical applications of radium in cancer therapy, although it has been utilized in radiation therapy long before she became interested in its medical use. In 1901, a French dermatologist named Dr. Henri-Alexandre Danlos and physicist Eugène Bloch pioneered the use of natural radium (radium-226) for therapy when they inserted it in tuberculous skin lesions [4]. This was later known as brachytherapy (see page 24).
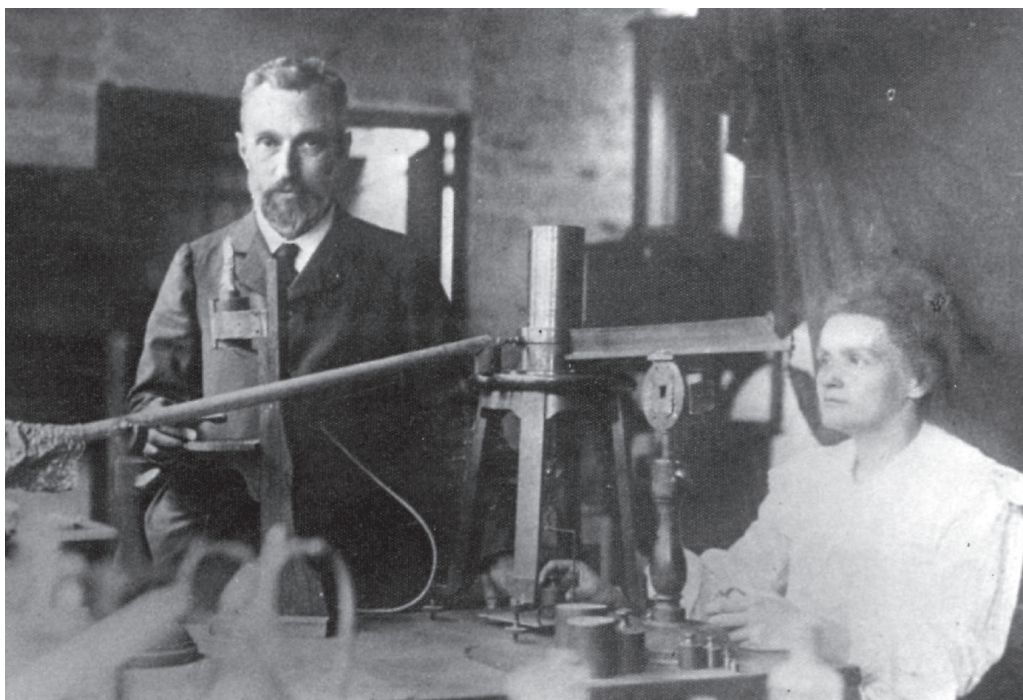

Fig. 1. Noble prize winners Marie and Pierre Curie.
Source: https://www.mariecurie.org.uk/who/our-history/marie-curie-the-scientist

Fig. 2. Radium bomb.
Source: https://collection.sciencemuseumgroup.org.uk/objects/co134669/radium-teletherapy-apparatus-the-radium-bomb-radium-teletherapy-apparatus.

In 1929, scientists Ernest Rock Carling, Stanford Cade and Frank Allchin invented the earliest radiotherapy machine called the radium bomb at a hospital in London [5]. Radium was placed in the egg-shaped lead-lined head (Fig. 2, upper left side) using a shutter operated by a bicycle brake cable. They believed that one (1) gram of radium held inches from the tumor might be more effective than radium-filled needles. In the Philippines, in 1938, the Commonwealth Act 398 created the Institute of X-ray and Radium Therapy which was later included in the Department of Radiology of UP-PGH [6] (Fig. 3). Radium bomb did not last long in the market and eventually was phased out in 1951 due to its low specific activity, low natural abundance and high cost. It was later replaced by cobalt-60 (Co-60) units which had higher specific

Fig. 3. Institute of X-ray and Radium Therapy, Philippine General Hospital.
Source: https://asorianofoundation.org/programs/cancer-care/cancer-services-program/
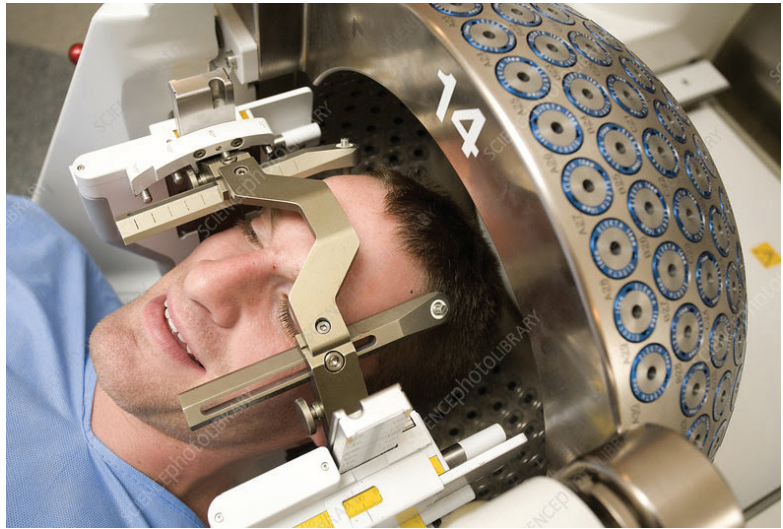
Fig. 4. Cobalt-60 gamma knife.
https://media.sciencephoto.com/image/c0063860/800wm/C0063860-Gamma_knife.jpg

activity and lower cost besides the fact that Co-60 emits high energy gamma photons that can be used to target deeper lesions. This technology is known as external beam radiotherapy (EBRT) or teletherapy. One of the famous personalities who underwent the procedure was Walt Disney for his lung cancer in 1966, he succumbed to the disease a few weeks later[7]. Co-60 is still used in gamma knife machines for the treatment of brain tumors (Fig. 4; also see page 23); however, the old Co-60 teletherapy machines have now been replaced by the non-radioactive LINAC (linear accelerator) machines (Fig. 5).
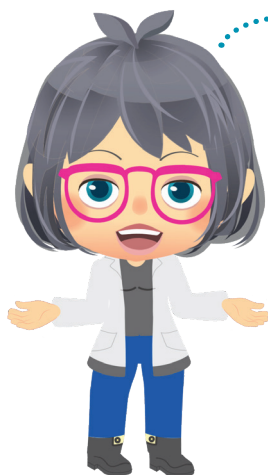
Other than its use in gamma knife and teletherapy for human applications, Co-60 is also used for industrial applications such as nondestructive testing and sterilization of medical devices, spices, export products and cosmetics, among others. PNRI has its own Co-60 multi-purpose irradiation facility.
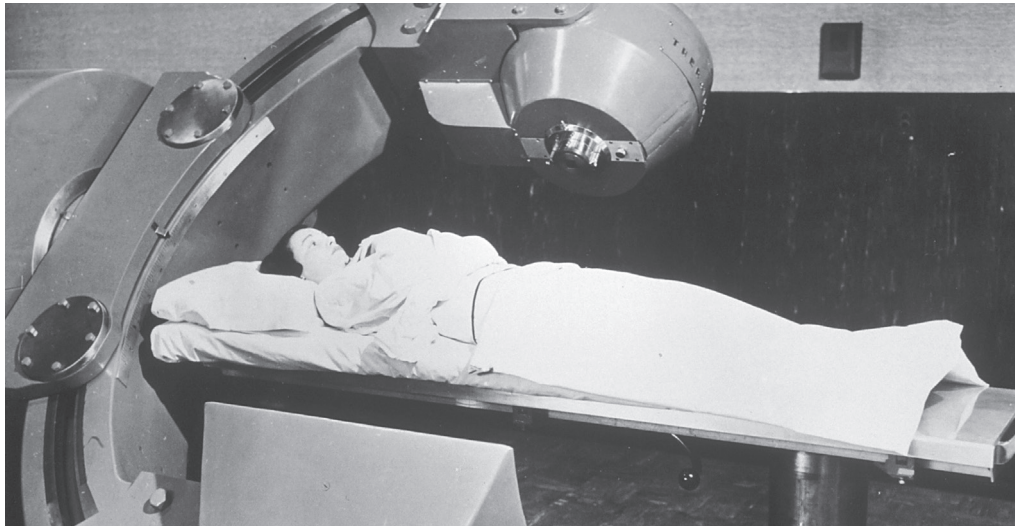
Fig. 5a. Cobalt-60 teletherapy machine
Source: Public Domain, https://commons.wikimedia.org/w/index.php?curid=10011965

During the same time the radium bomb was discovered, Nobel prize winner and physicist Dr. Ernest O. Lawrence invented the cyclotron in 1930. Through the help of his brother, Dr. John Lawrence, they were able to first utilize one of the radioisotopes produced in that cyclotron, phosphorus-32 (P-32), for the treatment of leukemia in 1936 [8]. This led to the birth of nuclear medicine, with P-32 becoming the first recorded clinical therapeutic application of radioisotopes.

Fig. 5b. Linear accelerator machine
Source: https://www.oncologysystems.com/blog/making-varian-linear-accelerator-vault-obi-board-imaging-ready

Fig. 6. The first cyclotron by Dr. E.O. Lawrence.
Source: https://www.kqed.org/quest/17535/homegrown-particle-accelerators

The accelerating chamber of the first cyclotron measured only five inches in diameter and boosted hydrogen ions to an energy of 80 keV (Fig. 6). This prototype later evolved to an 11-inch cyclotron which accelerates hydrogen ions up to 1 MeV energy, then to a 27-inch cyclotron capable of reaching nearly 5 MeV, and 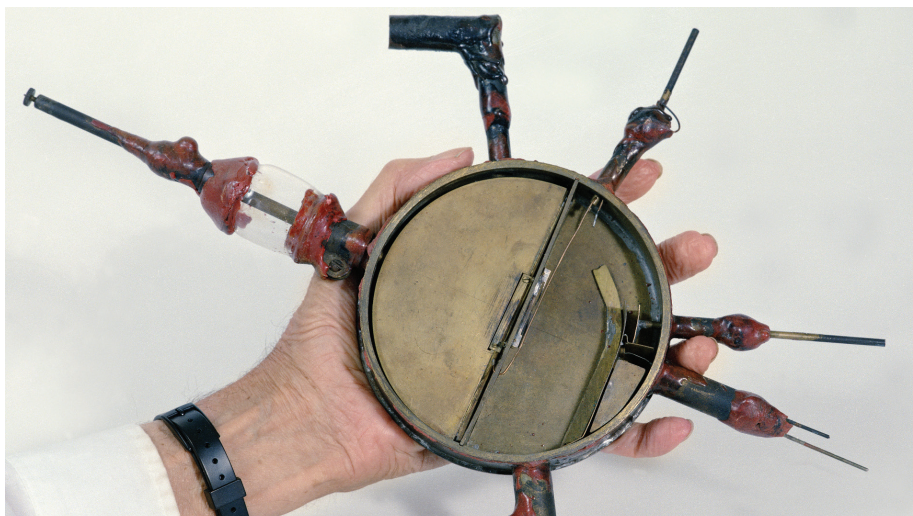was later replaced by a 37-inch cyclotron which accelerates deuterons to 8 MeV and alpha particles to 16 MeV (Fig. 7). This cyclotron was used by Dr. Glenn T. Seaborg to discover technetium, the first artificial element [9]. Carbon-11 (C-11) was the first positron emitting radioisotope produced by a cyclotron to be tested in humans. In the form of carbon monoxide C-11, Tobias and colleagues studied its fate in humans [10]. However, due to its short half-life, research on C-11 was shelved until later in the history of nuclear medicine.

Fig. 7. 37-inch cyclotron used to produce the first artificial element, technetium

Source: https://nara.getarchive. net/media/the-37-inch-cyclotron-accelerated-deuterons-to-8-mev-and-alpha-particles-to-246f02
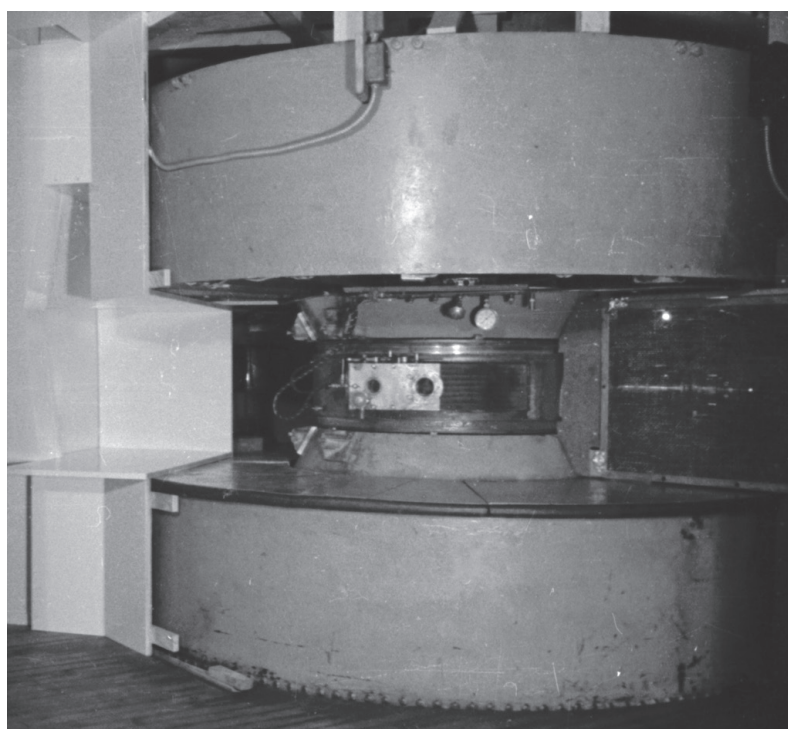
In 1938, the first radioactive Iodine (^{128}I) was administered by the founder of nuclear medicine, Dr. Saul Hertz, in rabbits to check on thyroid uptake. Dr. Hertz later developed and administered an atomic cocktail – a mixture of iodine-130 (I-130) and iodine-131 (I-131) to treat hyperthyroidism in 1941[11]. The results of the clinical trials were published in the Journal of American Medical Association in May 1946. He was also treating thyroid cancer using I-130, only finding out that it was was not effective due to its half life of only 12 hours. His research was halted when Dr. Hertz joined the US Army in World War II.

RADIO-IODINE HALTS ONE TYPE OF CANCER

Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors

The man shown in the contrasting portraits at right is a Brooklyn shoe salesman named Bernard Brunstein who is destined to become one of the most famous patients in medical history. Brunstein is the first person known to be cured (insofar as a cure can be established by medical tests on a living patient) of metastatic cancer, a form of the disease in which the malignancy spreads through the body from an original tumor. Metastatic cancer has always been 100% fatal. But Brunstein's tumors were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine.

When Brunstein was admitted to New York Memorial Hospital...

BERNARD BRUNSTEIN IN 1942 (LEFT); AS HE LOOKS TODAY

iodine is chemically identical with ordinary iodine, it gives off a powerful radiation that can kill any tissue that absorbs it in sufficient concentration. The chemical had never been effectively used as a treatment for cancer, but Brunstein agreed to try it in the hope that it might help. It did. Three months after he drank his first glassful of the tasteless, colorless liquid, his heart began to slow down and he started to put on weight. Geiger counters placed over the tumor sites revealed that there was a heavy concentration of radio-iodine in these areas. After three additional doses the tumors slowly began to diminish in size

Fig. 8. October 1948 Life Magazine article on successful therapy using iodine-131
Source: Life Magazine, October 1949. ISSN 0024-3019.

Dr. Samuel Seidlin, also an American doctor, used I-131 to treat patients with thyroid cancer [12]. One of the patients who were cured was a shoe salesman from Brooklyn who suffered from metastatic thyroid cancer after the surgical removal of the thyroid. This was published in Life Magazine in October 1949 (Fig. 8). After World War II, reactor-produced I-131 became more accessible allowing more therapeutic studies to be conducted, eventually making sodium iodide I-131 the first radiopharmaceutical issued a drug registration by the US FDA [13].

In 1958, researchers Walt Tucker, Powell Richards, and Margaret Greene of Brookhaven National Laboratory developed a way to generate the isotope on the spot in hospitals (Fig. 9). This device is called a generator (sometimes referred to as the "cow" because you are "milking" the generator)[14]. Because of this invention, technetium-99m earned an important role in nuclear medicine by becoming the workhorse of SPECT imaging after its clinical use as an imaging tool was discovered in 1961.
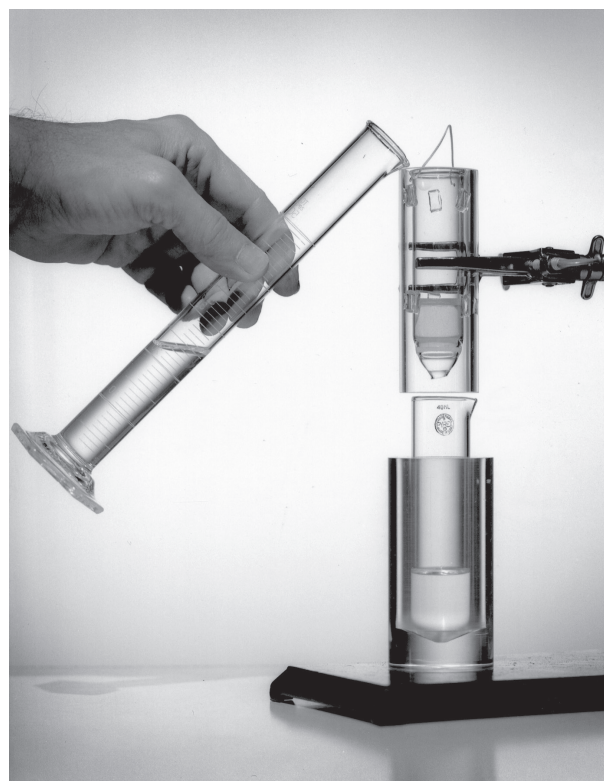

Fig. 9. First Technetium-99m generator (unshielded) of Brookhaven National Laboratory.
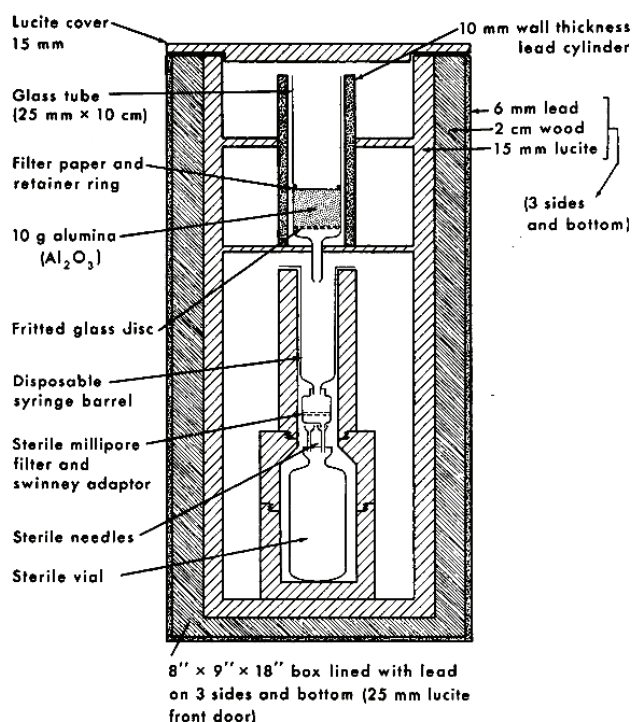Source: http://large.stanford.edu/courses/2019/ph241/sheppard1/

Fig. 10. The first Ge-68/Ga-68 generator.

Source: Yano Y, Anger HO (1964). A Gallium-68 Positron Cow for Medical Use. Journal of Nuclear Medicine, 5:484-487.

Fig. 11. RIA kits for insulin.

Source: https://amershammuseum.org/history/trades-industries/alchemists/

Technetium-99m (Tc-99m) is a decay product of molybdenum-99 (Mo-99), one of the products of the uranium fission in a nuclear reactor and can be collected by pouring a normal saline solution (0.9% w/v NaCl) inside an aluminum oxide column. Despite the current setup being practical, this crude generator offered limited radiation protection mechanisms compared to the current generator designs to date.

Prior to the development of modern cyclotrons in the 1960s, only large synchrocyclotrons whose proton energies ranging from 100 to 730 MeV existed [15,16] and were mainly dedicated to physics research rather than radionuclide production.

During that time, there was already a gaining interest in the potential use of positron emitters for brain tumor annihiscopy (a coincidence-based detection system long before the development of PET cameras) but the limited number of cyclotrons limited the mass production of the isotopes of interest.

Researchers at Abbott Laboratories tried to explore the possibility of using a longlived parent and a short-lived positron emitting daughter called the "positron cow". The first reported positron cow was the Germanium-68/Gallium-68 generator[17] (Fig. 10) which has already been utilized for medical purposes in 1964 [18].

The first in vitro clinical application of radioisotopes was discovered in 1964, when Dr. Amersham developed insulin radioimmunoassay (RIA) kits using iodine-125 for detecting insulin blood levels in diabetics [19] (Fig. 11). Other kits have also been developed such as RIA kits for thyroid hormones T3/T4 (triiodothyronine and thyroxine) for evaluation of thyroid status, malaria antigen, hepatitis B antigen, among others.

In 1976, Dr. Joanna S. Fowler and her colleagues from Brookhaven National Laboratory were able to synthesize [^{18}F] fluorodeoxyglucose (FDG) (Fig. 12)[20], which later became the workhorse of PET imaging. It was initially developed for the specific purpose of mapping brain glucose metabolism in living humans but was later shown to have good uptake in cancer cells, making FDG one of the most common modalities in cancer detection.

The interest in carbon-11 radiopharmaceuticals was revived in the 1970s after Drs. Michel M. Ter-Pogossian and Michael Phelps discovered Positron Emission Transaxial Tomography (PETT)[21] which was later renamed Positron Emission Tomography (PET) by allowing visualization of positron emitters such as [^{18}F] FDG. Advances in radiochemistry also paved way to radiolabeling of other endogenous biomolecules. Newer PET tracers have also been developed for human use such as strontium-82/rubidium-82 generator (Cardiogen-82®) for PET imaging of the heart, which became the first PET tracer approved by the US FDA for commercial use in 1989 (Fig. 13)[22].

Fig. 12. Dr. Joanna S. Fowler and her [^{18}F] Fluorodeoxyglucose synthesis setup.
Source: https://www.bnl.gov/newsroom/news.php?a=111461

Fig. 13. Cardiogen-82®, Metastron®, and Xofigo®.
Sources: (Left) https://imaging.bracco.com/us-en/products/nuclear-medicine-radiopharmaceuticals/ cardiogen-82. (Middle) https://www.medicaltourisrael.com/?p=13667. (Right) https://www.mims.com/hongkong/image/info/xofigo%20solution%20 for%20injection %201100%20kbq-ml/1,100%20kbq-ml%20x%206%20ml?id=95e45598-e0b5-4d70-a14c-a5fd011b92d2

Since the discovery of phosphorus-32 and iodine-131, other therapeutic applications of different radioisotopes have also been explored. Among the earliest discoveries include the beta emitting strontium-89 chloride (Metastron®) which was approved by US FDA for alleviating bone pain during cancer metastasis in 1993 (Fig. 13) [23], and the alpha emitting radium-223 dichloride (Xofigo®) which was approved by US FDA in 2013 for treatment of metastatic castration resistant prostate cancer (Fig. 13) [24]. Other radiopharmaceuticals are still under development while some have already been used in routine clinical setting.

To date, there are a total of 52 radiopharmaceuticals approved by US Food and Drug Administration for clinical use. These products contain carbon-11, nitrogen-13, oxygen-15, fluorine-18, rubidium-82, gallium-67, gallium-68, technetium-99m, indium-111, iodine-123, thallium-201, and xenon-133 for imaging, and strontium-89, yttrium-90, iodine-131, samarium-153, lutetium-177, and radium-223 for therapy.

https://www.cardinalhealth.com/content/dam/corp/web/documents/fact-sheet/cardinal-health-fda-approved-radiopharmaceuticals.pdf

PRODUCTION OF MEDICAL RADIONUCLIDES
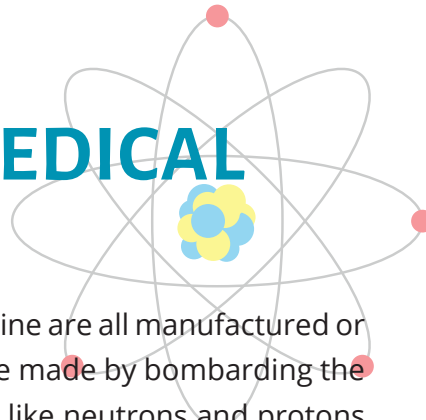
The radionuclides used in modern nuclear medicine are all manufactured or produced artificially. Generally, radionuclides are made by bombarding the nuclei of stable atoms with subnuclear particles like neutrons and protons to cause nuclear reactions that convert a stable nucleus into an unstable or radioactive one. These nuclear reactions can take place inside nuclear reactors and particle accelerators like cyclotrons and linear accelerators. Radionuclides used in medicine can also be produced by a radionuclide generator.
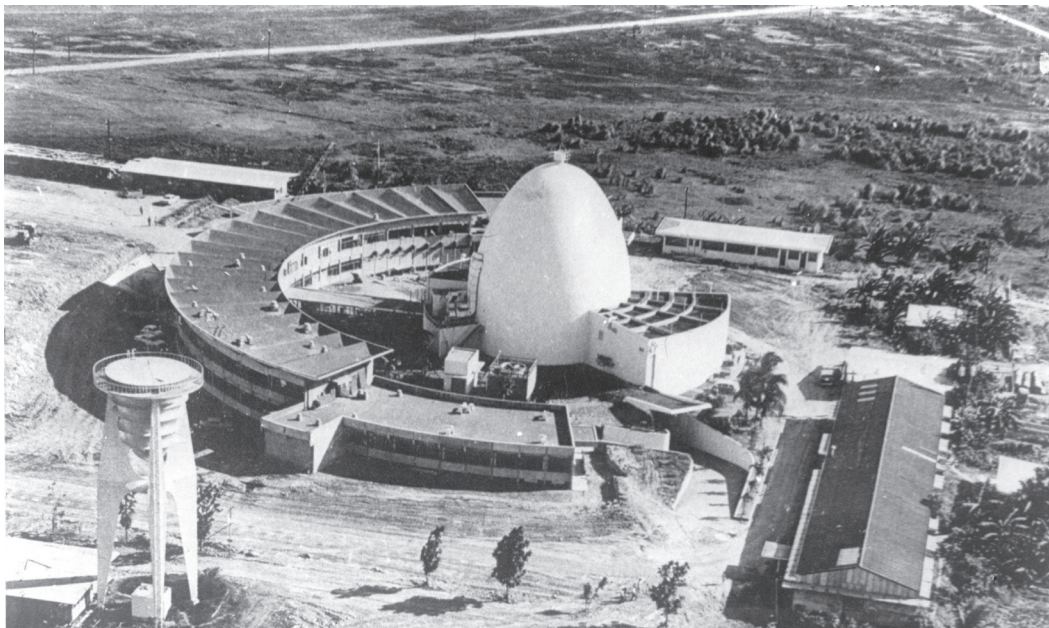

Fig. 14. Construction of the Philippine Research Reactor 1 (PRR-1).
Source: https://lakansining.wordpress.com/2017/01/24/commonwealth-avenue-quezon-city-monuments-in-the-philippine-nuclear-research-institute/

Research Reactor

Research reactors were a brainchild of US President Dwight Eisenhower's Atoms for Peace program. Research reactors are intended to provide a neutron source for research and other purposes although the most common use of reactors nowadays is the production of radioisotopes for medical applications. Radionuclides are produced in nuclear reactors by (1) fission product recovery or (2) neutron activation. The fission process that takes place in a reactor can lead to useful quantities of radionuclides important in medicine such as molybdenum-99 (Mo-99), the parent material in a

technetium-99m (Tc-99m) generator (See Radionuclide Generator). Fission is simply splitting the nuclei of an atom into two parts. These two parts become new smaller nuclides. Uranium-235 (U-235) is a commonly used fission nuclide in a research reactor. When bombarded with a neutron, U-235 produces the very unstable uranium-236 (U-236) which rapidly undergoes fission. More than 100 nuclides are found among the fission products of U-236. Since the U-235 fuel used in research reactors is encapsulated in steel rods, the fission products are retained in the steel casing. After the fuel rods have been depleted, they are removed from the reactor and moved to a chemical processing plant where the depleted fuel rods are opened in hot cells using remote control equipment (Fig 15). In the chemical separation process, various fission products are recovered from the depleted nuclear fuel rods. Among these recovered fission products are I-131, Sr-90, Cs-137, Xe-133, Co-60 and Mo-99.

Following the creation of the Philippine Atomic Energy Commission (PAEC) in 1958, the 1 MW Philippine Research Reactor 1 (PRR-1) was constructed in the early 1960s and started achieving criticality in 1963. Since then, numerous radionuclides were started to be produced for research, industrial and medical use. PAEC has been producing radionuclides mainly for medical purposes such as gold-198 (Au-198), P-32, I-131 and iridium-192 (Ir-192) for therapy, and chromium-51 (Cr-51) and Mo-99 (for a short time) for diagnosis until the upgrading of PRR-1 to a TRIGA type reactor in 1984 followed by an indefinite shutdown in 1988 [25-39]. TRIGA stands for Teaching, Research, Isotope Production General Atomic.

Neutron activation involves irradiating a stable target material with neutrons and converting it to a radioactive isotope upon absorbing the neutron. After irradiation, the targets are placed in a hot cell and processed chemically to release the product radionuclide. For instance, one of the main products of PRR-1, I-131, was produced via a neutron-beta particle (n,β) reaction by irradiating tellurium-130 followed by either dry or wet distillation. For dry distillation, telluric acid was irradiated in a dry pipe for a period of 3-4 weeks to produce 20 mCi I-131 at 60-70% recovery [28,40]. For wet distillation, the irradiated tellurium dioxide was dissolved in sodium hydroxide (NaOH) then sulfuric acid (H_2SO_4) was added followed by distillation of iodine (I_2) and subsequent reduction in a solution of NaOH trickling in a vertical absorber filled with glass beads to produce sodium iodide (NaI) [24,33]. Other procedures are used for radioiodination of PRR-1 produced tracers such as oleic acid and triolein [23], rose bengal, hippuran and insulin [24], L-thyroxine and human serum albumin [27], and mono- and di-iodotyrosine [28].

Fig. 15. Argonne National Laboratory research reactor hot cells.
Source: https://commons.wikimedia.org/w/index.php?curid=17523866
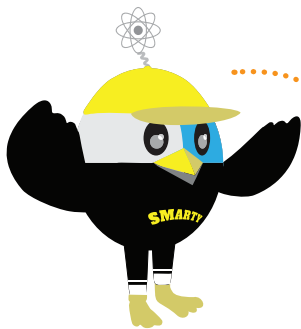
Hot cells are heavily shielded enclosures. Radio-active materials inside the hot cell are handled remotely using electro-mechanical arms called manipulators.

Another major PRR-1 product, P-32, was produced via neutron-proton (n,p) reaction by irradiating natural sulfur powder followed by melting it and passing through a layer of magnesia (MgO) which absorbs P-32. Magnesia was then dissolved in hydrochloric acid (HCl) and magnesium (Mg) was removed using a cation exchanger. The effluent containing the P-32 was evaporated to dryness, treated with hydrogen peroxide (H_2O_2), and diluted with pyrogen-free water or dilute HCl [26]. Another product, Cr-51 was produced by irradiating potassium chromate (K_2CrO_4) then dissolving it in 10% potassium chloride (KCl) solution and neutralized with dilute NaOH. Chromium (III) hydroxide ($Cr(OH)_3$) was filtered off, washed, re-dissolved with NaOH and H_2O_2, and the resulting solution was collected then evaporated to dryness and adjusted for isotonicity [27].

Mo-99, the parent radionuclide of Technetium-99m (Tc-99m), was produced using an enrichment technique called a powder recoil. Natural molybdenum (usually molybdenum trioxide or ammonium molybdate) was mixed with a recoil catcher (a substance to improve specific activity of Mo-99 product). After irradiation, the catcher with recoil Mo-99 was separated from the bulk molybdenum by selective dissolution [28]. Production of Tc-99m from irradiated molybdenum was also performed by dissolving irradiated molybdenum trioxide in 5N NaOH and methylethylketone (MEK) was introduced into the extractor through a capillary with constant stirring. The overflow which contains MEK with Tc-99m was collected and evaporated to dryness [29]. Tc-99m was used to label PRR-1 products sulfur colloid and human serum albumin [30].

Particle Accelerator

Particle accelerators produce a beam of charged particles such as electrons, protons, deuterons, alpha particles and heavy ions that are artificially accelerated to very high energies. When directed to a target material, these charged particles can cause nuclear reactions that result in the formation of radionuclides in a manner similar to neutron activation in research reactors. Particle accelerators offer an advantage over nuclear research reactors due to cheaper operating and decommissioning costs, and lower amounts and less hazardous radioactive wastes [41]. Linear accelerators, Van de Graaff accelerators, tandem cascade accelerators, cyclotrons, and variations of cyclotrons are among the many types of particle accelerators. The cyclotron, however, is the most widely used type of particle accelerator for production of radionuclides used in nuclear medicine.

Cyclotron

As its name suggests, a cyclotron accelerates charged particles in a spiral path. This allows for a much longer acceleration path compared to linear accelerators. The basic components of a cyclotron is shown in Fig 16. The acceleration chamber (kept in vacuum) of a cyclotron is placed between the poles of a large magnet which creates a homogeneous magnetic field perpendicular to the chamber. This magnetic field causes the charged particles to move in a circular path. A stream of charged particles produced from an ion source is fed into the center of the chamber. The charged particles are then accelerated out from the center and around the circular path by a high frequency alternating voltage applied across two or more hollow electrodes called 'dees' (because of their shape). This voltage alternately

attracts and repels the charged particles as they pass through a gap from one dee to the next causing them to accelerate. As the charged particles gain more energy, they spiral outwards until they reach the outer edge of the chamber and collides with the target material. Protons and deuterons are the common bombarding particle utilized in medical cyclotrons.
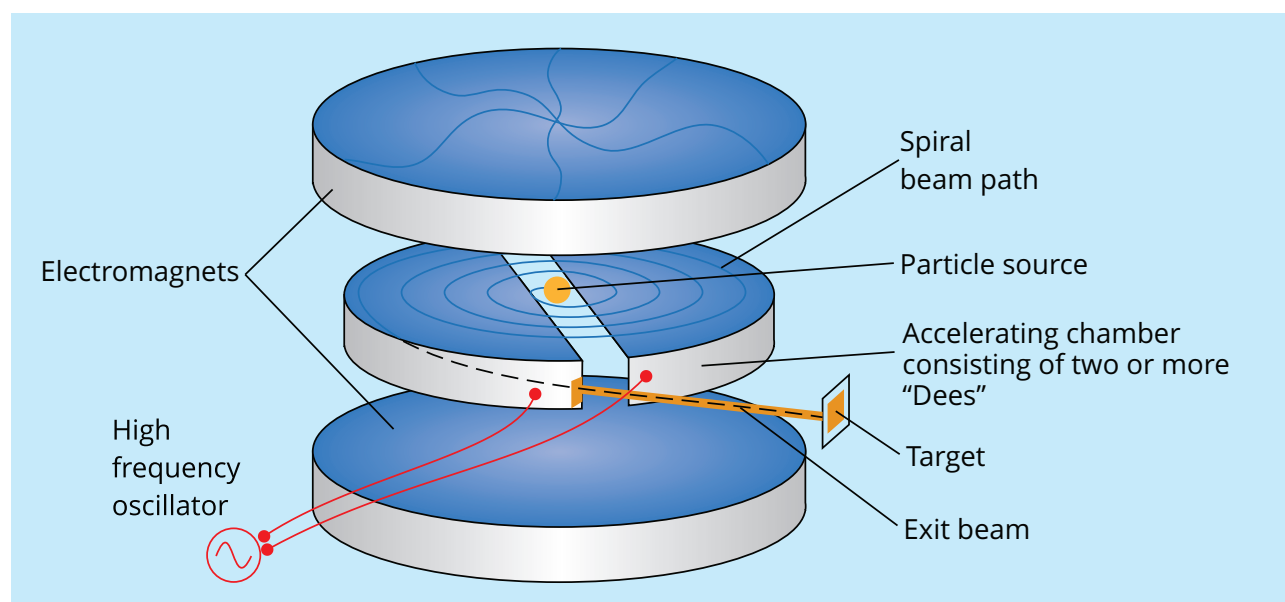

Fig. 16. Basic components of a cyclotron.

The smallest cyclotron in the world is ABT Molecular Imaging BG-75, a 7.5 -MeV self-shielded single particle cyclotron that bombards only protons and mainly intended for production of $[^{18}F]$ FDG; while the largest cyclotron is the TRIUMF cyclotron in Vancouver, Canada which is a 500-MeV proton multipurpose cyclotron (Fig. 17).

Common medical cyclotrons range from 16-22 MeV of proton energy depending on the types of radionuclides intended to be produced. Radionuclides/radioisotopes produced in medical cyclotrons include fluorine-18 (F-18), carbon-11 (C-11), oxygen-15 (O-15), nitrogen-13 (N-13), and iodine-123 (I-123). Unlike the old days where cyclotrons are confined to research facilities, cyclotrons are becoming more and more of a staple in hospitals worldwide such as Figure 18 which is one of the most popular models used worldwide. The production of radioisotopes using a cyclotron would depend on two specific characteristics of particle beams -- the beam must have sufficient energy to bring about the required nuclear reactions, and there must be sufficient beam current to give practical yields [43]. There is a minimum energy requirement for the production of each radioisotope, below which a nuclear reaction will not occur. At higher energies, there
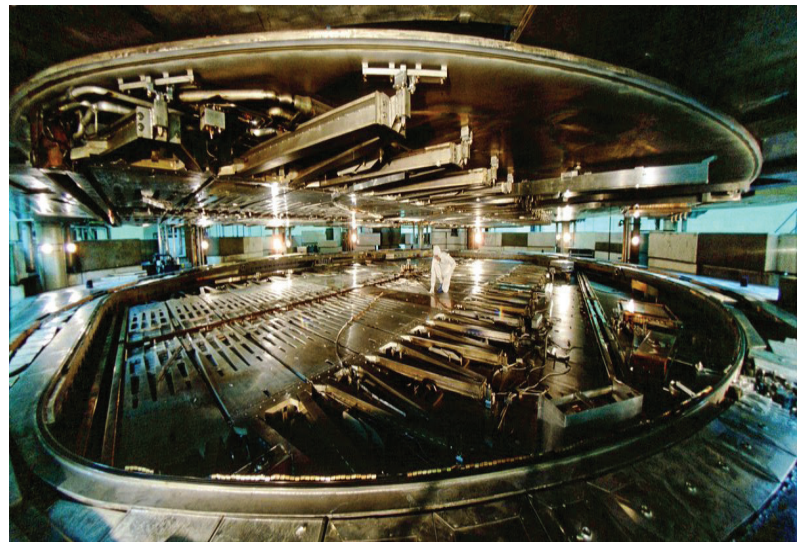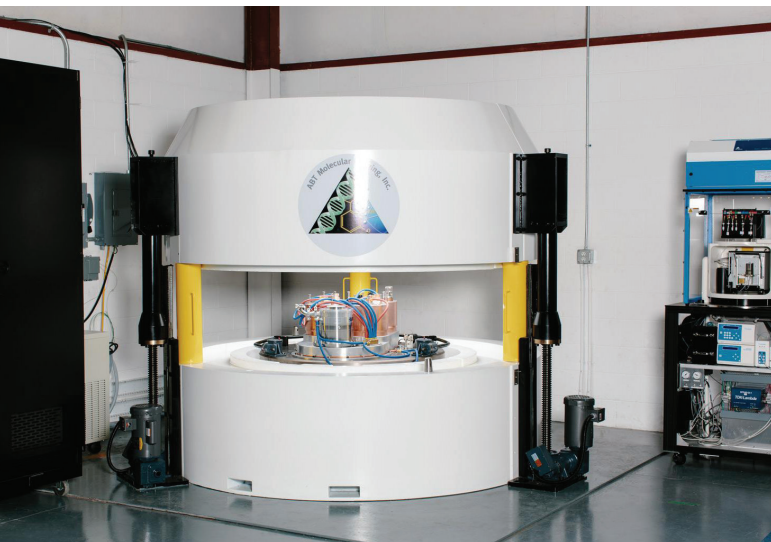
Fig. 17. Smallest (left) and largest (right) cyclotrons in the world.
Source: (Left) https://www.facebook.com/1578002525797622/photos/a.1578009145796960/ 1578009455796929/?type=3&theater
(Right) https://cycops.triumf.ca/homepage/tank5.jpg

is a possibility for unwanted side nuclear reactions since there are more reactions that may be activated at higher energies.

Currently there are four operating cyclotrons throughout the country – St. Luke's Medical Center and National Kidney and Transplant Institute (K-Health Corporation) in Quezon City, Perpetual Help Medical Center (Neo Isotope World) in Las Piñas, and Chong Hua Medical Center in Mandaue City, Cebu. Installation of two additional cyclotrons are underway– one in Vicente Sotto Memorial Medical Center in Cebu City, Cebu, and another in Southern Philippines Medical Center in Davao City.

Fig. 18. 16 MeV cyclotron by GE Healthcare.
Source: https://www.gehealthcare.com/-/jssmedia/56a14eb9525248aa90640c9b72d9c6ae.jpg? h=371&la=en-US&w=13 49&hash=E200FB09276ED7D9A8CA4B0E564FE1DE
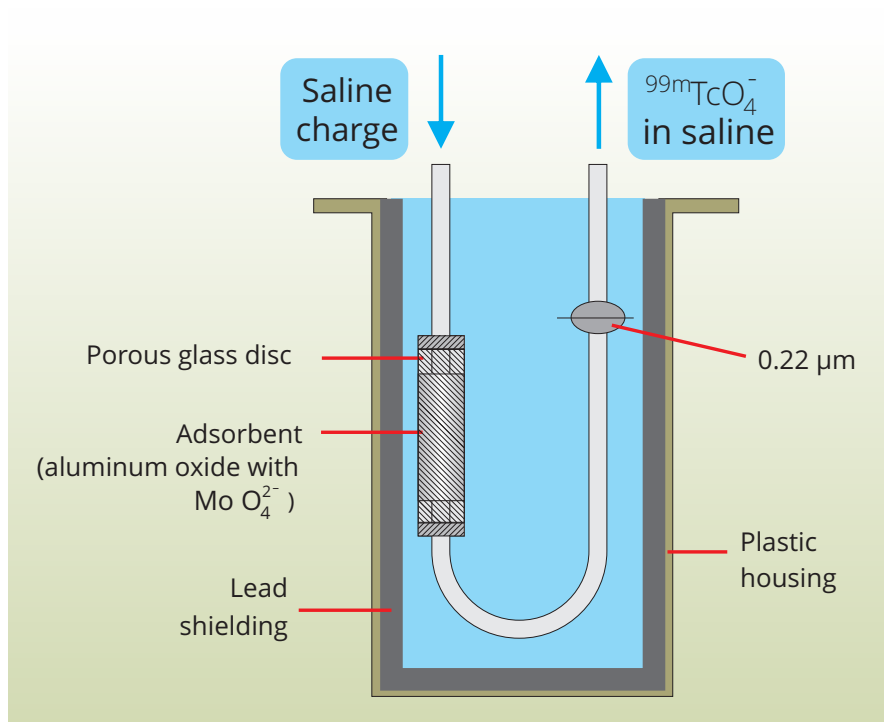
Fig. 19. Components of a Mo-99/Tc-99m generator
Source: HHW/Radiopharmacy/ VirRad/Eluting_the_Generator/ Generator_Module/Design_ principles/ modules.gif

Radionuclide Generator

A radionuclide generator is a device used to effectively separate a longer half-life decaying parent and a shorter half-life daughter radionuclide such that the daughter is obtained in its pure radionuclidic and radiochemical form. Compared to research reactors and cyclotrons, generators provide an inexpensive and convenient alternative to supply short-lived radionuclides [44]. The most widely used generator is the molybdenum-99/ technetium-99m (referred to as Moly) generator which is used in 30 million procedures per year which is about 80% of all nuclear medicine procedures worldwide[45]. Other useful generators are the germanium-68/gallium-68 and strontium-82/rubidium-82 for PET imaging, and tungsten-188/ rhenium-188 and strontium-90/yttrium-90 for therapy. Figure 19 illustrates the typical components of a Moly generator. The most critical component of the Moly generator is the column, usually a glass containing aluminum oxide where the parent radionuclide Mo-99 ($t_{1/2}$ = 66 hours) will strongly bind to and therefore is not washed off upon subsequent elution of the daughter radionuclide technetium-99m ($t_{1/2}$ = 6 hours). Unlike the original technetium generator in Figure 9, modern generator designs take into consideration radiation protection for operator safety. All radionuclide generators are provided with lead shield in a plastic housing that help attenuate the radiation emitted by both parent and daughter radionuclides to reduce the dose received by the staff eluting the daughter radionuclide [46].

The PNRI constructed its molybdenum-99/technetium-99m generator production facility in 2011 which was completed in 2012 through the technical and financial assistance of the International Atomic Energy Agency (IAEA) and the Department of Science and Technology - Philippine Council for Industry, Energy and Emerging Technology Research and Development (DOST-PCIERRD) (Fig. 20). The facility has a production capacity of up to fifty (50) 1-Curie generators per batch. The PNRI-made Mo-99 generator, GammaGen[TM], which uses low enriched uranium-fission Mo-99 as its starting material.

Fig. 20. DOST-PNRI Generator Production Facility. Source: PNRI

RADIONUCLIDES USED IN MEDICINE
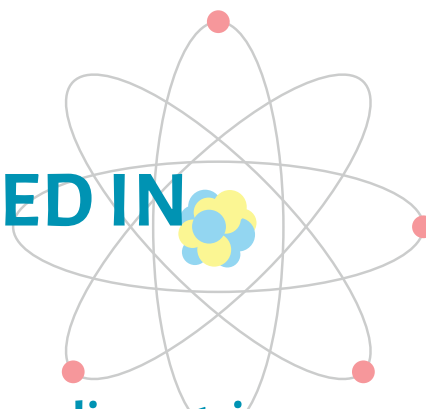
Radioimmunoassay and Immunoradiometric assays

An immunoassay is a biochemical test that is used to detect or quantify the presence or concentration of a specific substance in a solution using an antibody or an antigen. Antibodies are molecules used by our immune system to search and recognize other molecules particularly those which are found in potential pathogens. In an immunological reaction, an antibody will bind to a specific antigen. Because of this, immunoassays are very sensitive and specific. They are used to quantify amounts of hormones in a sample, detect cancer cells in a blood sample or any other biomarker, even viruses. A pregnancy test is an example of an immunoassay. In addition to the binding of an antibody to its antigen, the other key feature of all immunoassays is a means to produce a measurable signal in response to the binding. Most immunoassays involve chemically linking antibodies or antigens with some kind of detectable label. Many labels are detectable because they either emit radiation, produce a color change in a solution, fluoresce under light, or can be induced to emit light.

Radioimmunoassays (RIA) and immunoradiometric assays (IRMA) use a radioisotope to label and/or detect the antigen of interest. The extremely high sensitivity of RIA and IRMA is a major advantage. The test can be used to determine very small quantities of antigens and antibodies in the serum or blood. Figure 21A illustrates how RIA works. IRMA works in a similar manner. The only difference is that in IRMA an antibody-antigen-antibody complex is formed after the reaction, while an antibody-antigen complex is formed in RIA. Figure 21B provides a simple illustration comparing the general principle of these two techniques. Iodine-125 was the radioisotope of choice for RIA because of its half-life of 60 days that permits the preparation of labeled antigens with useful shelf lives of up to several months [47]. Other radioisotopes that have been used in RIA assays are tritium (hydrogen-3) and cobalt-57 [48].
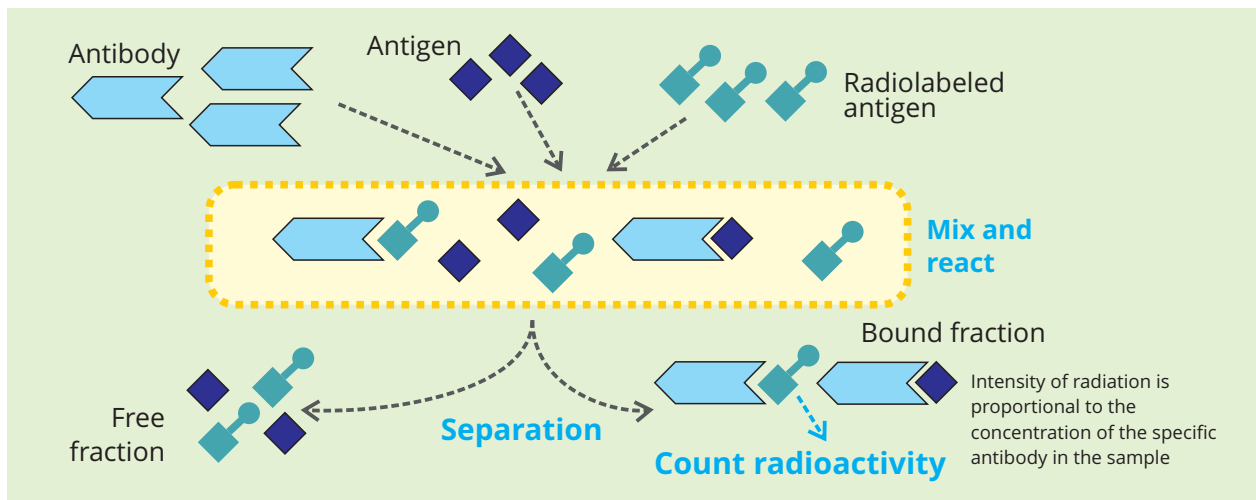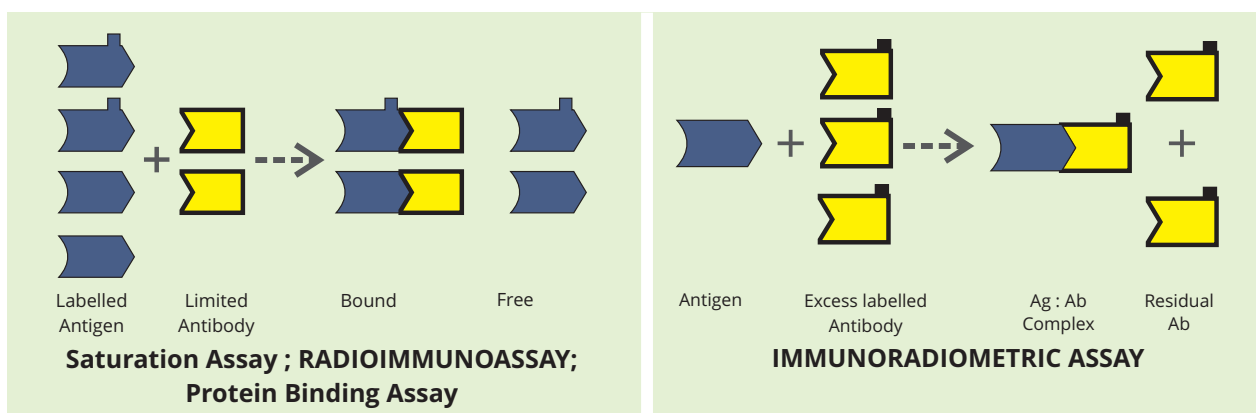
Fig 21A. How radioimmunoassay works.

**Saturation Assay ; RADIOIMMUNOASSAY;
Protein Binding Assay**

IMMUNORADIOMETRIC ASSAY

Fig. 21B. Radioimmunoassay vs immunoradiometric assay.
Source: https://www.osti.gov/etdeweb/servlets/purl/605392

The PAEC/PNRI has produced various RIA kits for in vitro detection of certain diseases such as insulin, triiodothyronine (T3), thyroxine (T4) and human growth hormone [49] tuberculosis antigen [50], and hepatitis B surface antigen [51]. The PNRI in collaboration with Research Institute for Tropical Medicine developed an IRMA procedure for malaria disease surveillance in the Philippines [39, 50].

Radiation Oncology

Radiation oncology is a branch of medicine devoted to the treatment of both malignant and benign disease using ionizing radiation [52]. The general principle involves delivering therapeutic radiation dose to disrupt the ability of cancer cells to grow and divide, killing cancer cells, slowing their growth, and shrinking tumors to relieve the patient or enable surgery [53]. Ionizing radiation can be delivered through external beam radiation therapy or implantation of radionuclides in a procedure called internal radiation therapy.

External beam radiation therapy

External beam radiotherapy (EBRT), also known as teletherapy, intends to give a narrow, well aligned beam of radiation at distances of usually 20-100 cm from the gamma energy source [50]. Before the development of linear accelerators (LINAC), teletherapy machines used cobalt-60 ($t_{1/2}$=5.27 years) and cesium-137 ($t_{1/2}$=30 years) as sources. The old cobalt-60 teletherapy machines have the following components: source, shielding, shutter, rotating arm with counterweight, gantry, and patient support assembly. Several hospitals in the Philippines still use these machines due to lesser maintenance costs and infrastructure requirements, lower power demands, and simpler quality assurance as compared to LINAC machines [55]. However, LINAC machines are currently the most commonly used machines for radiotherapy, There are currently 57 LINAC machines across the country, and the number is still growing.
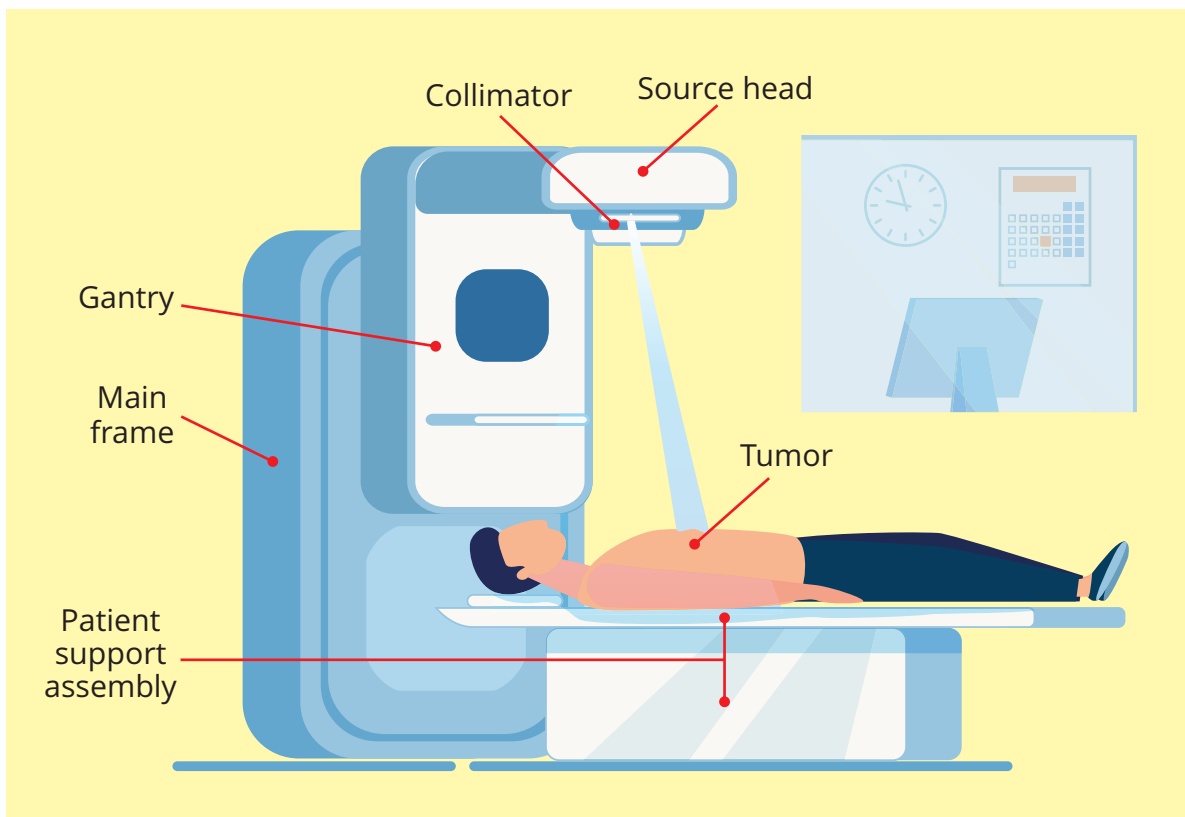
Fig. 22. Parts of cobalt-60 teletherapy machine.
Source: https://ingeniumcanada.org/artifact/atomic-energy-of-canada-ltd-cobalt-60-therapy-machine

Gamma knife (Fig. 23), a form of stereotactic radiosurgery, is not a surgical technique because no incision is involved. Instead, it uses specialized equipment to focus about 200 very narrow beams of radiation to focus usually on a head tumor with submillimeter accuracy [56]. It is a safer alternative to neurosurgery especially in cases wherein a tumor is too hard to reach and the patient is not healthy enough to undergo standard surgery.
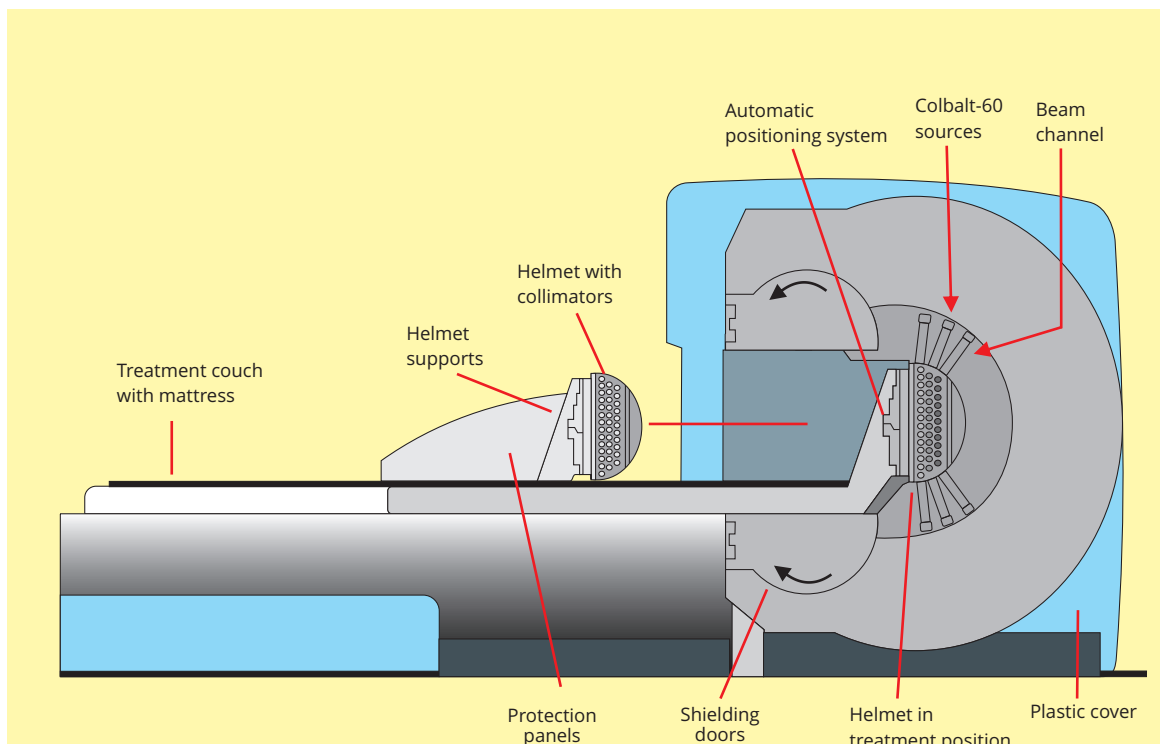

Fig. 23. Parts of Gamma knife.

A less common type of external beam radiotherapy is proton therapy which uses protons to kill cancer cells. It offers the advantage of depositing over a narrow range with minimal entry and exit, and scattered radiation dose to healthy tissues.

Internal radiation therapy

In contrast to teletherapy, internal radiation therapy, also known as brachytherapy, uses sealed radiation sources which are inserted to the body and placed next to the tumor being irradiated [57]. The inserted source can be either temporary (high dose rate) or permanent (typically low dose rate) (Fig. 24). Low dose rate brachytherapy uses short-range isotope such as iodine-125 [58] while high dose rate brachytherapy uses iridium-192 [59]. It is usually indicated for cervical, prostate, breast or esophageal cancers.
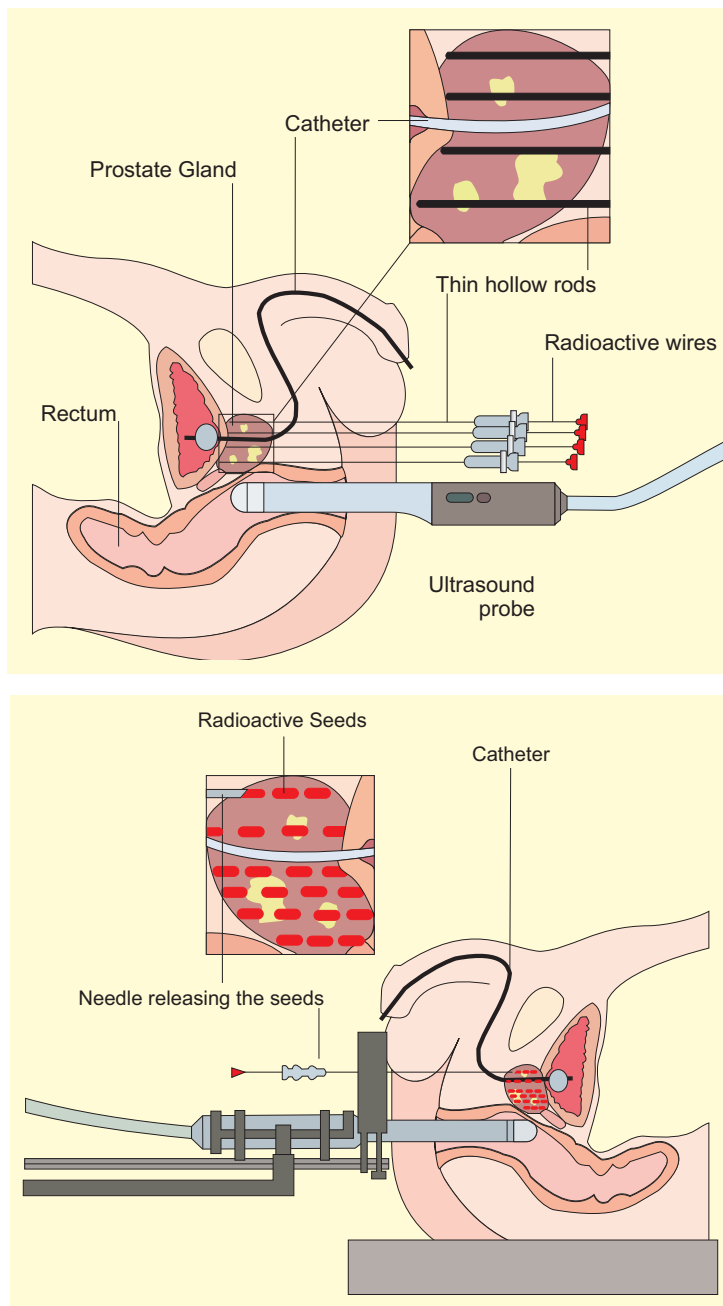

Fig. 24. High Dose Rate (above) vs Low Dose Rate (below) Brachytherapy for prostate cancer therapy.
Source: https://tackleprostate.org/brachytherapy.php

Nuclear Medicine and Radiopharmaceuticals

Nuclear medicine is a branch of medicine that uses small amounts of radioactive substances to make pictures of areas inside the body, visualize physiologic functions of vital organs and to treat diseases. It makes use of substances called radiopharmaceuticals which are radioactive drugs intended to target cells, tissues and organs. They usually consist of the following – the radionuclide (with or without a chelating agent), a linker, and a targeting moiety that can be a small molecule, a peptide, or an antibody (Fig. 25) [60].
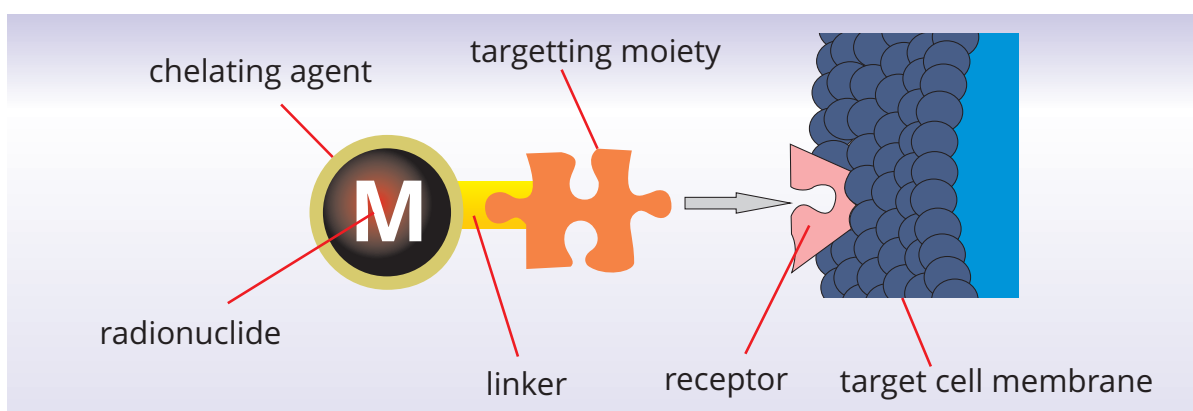

Figure 25. Components of radiopharmaceuticals.
Source: https://www.researchgate.net/profile/Amirreza_Jalilian/publication/312059806/figure/fig3/ AS:626158680961025@1526299271624/ Components-of-a-designed-targeting-radiopharma ceutical_W640.jpg

Radionuclides can be used for either imaging or for therapy depending on the type of decay of the radionuclide. If it emits a gamma ray or a positron, the radionuclide can be used for imaging. If it emits a beta or an alpha particle, the radionuclide can be used for therapy. Radiopharmaceuticals can be either inhaled, taken by mouth, or injected mostly through the veins but can also be injected through the spine, joints or arteries (liver arteries in particular). Because they are given to humans, they are considered as drugs; therefore, these must be tested and comply with the quality and safety standards and requirements of the Food and Drug Administration (FDA).

Radiopharmaceuticals given to patients are in 10^{-8} to 10^{-12} mol/L (nano to picomolar) concentrations, which are sufficiently safe for human use and will not pose life-long harmful effects (radiation or drug-related chronic toxicity) to humans [61]. Any adverse reactions to radiopharmaceuticals are rare, mild and temporary and require little to no medical treatment [62,63]. Major precautions and contraindications include pregnancy and breastfeeding mothers due to risk of radiation exposure in fetuses and neonates [64].

Radiopharmaceuticals for Imaging

Imaging radiopharmaceuticals are radiotracers that reveal the physiological state of a certain disease. Imaging techniques using these radiopharmaceuticals are Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). SPECT can measure gamma rays of different energies, while PET can measure two (2) 511-keV gamma rays travelling 180° apart and the signal detected is equivalent to the number of positrons causing annihilation with the electrons in that body part. Because of higher gamma energy, PET radiopharmaceuticals offer better image resolution and higher sensitivity than SPECT, although SPECT radiopharmaceuticals are cheaper and more readily available since commonly used PET radiopharmaceuticals require an in-house cyclotron due to their relatively short physical half-lives (Fig. 26).
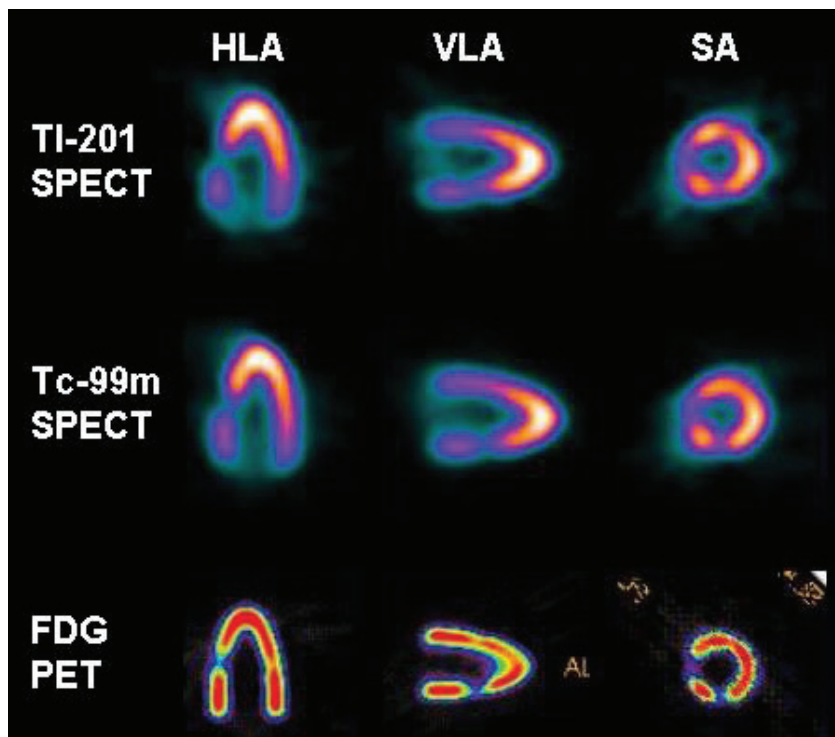

Figure 26. Comparing ^{201}Tl (t$^{1/2}$=3 days) and ^{99m}Tc (t$^{1/2}$=6 hours) SPECT and ^{18}FDG (t$^{1/2}$=1.8 hours) PET for myocardial perfusion scan.
Source: https://www.actascientific.com/ASPS/pdf/ASPS-03-0252.pdf

To produce [^{18}F]FDG, Fluorine-18 is combined with glucose through a series of chemical reactions. It is given to patients to locate areas that use a lot of glucose like inflamed tissues, cancer cells and the brain. The gamma rays emitted are then captured by sensors that are fed to a computer to generate images. From the images, radiologists and physicians can give proper diagnosis and consequently effective treatment.

Because SPECT and PET radiopharmaceuticals only reveal physiological abnormalities, they can be combined with CT or MRI scans which reveal the anatomical state of a disease as in the case of detecting thyroid cancer metastases in neck lymph nodes (Fig. 27) [65].
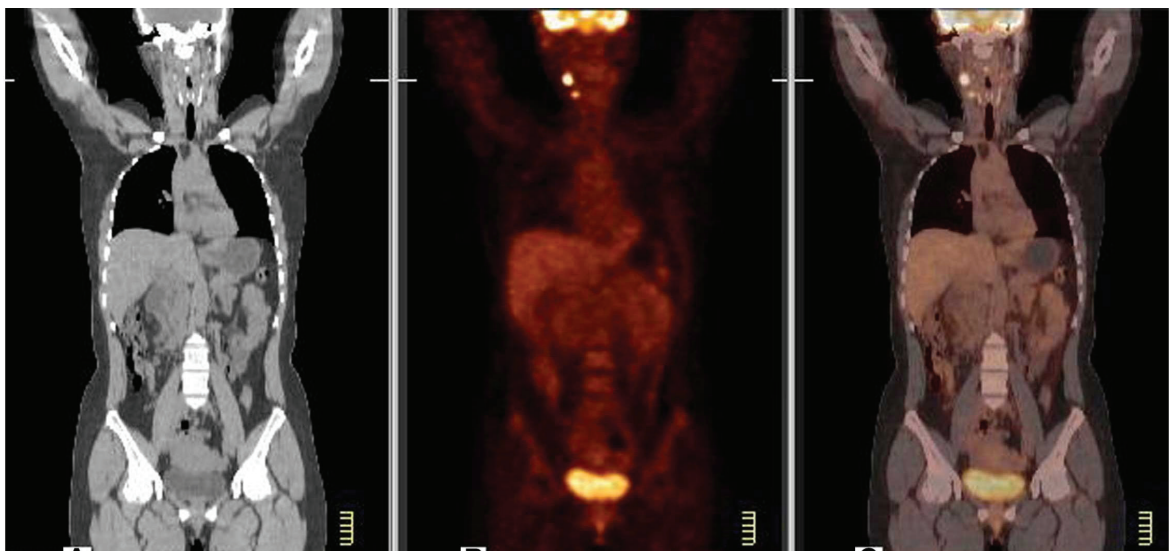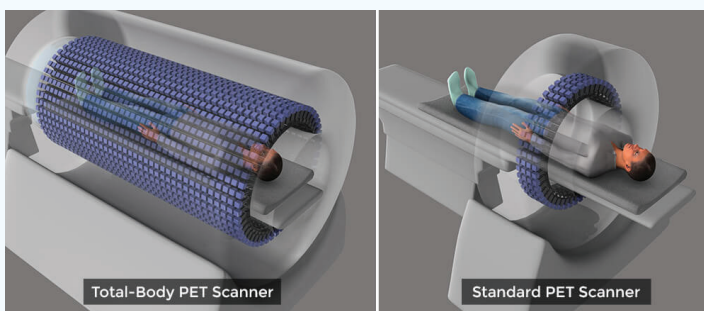

Figure 27. (from left to right) CT scan, PET scan, combined PET-CT scan of neck lymph node metastasis using [^{18}F]FDG as PET radiotracer.
Source: https://www.spandidos-publications.com/article_images/ol/11/4/ol-11-04-2420-g00.jpg.


One of the recent developments in nuclear medicine is the Total Body PET Scanner. It offers extremely high sensitivity and greater efficiency compared to Standard PET scanners.

Source: https://www.cancer.gov/sites/g/files/xnrzdm211/files/styles/cgov_article/public/ cgov_image/
media_image/100/000/2/files/total-body-PET-standard-PET-enlarge.jpg?h=0bca35a5 &itok=uqLPt4zDv

Radiopharmaceuticals for Therapy

Therapeutic radiopharmaceuticals are used for treatment or management of diseases. They can be classified into beta and alpha radionuclide therapy. Currently, therapeutic radiopharmaceuticals are used for the treatment of thyroid cancer, neuroendocrine tumors, prostate cancer (Fig. 28) [66], and lymphoma (cancer of lymph node). These can also be used to lessen or eliminate bone pain in patients with stage IV cancer and for management of arthritis (Fig. 29) [67].
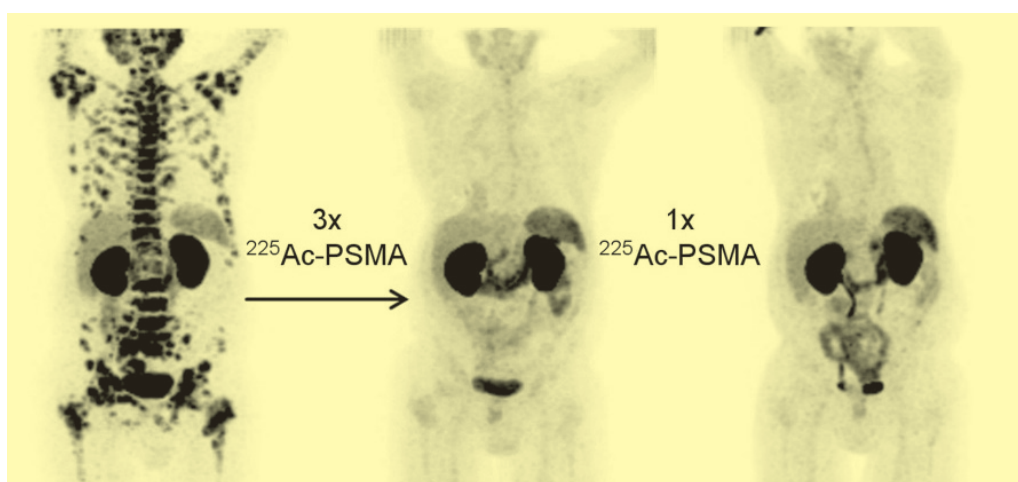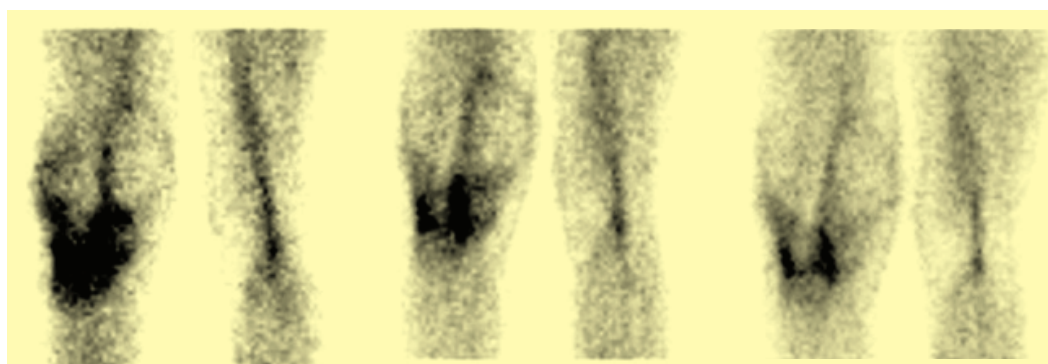

12/2014	7/2015	9/2015
PSA = 2,923 ng/mL	PSA = 0.26 ng/mL	PSA < 0.1 ng/mL

Figure 28. Example of clinical application of an alpha-emitting therapeutic radiopharmaceutical, ^{225}Ac-PSMA for Stage IV prostate cancer.
Source: http://jnm.snmjournals.org/content/57/12/1941/F1.large.jpg

Pretherapy bone scan	3-month post therapy bone scan	6-month post therapy bone scan

Figure 29. Example of clinical application of ^{90}Y-citrate for reduction of knee joint inflammation in a patient with osteoarthritis.
Source: https://ars.els-cdn.com/content/image/1-s2.0-S0969805115000189-gr8.jpg

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Nuclear 101

Nuclear Science and Health

AUTHOR

Joanna Michelle Chua-Aniago
Rommel Mascariñas
Maria Teresa Borras
Adelina DM Bulos
Philippine Nuclear Research Institute

REVIEW AND EVALUATION TEAM

Delmar R. Arzabal
Rizal Medical Center

Alfons Jayson O. Pelgone
Philippine Normal University

Ana Jamille A. Restubog
Department of Education - Quezon City

EDITORIAL TEAM

Jasmine Angelie V. Albelda,
Hans Joshua V. Dantes
Rissa Jane V. Amper

LAY-OUT, DESIGN & ILLUSTRATION

Metamedia Information Systems Corp.

**DOE-NEPIO Human Resource
Technical Working Group**

Angelina V. Manga, CESO IV
Former Administrative Service Director and Head
NEPIO HR-TWG

Ma. Cecilia P. Baldos
Chief Administrative Officer
Human Resource Management Division (HRMD)

Josefina D. Nuestro
Administrative Officer V
HRMD

Salve P. Orcine
Supervising Administrative Officer
HRMD

Daisy D. Raguini
Administrative Officer V
HRMD

Rosalina T. Rapi
Supervising Administrative Officer
HRMD

Kathleen T. Regala
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