Radiation and radioisotopes for human healthcare applications

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The use of radiation and radioisotopes in human healthcare has been one of the early developments in the non-power applications of nuclear science. The field encompasses different facets of the use of radiation in the diagnosis and therapy of a wide variety of diseases, particularly cancer, the formidable challenge of the present century. There has been a significant advancement in different areas such as diagnostic radiology, diagnostic nuclear medicine, therapeutic radiation and therapeutic nuclear medicine, including theranostic applications in personalized medicine. The R&D efforts of the Department of Atomic Energy towards ensuring indigenous availability of established radiopharmaceuticals and treatment modalities as well as to develop emerging ones for state-of-the-art radiation-related services have been significant over the years. This article presents the current status, recent developments, clinical translation of developed products and prospects related to the use of radioisotopes and radiation in the two premiere research institutions of DAE, viz. BARC and TMC.

Keywords: Cancer, diagnostic radiology, nuclear medicine, radioisotopes, theranostics.

Introduction

HOMI J. Bhabha, the architect of the Indian nuclear programme, established the Atomic Energy Commission in 1948, followed by the Department of Atomic Energy (DAE) in 1954. His mighty vision of the immense potential in the use of radioisotopes and radiation for the benefit of mankind was given shape in the early commissioning of the research reactors in India for the production of medical radioisotopes. Bhabha's vision of the use of nuclear energy for healthcare applications has been penned by him in his appointment letter to Jeejeebhoy, the first Head of the Radiation Medicine Centre (RMC), Mumbai, 'To promote the use of radioisotopes in medicine, for research, clinical investigation and therapy'. This gave birth to the present-day RMC in 1963, as the pioneering institution for the growth and development of nuclear medicine in India. It also clearly evidences that the application of nuclear radiation in human healthcare was not a by-product of the nuclear energy programme, but it was indeed one of the core visions of Bhabha for India. It was at this time that the Tata Memorial Centre, Mumbai and the then Cancer Research Institute were included by Bhabha under the administration of DAE, Anushakti Bhavan, Mumbai. Bhabha's anticipation of the major utility of radiation in diagnostics and therapeutics in medicine in general and cancer in particular, brought RMC juxtaposed to the Tata Memorial Centre, the stellar cancer hospital in India. Over the years, the dedicated pursuit of this vision has resulted in a strong synergy between the nuclear medicine physicians in RMC and oncologists in Tata Memorial Hospital (TMH), resulting in the practice of evidence-based use of radioisotopes and radiation in the early diagnosis and treatment of a large number and variety of cancers.

This article presents a comprehensive overview of the use of radioisotopes and radiation in medicine as well as oncological applications. The different aspects which have been discussed include diagnostic radiology, diagnostic nuclear medicine, therapeutic radiation, therapeutic nuclear medicine, radiation biology aspects and prospects related to the field.

Diagnosis with radiation

Diagnosis of cancer or other disease states is possible using radiation. Extensive and varied diagnostic studies which can be carried out utilize broadly two types of techniques, viz. radiology and nuclear medicine imaging techniques. A brief outline of these modalities is presented below.

Diagnostic radiology

The delivery of quality healthcare depends upon precise diagnosis and assessment of response to treatment. For

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both imaging modalities play an important role. Most of the imaging in modern medicine is now done using X-rays. Radiation is an integral part of imaging modalities like radiography, fluoroscopy, computed tomography (CT) scan, mammography, PET CT, etc.[1]. An overview of their role in the surveillance, diagnosis and treatment is elaborated.

Radiography: This is the science of using radiation to get an image of the bones, vessels, soft tissue and organs. It is one of the widely available and widely used investigations, especially in the evaluation of the respiratory system for tuberculosis, pneumonia, acute or chronic lung disease, large mass lesions as well as for cardiac disease like cardiomegaly and pericardial effusions. X-rays also have a significant role in the early diagnosis of trauma (fractures), particularly in emergency cases and ICU set-ups where patients cannot be shifted. However, limited and judicious use in pregnant patients is necessary keeping in mind the effects of radiation on the foetus.

Fluoroscopy: This is a modality that uses X-rays to obtain real-time images of an organ or structure inside a patient, with a relatively lesser dose to the patient compared to a CT scan. It is used in both diagnosis and therapeutic manoeuvres. Fluoroscopy finds multiple uses in the evaluation of motility disorders like achalasia, identification of strictures and malignancies and also for the identification of gastroesophageal reflux disease. It helps in the identification of post-operative leaks, disorders of the uterus and fallopian tubes through hysterosalpingography as well as in paediatric disorders. The radiation dose of a fluoroscopic examination is relatively less compared to a CT scan; however, the latter offers better anatomic detail.

Orthopantogram (OPG): This is a tomographic radiograph that uses a focal trough that approximates the mandibular curve to provide a view of the facial skeleton and teeth. It is a modality used by dentists for obtaining information about the patients' dentition, evaluating dental infections and decay, as also trauma, and for jaw lesion characterization[2]. The amount of radiation that the patient receives in an OPG is about 0.014 mSv, which is less than the dose of ~0.02 mSv received in a chest X-ray.

Dual-energy X-ray absorptiometry (DEXA) scan: This is an imaging modality that uses X-rays for the evaluation of bone mineral density. This is the average concentration of minerals in a specified section of the bone. DEXA is an imaging modality that uses low radiation, is precise and can be taken across different regions of the body. DEXA scan is an important tool in the evaluation and prevention of fractures, especially in the high-risk group of patients by the early treatment protocol[3].

Mammography: Dedicated X-ray imaging of the breast is known as mammography. This is widely used as a screening tool for detecting early breast cancer, as a diagnostic tool for characterizing breast pathologies and for surveillance of treated breast cancer patients[4].

CT scan: This is an imaging modality in which X-rays are used to obtain cross-sectional images[5]. A CT machine consists of an X-ray machine with a row of detectors on the opposite side located in a gantry which rotates around the patient as the patient table moves through the gantry. The data obtained are based on the number of X-rays attenuated by the tissue in the track of the X-ray beam. The data are analysed using complex algorithms to provide an image that appears like an axial slice through the body of the patient. Once the data are obtained, there are multiple post-processing techniques that can be used to view the sagittal and coronal images of the patient.

CT scan is the first line of imaging in cases of trauma to the head to identify the intracranial bleeds and damage to brain parenchyma. It also helps identify fractures, and damage to any organs in the body which may not be visible externally, especially in cases of blunt injury. In the case of malignancy, a CT scan gives the location of the tumours and relation to the adjacent structures which helps in defining the treatment and any intervention if required.

Cardiac CT is now being increasingly used across the world for screening of cardiac vascular problems and also in the evaluation of post-operative grafts as it is non-invasive and provides good anatomical detail. Calcium scoring a technique in cardiac CT gives scoring for the amount of calcium in the coronary vessels which helps in predicting the incidence of cardiac ischaemic events.

Digital subtraction angiography (DSA): This is the study of vessels under fluoroscopy by the injection of contrast through them and capturing the images[6]. DSA is helpful in the evaluation and therapy of vascular pathologies, guidance of biopsies and also for therapeutic interventions like vertebroplasty, where bone cement is injected into the pathological vertebra.

Interventional radiology: This is the facet of radiology that deals with diagnosing various pathologies which cannot be identified with imaging alone like a CT/fluoroscopy-guided biopsy or for differentiating a change in the post-operative patient versus a recurrence of cancer by obtaining tissues from the area of pathology using a minimally invasive approach.

Interventional radiology also deals with various image-guided therapies, like trans-arterial chemo-embolization (TACE) or trans-arterial radio-embolization (TARE), especially in treatment of cancers. Ablation of tumours of different pathologies also include radiofrequency, microwave or cryoablation techniques.

Diagnostic nuclear medicine

The practice of nuclear medicine involves the administration of a fixed amount of radioisotope-labelled pharmaceuticals

to a patient. Depending on the emission characteristic of these agents they can either be used for diagnostics or for therapeutic indications. Most diagnostic tracers are either labelled with a gamma-emitting radionuclide like technetium-99m (^{99m}Tc) or a positron-emitting one like fluorine-18 (^{18}F). When a gamma-emitting radiopharmaceutical is administered to a patient, it localizes to specific organ sites based on the property of the pharmaceutical and emits radiation. As the gamma rays have higher penetration power they come out of the body and can be easily detected with the help of radiation detectors. This basic principle is used in most of the nuclear medicine imaging procedures. One of the first such detectors used for imaging in 1951 was the rectilinear scanner invented by Benedict Cassen[7]. Then came the Anger camera, developed by Haul Anger in 1958, which is considered to be the forerunner of all other gamma cameras to follow[8]. In 1964, Paul Harper started using ^{99m}Tc for imaging, which proved to be a game-changer in gamma-camera imaging. ^{99m}Tc not only has emission characteristics favourable for gamma camera imaging but is also chemically suitable for tagging with a wide array of pharmaceuticals[9]. In 1951, Wren and co-workers discovered the favourable imaging characteristics of positron-emitting radioisotopes, which ultimately helped in paving the way for using positron-emitting radiotracers[10]. Along with the development of radiotracers, over the years, newer and improved imaging techniques have been introduced. Initial gamma camera imaging was planar, and did not offer good resolution and anatomical localization. However, technologies for tomographic reconstruction have changed the scenario, thereby allowing the development of positron emission tomography (PET) imaging by Phelps and colleagues, and single-photon emission computerized tomography (SPECT) by Kuhl and colleagues in the 1970s (refs 11, 12). The advent of the metabolic tracer ^{18}F fluorodeoxyglucose (FDG) and its use in PET imaging have become ubiquitous in medical practice and driven the growth of diagnostic nuclear medicine. In recent times, the development of fusion imaging modalities such as PET-CT and SPECT-CT has revolutionized diagnostic imaging, especially in the field of oncology. Fusion imaging not only provides us with crucial functional information regarding disease processes, but also provides precise anatomical locations of the diseased sites.

SPECT radiopharmaceuticals: Table 1 summarizes a few of the most commonly used SPECT radiopharmaceuticals.

PET radiopharmaceuticals: Table 2 lists the PET radiopharmaceuticals commonly used in the diagnosis of various cancers and their physiological indications.

Intervention radiology-guided radionuclide therapy: Apart from conventional methods of delivering radionuclide therapy via the intravenous route (^{177}Lutetium DOTATATE injection) or the oral route (^{131}Iodine), other routes of administration are also in use. In recent years, intra-arterial delivery of radionuclides to malignant liver lesions has gained attention. These therapies are given in collaboration with intervention radiologists. Two primary types of intra-arterial radionuclide therapies are currently in practice. The first is intra-arterial brachytherapy, also known as trans-arterial radio-embolisation (TARE), where tiny glass or resin particles containing beta-emitting radionuclides such as ^{90}Yttrium are administered directly in the common hepatic artery and its branches to irradiate the heptic tumour bed directly[13]. This is a targeted therapy with less systemic side effects. The types of tumour primarily targeted in this procedure are hepatocellular cancer and liver metastasis of colorectal cancers. Another relatively new form of intra-arterial therapy that is being practised is the intra-arterial administration of ^{177}Lutetium DOTATATE in metastatic neuroendocrine tumours (NET) with liver dominant disease[14,15]. This method provides more radiation to the liver lesions as opposed to the conventional intravenous method.

Therapy with radiation

Radiation therapy involves the use of high-energy ionizing radiation to damage the DNA of cancer cells and destroy their ability to divide and grow. It may be delivered externally using teletherapy machines or via the use of sealed radioactive sources placed inside the patient on a temporary or permanent basis (brachytherapy). As opposed to the use of sealed radiation sources used in radiation oncology, unsealed radiation sources in the form of radioactive drugs, viz. radiopharmaceuticals are used in nuclear medicine. These radiopharmaceuticals are highly target-specific and usually contain radioisotopes which are particulate emitters. Several radionuclides which decay by the emission of beta particles (β^-), alpha particles (α), or Auger electrons (AE) and conversion electrons (CE) are utilized as therapeutic radionuclides in radiopharmaceutical preparations, intended for use in therapeutic nuclear medicine. The following section briefly describes two possibilities of cancer therapy using radiation.

Therapeutic radiation

Radiation found use in cancer therapy merely months after its discovery by Wilhelm Conrad Roentgen in 1895. Early teletherapy machines, however, capable of generating very low-energy X-rays, failed to deliver curative radiation doses without producing unacceptable normal tissue destruction. Then, at the turn of the 20th century, radioactivity was discovered by Antoine-Henri Becquerel. Soon, radium tubes were being applied in direct proximity to tumours as early forms of brachytherapy developed. Once again, initial optimism gave way to caution as hazardous effects of radiation, particularly secondary malignancies, came to light. Despite these and numerous other stumbling blocks, a

Table 1. SPECT radiopharmaceuticals

Radiopharmaceutical	Physiological principle	Clinical use
^{99m}Tc-MDP[a]	Bone turnover	Skeletal metastasis, primary bone tumour, infection, etc.
^{99m}Tc-DTPA[b]	Glomerular filtration	Renal function
^{99m}Tc-EC[c]	Tubular secretion	Renal function
^{99m}Tc-DMSA[d]	Cortical fixation	Renal cortical imaging
^{99m}Tc-Sestamibi	Myocardial perfusion	Coronary artery disease
^{201}Tl-chloride	Myocardial perfusion	Coronary artery disease
^{99m}Tc-ECD[e]	Brain perfusion	Epilepsy, dementia, etc.
^{99m}Tc-MAA[f]	Lung perfusion	Pulmonary embolism
^{67}Ga-citrate	Iron-binding protein	Tumour imaging, infection
Na^{123}I	Sodium iodine symporter (NIS)	Thyroid pathology
^{123}I-MIBG[g]	Presynaptic uptake	Neuroectodermal tumours
^{111}In labelled leukocytes	Chemotaxis	Infection imaging

[a]Methylene diphosphonate; [b]Diethylenetriaminepentacetic acid; [c]Ethylenedicysteine; [d]Dimercaptosuccinic acid; [e]Ethyl cysteinate dimer; [f]Macroaggregated albumin; [g]Meta-iodobenzylguanidine.

Table 2. Commonly used PET radiopharmaceuticals

Radiopharmaceutical	Physiological principle	Clinical use
^{18}F FDG	Glucose metabolism	Tumour imaging, infection imaging
^{18}F NaF	Bone turnover	Bone metastasis
^{68}Ga PSMA[a]	Receptor imaging	Prostate carcinoma
^{68}Ga DOTA-NOC	Receptor imaging	Neuro-endocrine tumour
^{82}Rb-chloride, $^{13}NH_3$	Myocardial perfusion	Coronary artery disease

[a]Prostate-specific membrane antigen.

constantly improving understanding of the biological effects of radiation along with technological advancements in imaging and treatment delivery have expanded the scope of therapeutic radiation oncology over the last century.

One of the most significant breakthroughs came in 1911, when Claudius Regaud demonstrated that a ram's testes could be sterilized without burning the scrotal skin if subjected to divided doses of radiation instead of a single large dose. Likening the testes to proliferating tumours and the scrotum to dose-limiting normal tissue, this model laid the foundation for fractionated radiotherapy. Subsequently, teletherapy machines evolved from 200 keV Coolidge tubes of the 1910s to the first 6-megavoltage capable linear accelerators (LAs) devised in the 1960s. However, the more compact and relatively cost-effective cobalt-60 units were the preferred teletherapy machines of the time. In this era, target volumes were determined on orthogonal X-rays based on estimates of tumour location and treatment delivery led to homogeneous dose-deposition within the target and surrounding normal tissue alike. The integration of CT with treatment planning and the development of more sophisticated LAs equipped with multi-leaf collimators (MLCs) in the 1980s led to three-dimensional conformal radiotherapy (3DCRT) gaining prominence. Comprised of small metallic leaves capable of independent movement, these MLCs could instantly wrap around the shape of a target, thereby sparing surrounding tissue. Unfortunately, 3DCRT failed to evade sensitive normal tissue directly traversed by photon beams. A resolution to this issue was envisioned as early as 1978, when computer-programmed radiation delivery was first conceptualized. However, intensity-modulated radiation therapy (IMRT) would become a reality only in the late 1990s. With the help of complex dose optimization algorithms, IMRT has enabled the delivery of intricate, even concave, dose distributions. Parallel advancements in immobilization, motion management and on-board image guidance (IGRT) have ensured that IMRT can be delivered with millimetre precision.

Advancements in brachytherapy have also kept pace with teletherapy. Early low-dose rate (LDR) brachytherapy systems using radium-226 and radon-222 sources were preloaded and applied manually over 1–2 sessions, each lasting several days. Concerns pertaining to radiation exposure to personnel and safe disposal prompted the use of artificially produced radionuclides. High specific-activity sources, such as Cobalt-60 and Iridium-192, could deliver a high dose rate (HDR) brachytherapy, which reduced treatment time from days to hours. It was also possible to fashion them into miniature sources which were instrumental in the development of remote after-loading. Dose optimization was also made possible with the stepping source dosimetry system, which used a single source passing through multiple channels to generate the desired dose distributions. Improvements in modern teletherapy capabilities have, however, led to a steady decline in the brachytherapy procedure. Nevertheless, it remains vital to the success of select radiotherapy protocols.

Over time, the utility of radiotherapy has expanded beyond the treatment of inoperable tumours. In fact, radiation has replaced surgery as the definitive modality of treatment

in cancers of the nasopharynx, anal canal and cervix[16–18]. As a part of organ-preservation strategies, radiotherapy has offered an alternative to morbid surgeries, including larynxgectomies and cystectomies[19,20]. Long confined to locoregional therapy, the recent description of an oligometastatic state has extended the utility of radiotherapy to target metastatic deposits as well. The use of very high radiation doses of 1–5 fractions delivered with extreme precision using stereotactic body radiotherapy (SBRT) in oligometastatic cancers has been shown to improve not just local control but also prolong survival[21]. For palliation of bone metastasis, radiotherapy has emerged as the gold standard for pain alleviation. As an emergency measure, radiotherapy is often the final recourse to combat spinal-cord compression and raised intracranial pressure triggered by spinal and brain metastases respectively.

Today, radiotherapy is required by more than half of all cancer patients at some point during their treatment. Going forward, newer innovations such as ultrahigh dose-rate FLASH irradiation and wider accessibility to proton and heavy-ion therapies may further broaden the scope of radiotherapy in cancer care. If history is any guide, radiotherapy will only get safer, more reliable and more effective in the future.

Therapeutic Nuclear Medicine and Theranostics

Targeted radionuclide therapies and theranostics are areas of great interest in the field of nuclear medicine. Radiopharmaceuticals designed for therapy are agents which deliver therapeutic doses of particulate and ionizing radiation (by emission of α, β^-, AE and CE) to diseased sites. Targeted radionuclide therapy is a treatment modality that makes use of molecular vectors for transporting the radionuclides to specific biological sites by virtue of their specific affinity, exerting therapeutic effect by inducing cytotoxicity to the tumour cells. Recent advances in this area include a host of therapeutic radiopharmaceuticals by combining radionuclides (viz. ^{131}I, ^{32}P, ^{166}Ho, ^{188}Re, ^{177}Lu, ^{90}Y) with an array of receptor-avid and immune-derived molecular vectors, designed to treat a variety of cancers.

With the introduction of new isotopes produced in the medium-flux Dhruva reactor and made available through the Board of Radiation and Isotope Technologies (BRIT), several therapeutic modalities have been made possible in the therapeutic arena, in line with newer developments in nuclear medicine, that looked beyond the conventional therapeutic isotopes (^{131}I, ^{153}Sm, ^{166}Ho, ^{32}P) having limited applications in oncology. This broadening of the scope of therapeutic nuclear medicine has led to the unravelling of the potential of Lutetium-177. The emergence of ^{177}Lu as the ideal metallic-analogue of radioiodine has revolutionized the field of radionuclide therapy in India. The production of ^{177}Lu from enriched ^{176}Lu targets via the direct (n, γ) route in the medium-flux Dhruva reactor has been standardized at BARC[22]. The favourable nuclear characteristics and feasible production route of high specific-activity ^{177}Lu in substantial amounts with adequate radionuclide purity are the prime factors for the widespread interest in its clinical use. The long half-life of this radionuclide offers distinct logistical advantages, particularly in countries with limited reactor facilities. The chemistry of the radiolanthanide Lu^{3+} allows facile radiolabelling of different molecules either directly or through bifunctional chelating agents. A number of agents have been labelled for the development of a variety of targeted radiopharmaceuticals, the noteworthy ones being ^{177}Lu-DOTA-TATE and ^{177}Lu-PSMA for the treatment of neuroendocrine and prostate malignancies respectively[23]. ^{177}Lu satisfies the essential requirement of 'theranostics'[24], a term explained later with clinical examples in this section. ^{177}Lu has promising potential in radioimmunotherapy (RIT), a therapeutic modality that involves the use of radiolabelled monoclonal antibodies in the treatment of cancers such as non-Hodgkins lymphoma, breast cancer, etc. The availability of several ^{177}Lu-labelled radiotherapeutics as an affordable and efficacious treatment option has changed the therapeutic nuclear medicine scenario in India. Another significant developmental work carried out in BARC recently is the sourcing of the promising therapeutic radioisotope Yttrium-90 from Strontium-90, recovered from HLLW, exemplifying the recovery of wealth from waste in the area of therapeutic radiopharmaceuticals. The development of a ^{90}Sr–^{90}Y generator based on the supported liquid membrane technology and formulation of ^{90}Y-based radiopharmaceuticals have been clinically translated in cancer patients[25].

Radioiodine therapy with Iodine-131 has grown over the last 70 years to play a pivotal role in the management of thyroid cancer and certain benign thyroid disorders (hyperthyroidism). The first, Iodine-131 treatment was undertaken by Saul Hertz in the Massachusetts General Hospital, USA in 1941; the year 2021 marked the 80th anniversary of this extraordinary feat in the management of thyroid disease. The Iodine-131 treatment in thyroid disorders is based upon the principle of sodium iodide symporter (NIS), an integral membrane protein residing in the basolateral membrane of thyroid epithelial cells that symports two sodium ions for every iodide ion, which leads to 20–40-fold concentration of iodine in the thyroid gland compared to its plasma concentration. This enables selective delivery of radiation dose to thyroid tissues with minimal radiation to other non-target tissues. The main routine clinical uses of Iodine-131 have been in ablation and treatment of differentiated thyroid cancer, and Graves' disease and toxic nodular goiters[26].

^{131}I-metaiodobenzylguanidine (^{131}I-mIBG) is another radiopharmaceutical using ^{131}I, that has been clinically employed in the treatment of metastatic/inoperable neural-crest tumours such as pheochromocytoma, paraganglioma, neuroblastoma and medullary thyroid carcinoma. ^{131}I-mIBG is taken into these tumour cells primarily by the noradrenaline transporter molecule through an energy-dependent

Table 3. Therapeutic and Theranostic Radiopharmaceuticals clinically translated to patients

Therapeutic radiopharmaceuticals/theranostic applications*	Clinical use
^{177}Lu-DOTATATE/^{68}Ga-DOTATATE* (DOTATATE – DOTA-tyrosine-octreotate)	Neuroendocrine cancer
^{177}Lu-EDTMP* (EDTMP – ethylediaminetetramethylene phosphonate)	Bone-pain palliation
^{177}Lu-DOTMP* (DOTMP – 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl-tetrakis(methylphosphonic acid))	Bone-pain palliation
^{177}Lu-HA* (HA – hydroxyapatite)	Radiation synovectomy
^{177}Lu-Trastuzumab*	Breast cancer
^{177}Lu-Rituximab*	Non-Hodgkins lymphoma
^{177}Lu-PSMA/^{68}Ga-PSMA (PSMA – prostate-specific membrane antigen)	Prostate cancer
^{166}Ho-HA*	Radiation synovectomy
^{188}Re-HEDP* (HEDP – hydroxyethylenediphosphonate)	Bone-pain palliation
^{188}Re-DEDTC* in lipiodol (DEDTC – diethyldithiocarbamate)	Hepatocellular carcinoma
^{131}I-Rituximab*	Non-Hodgkins lymphoma
^{131}I-Lipiodol*	Hepatocellular carcinoma
^{90}Y-DOTATATE/^{68}Ga-DOTATATE*	Neuroendocrine cancer
^{90}Y-DTPA-Rituximab	Non-Hodgkins lymphoma
^{90}Y-glass microsheres	Liver cancer

type-I amine uptake mechanism. This active uptake, which is specific, high-affinity, saturable and ATPase-dependent, is characteristic of sympathoadrenal cells and tumours arising from them. ^{131}I-labelled mIBG is an effective form of therapy in metastatic neural crest tumours that concentrates this radiopharamaceutical adequately, where surgery is not possible and can be employed successfully in both extremes of age[27].

In recent years, the term 'theranostics' has been frequently referred to denote combining diagnostic and therapeutic capabilities into a single agent with a tumour cell-specific target. The clinical objective of theranostics is to develop more specific, individualized therapies for various cancers, which has generated considerable interest in clinical oncology practice[28]. Receptor overexpression in tumours as a therapeutic target has been a major development in the field: two developments where this has found notable success are (i) [^{68}Ga]Ga-DOTATATE/^{177}Lu-DOTATATE-based[29] theranostics and peptide receptor radionuclide therapy (PRRT) in metastatic/advanced neuroendocrine neoplasms (NENs) and (ii) [^{68}Ga]Ga-PSMA-based theranostics and peptide receptor radioligand therapy (PRLT) in metastatic castration resistant prostate carcinoma (mCRPC). The former is based upon the predominance of somatostatin receptor subtype-2 ($SSTR_2$) in the NENs, targeted by intravenously administered, unsealed radiopharmaceutical [^{177}Lu]Lu-DOTATATE (DOTATATE = $DOTA^0$-(Tyr^3)-octreotate). Similarly, prostate-specific membrane antigen (PSMA), a type-II membrane glycoprotein, whose expression is up-regulated by several fold in prostate cancer cells, has been the basis for molecular imaging and therapy with ^{177}Lu-PSMA-617, a urea-based small molecule protein inhibitor designed to bind with high affinity to PSMA[30].

In addition, there have been other new developments in therapeutic nuclear medicine, such as the evolution of the α-emitting radionuclides (with Actinium-225 and Radium-223), that demonstrated better cell-killing due to high linear energy transfer (LET); transarterial radioembolization (TARE) for liver tumours (such as unresectable hepatocellular carcinoma), radioimmunotherapy employing ^{131}I/^{177}Lu-DOTA-Rituximab for the treatment of relapsed follicular, mantle cell, or other lymphomas, and ^{177}Lu-trastuzumab for HER2 or Erb2/neu positive metastatic/advanced breast malignancies, and so on. It is expected that these developments in the coming years would further expand the domain of Nuclear Medicine Therapeutics and Theranostics.

Table 3 shows some of the therapeutic and theranostic pairs of radiopharmaceuticals recently developed in BARC and clinically translated to patients.

Potential effects of radiation

Radiation is often categorized as either ionizing or non-ionizing. Gamma-rays, X-rays, and the higher-energy ultraviolet part of the electromagnetic spectrum are ionizing, whereas the lower-energy ultraviolet, visible light, infrared, microwaves and radiowaves are non-ionizing. Ionizing radiation is capable of inducing DNA damage, introducing mutations and causing cell death, whereas non-ionizing radiation differs in the way it acts on tissues. However, exposure to intense, direct amounts of non-ionizing radiation may also damage the tissues by generating heat[31].

Double-stranded break (DSB) in DNA is the predominant mode of cell-killing after exposure to ionizing radiation. DSBs can result in unstable chromosomal aberrations that can lead to either death or senescence of the cells. There are two mechanisms by which radiation ultimately affects cells – direct and indirect action. In direct action, the radiation interacts directly with the atoms of the DNA molecule or some other cellular component critical to the cell's survival. In indirect action, the radiation interacts with water molecules producing radicals such as hydroxyl (OH), damaging the DNA. Damage to the cell becomes apparent when it is called upon to divide[32].

The effects of radiation can be stochastic or deterministic. Stochastic effects are those for which the probability increases with dose, without a threshold. Radiation-induced

malignancy is a stochastic effect. Deterministic effects are those for which incidence and severity depend on the dose, but there is a threshold dose. Radiation-induced skin erythema is a deterministic effect[33]. Radiation can cause early as well as late effects to the normal tissues. Early effects are due to acute cell killing and involve tissues with rapid cell turnover that can be repaired over time. The mechanism of late effects includes vascular damage and fibrosis, which affects tissues without rapid cell turnover and cannot be completely repaired[34].

The potential for radiation-induced cancer depends on the amount and accumulation of exposure over a long time. Lower exposure levels like background radiation, nuclear medicine, CT scans or diagnostic X-rays carry low risks. Nonetheless, evidence suggests that diagnostic radiation levels are associated with a low level of risk for inducing disease many years after exposure. Figure 1 show some of the commonly used diagnostic procedures and the associated radiation exposure.

In the International Commission on Radiological Protection (ICRP) Publication 103 (2007), the lifetime risk of cancer incidence has been calculated for each organ, averaged over all ages, both sexes, and compared between Health Protection Agency (HPA) and nominal risk coefficients. What emanates is that these risks are low and depend on the organ exposed, the radiation doses and the age at exposure, ranging from 0.16 for the esophagus and 1.08 for the lung. This also draws attention to the fact that radiation, whether background, diagnostic or therapeutic, is only one of the causes of cancer, and a large number of other causes/factors like tobacco abuse and lifestyle contribute a greater extent to oncogenesis.

Therapeutic radiation, being an integral part of cancer treatment, may be associated with a risk of development of second cancers, also known as radiation-induced second malignancies (RISMs). Currently, 17%–19% of patients develop a second malignancy after their primary treatment[35], of which radiotherapy (RT) contributes to only around 5% (ref. 36). The risk of RISM increases proportionately with increasing duration of survival. In a systematic review of 3434 second cancer patients across 11 second solid cancers, the dose–response relationship for second cancer was found to be almost linear with no threshold dose[37].

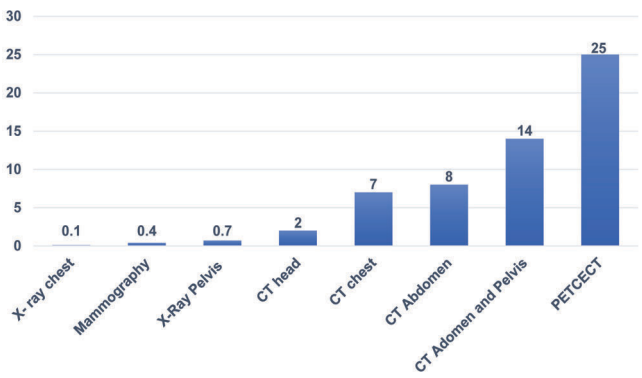

Figure 1. Common diagnostic procedures and associated radiation exposure (mSv).

Radiation protection is essential to safeguard people from the harmful effects of exposure to ionizing radiation. The three fundamental factors for radiation protection include time, distance and shielding. Protection standards, including annual dose limits, are set by the ICRP internationally and the National Council on Radiation Protection and Measurements (NCRP) nationally. The goal should be to keep radiation doses as low as reasonably achievable (ALARA).

Conclusion and future prospects

Radiation has become an integral and ubiquitous part of modern healthcare both in terms of diagnosis and treatment. Advances in radiodiagnosis in the past few decades, including cross-sectional imaging and integration of anatomical and metabolic imaging, have resulted in an unprecedented ability to image the human body with high precision and accuracy. High-precision imaging combined with developments in catheterization, medical contrast agents, instrumentation and related fields has also resulted in a previously unattained ability to perform interventional radiological procedures for diagnosis and treatment, which have replaced open surgical techniques in many instances. These advances have made more complicated procedures possible and reduced the risks of many other procedures. There have also been unprecedented advances in radiotherapy resulting in higher tumour target dose delivery with lesser exposure to normal tissue, which has led to higher cure rates in many cancers. Lastly, treatment with radioisotopes has come of age with the discovery of novel isotopes and chelating agents which have enhanced our ability to deliver targeted radiation to many tumours.

It is likely that these advancements will continue in the coming few years and decades. Imaging modalities are likely to become integrated with artificial intelligence techniques, which is likely to lead to less reliance on scarce human expertise and enable scalability in many currently underserved parts of the world. Heavy particle-based radiotherapy and novel radioisotope agents are likely to result in treatments with exquisite specificity and contribute to the development of currently evolving precision medicine paradigm. As with any other technology, healthcare providers and institutions should continue to develop and invest in processes, which will minimize the risks of diagnosis and treatment with radiation-based techniques.

1. Hricak, H. *et al*., Managing radiation use in medical imaging: a multifaceted challenge. *Radiology*, 2011, **258**, 889–905.
2. Kumar, M., Shanavas, M., Sidappa, A. and Kiran, M., Cone beam computed tomography – know its secrets. *J. Int. Oral Health*, 2015, **7**, 64–68.

3. Lorente-Ramos, R., Azpeitia-Armán, J., Muñoz-Hernández, A., García-Gómez, J. M., Díez-Martínez, P. and Grande-Bárez, M., Dual-energy X-ray absorptiometry in the diagnosis of osteoporosis: a practical guide. *Am. J. Roentgenol*., 2011, **196**, 897–904.
4. Joe, B. N. and Sickles, E. A., The evolution of breast imaging: past to present. *Radiology*, 2014, **273**, S23–S44.
5. Liguori, C. *et al.*, Emerging clinical applications of computed tomography. *Med. Devices (Auckl.)*, 2015, **8**, 265–278; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4467659/.
6. Okamoto, K., Ito, J., Sakao, K. and Yoshimura, S., The principle of digital subtraction angiography and radiological protection. *Interv. Neuroradiol*., 2000, **6**, 25–31.
7. Blahd, W. H., Ben Cassen and the development of the rectilinear scanner. *Semin. Nucl. Med*., 1996, **26**, 165–170.
8. Stefanović, L., The beginnings and development of diagnostic imaging in nuclear medicine. *Med. Pregl*., 2001, **54**, 289–296.
9. Eckelman, W. C., Radiolabeling with technetium-99m to study high-capacity and low-capacity biochemical systems. *Eur. J. Nucl. Med.*, 1995, **22**, 249–263.
10. Wrenn, F. R., Good, M. L. and Handler, P., The use of positron-emitting radioisotopes for the localization of brain tumors. *Science*, 1951, **113**, 525–527.
11. Phelps, M. E., Hoffman, E. J., Mullani, N. A. and Ter-Pogossian, M. M., Application of annihilation coincidence detection to transaxial reconstruction tomography. *J. Nucl. Med*., 1975, **16**, 210–224.
12. Kuhl, D. E., Edwards, R. Q., Ricci, A. R., Yacob, R. J., Mich, T. J. and Alavi, A., The Mark IV system for radionuclide computed tomography of the brain. *Radiology*, 1976, **121**, 405–413.
13. Kallini, J. R., Gabr, A., Salem, R. and Lewandowski, R. J., Transarterial radioembolization with yttrium-90 for the treatment of hepatocellular carcinoma. *Adv. Ther*., 2016, **33**, 699–714.
14. Thakral, P., Sen, I., Das, S. S., Manda, D., Virupakshappa, C. B. and Malik, D., Dosimetric analyses of intra-arterial versus standard intravenous administration of 177Lu-DOTATATE in patients of well differentiated neuroendocrine tumor with liver-dominant metastatic disease. *Br. J. Radiol.*, 2021, **94**, 20210403.
15. Ebbers, S. C., Braat, A. J. A. T., Moelker, A., Stokkel, M. P. M., Lam, M. G. E. H. and Barentsz, M. W., Intra-arterial versus standard intravenous administration of lutetium-177-DOTA-octreotate in patients with NET liver metastases: study protocol for a multicenter, randomized controlled trial (LUTIA trial). *Trials*, 2020, **21**, 141.
16. Al-Sarraf, M. *et al*., Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J. Clin. Oncol.*, 1998, **16**, 1310–1317.
17. Nigro, N. D., Seydel, H. G., Considine, B., Vaitkevicius, V. K., Leichman, L. and Kinzie, J. J., Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. *Cancer*, 1983, **51**, 1826–1829.
18. Gupta, S. *et al*., Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: a randomized controlled trial. *J. Clin. Oncol.*, 2018, **36**, 1548–1555.
19. Wolf, G. T. *et al*., Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N. Engl. J. Med.*, 1991, **324**, 1685–1690.
20. James, N. D. *et al*., Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N. Engl. J. Med.*, 2012, **366**, 1477–1488.
21. Palma, D. A. *et al*., Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*, 2019, **393**, 2051–2058.
22. Pillai, M. R. A., Chakraborty, S., Das, T., Venkatesh, M. and Ramamoorthy, N., Production logistics of 177Lu for radionuclide therapy. *Appl. Radiat. Isot*., 2003, **59**, 109–118.
23. Banerjee, S., Pillai, M. R. A. and Knapp, F. F., Lutetium-177 therapeutic radiopharmaceuticals: linking chemistry, radiochemistry, and practical applications. *Chem. Rev*., 2015, **115**, 2934–2974.
24. Das, T. and Banerjee, S., Theranostic applications of lutetieum-177 in radionuclide therapy. *Curr. Radiopharm.*, 2016, **9**, 94–101.
25. Mitra, A. *et al*., On the separation of yttrium-90 from high-level liquid waste: purification to clinical-grade radiochemical precursor, clinical translation in formulation of 90Y-DOTATATE patient dose. *Cancer Biother. Radiopharm*., 2021, **36**, 143–159.
26. Avram, A. M., Zukotynski, K., Nadel, H. R. and Giovanella, L., Management of differentiated thyroid cancer: the standard of care. *J. Nucl. Med*., 2022, **63**, 189–195.
27. Pryma, D. A. *et al*., Efficacy and safety of high-specific-activity ^{131}I-MIBG therapy in patients with advanced pheochromocytoma or paraganglioma. *J. Nucl. Med*., 2019, **60**, 623–630.
28. Ahmadzadehfar, H., Rahbar, K., Essler, M. and Biersack, H. J., PSMA-based theranostics: a step-by-step practical approach to diagnosis and therapy for mCRPC patients. *Semin. Nucl. Med*., 2020, **50**, 98–109.
29. Basu, S. *et al*., One decade of 'bench-to-bedside' peptide receptor radionuclide therapy with indigenous [^{177}Lu]Lu-DOTATATE obtained through 'direct' neutron activation route: lessons learnt including practice evolution in an Indian setting. *Am. J. Nucl. Med. Mol. Imag*., 2020, **10**, 178–211.
30. Suman, S. *et al.*, Therapeutic efficacy, prognostic variables and clinical outcome of ^{177}Lu-PSMA-617 PRLT in progressive mCRPC following multiple lines of treatment: prognostic implications of high FDG uptake on dual tracer PET-CT vis-à-vis Gleason score in such cohort. *Br. J. Radiol*., 2019, **92**, 20190380.
31. The Electromagnetic Spectrum: Non-Ionizing Radiation; https://www.cdc.gov/nceh/radiation/nonionizing_radiation.html (last accessed on 10 July 2022).
32. Hall, E. J. and Giaccia, A. J., *Textbook of Radiobiology*, 2019, 8th edn.
33. Hamada, N. and Fujimichi, Y., Classification of radiation effects for dose limitation purposes: history, current situation and future prospects. *J. Radiat. Res*., 2014, **55**(4), 629–640; doi:10.1093/jrr/rru019. Epub 2014 May 3. PMID: 24794798; PMCID: PMC4100010.
34. Leenhouts, H. P. and Chadwick, K. H., The molecular basis of stochastic and nonstochastic effects. *Health Phys*., 1989, **57**, 343–348.
35. Morton, L. M., Onel, K., Curtis, R. E., Hungate, E. A. and Armstrong, G. T., The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. *Am. Soc. Clin. Oncol. Educ. Book*, 2014, e57–e67; doi:10.14694/EdBook_AM.2014.34.e57.
36. Dracham, C. B., Shankar, A. and Madan, R., Radiation induced secondary malignancies: a review article. *Radiat. Oncol. J.*, 2018, **36**, 85–94.
37. Berrington de Gonzalez, A. *et al.*, Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. *Int. J. Radiat. Oncol. Biol. Phys*., 2013, **86**, 224–233.

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