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NEWSLETTER

ESCALATING WITH EVOLVING TECHNOLOGIES

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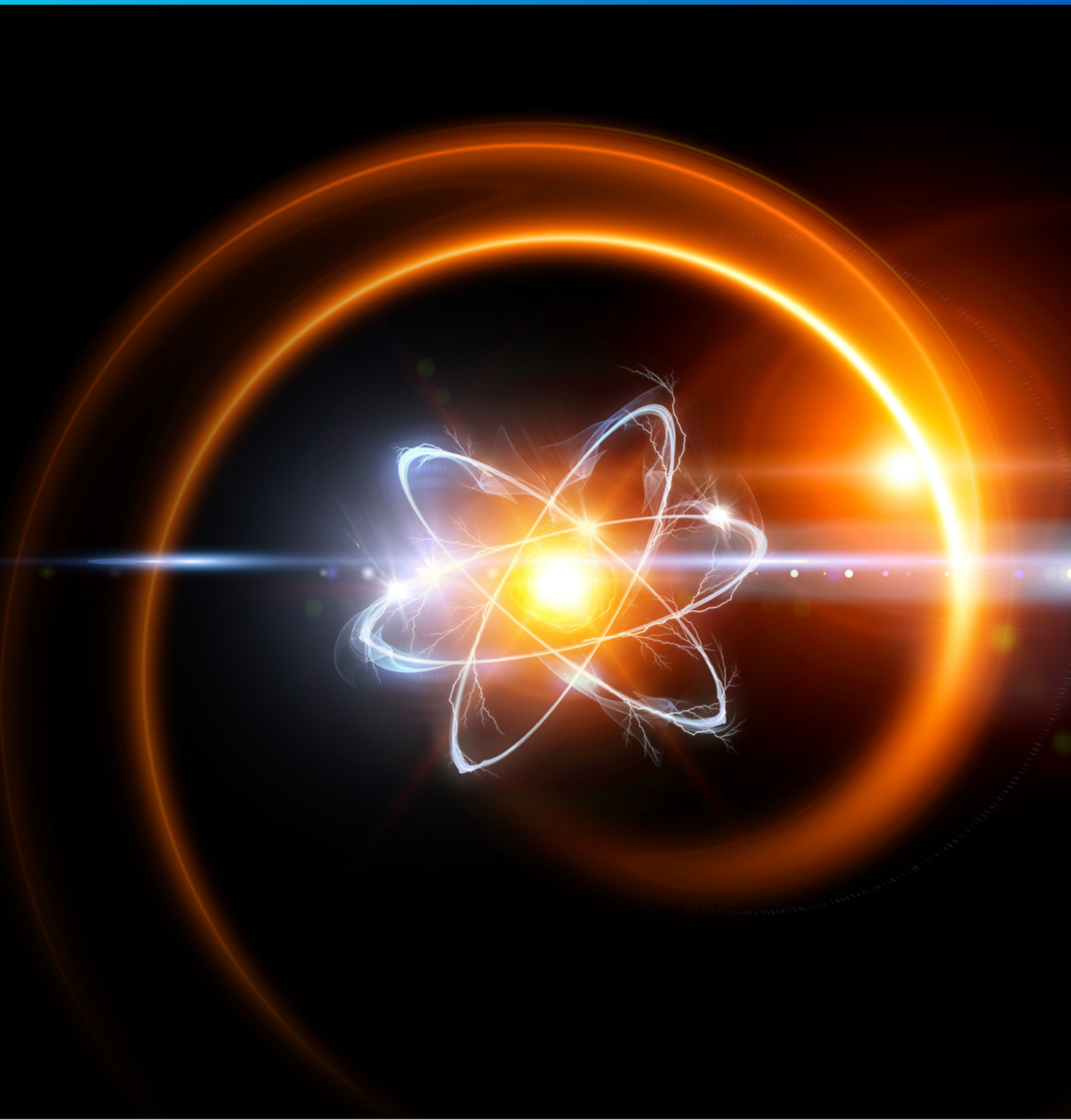

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पधारो म्हारे देस

Dear Colleagues,

This is great pleasure, I wish to apprise you all that India has been chosen as “The Highlight Country” for the upcoming SNMMI meeting to be held in Chicago, USA from 24th to 27th June 2023.

SNMMI, USA is an international scientific and professional organizations with over 15,000 professional members - physicians, technologists, and scientists, and allied professionals who are working in the field of nuclear medicine. The organization, founded in 1954, provides a customized approach to the identification, diagnosis, and treatment of disease, with a goal of advancing personalized medicine

The initiative of Sir Homi J Bhabha having Chaired the first congress on “Atoms for Peace” at Geneva, Switzerland in 1955 was an eye opener to the entire world, which gave birth to the discipline of Nuclear Medicine. The society of Nuclear Medicine (SNM-India) was founded and registered in 1967. SNMI-India over the last 55 years, had been organizing annual conferences, CMEs, thematic workshops and had been partnering with ICNM, IASNM, SNMMI, EANM, WFNMB, WARMTH amongst many others for mutual interests.

With the exponential growth of Nuclear medicine in India over the last 2 decades and with our regular participation and display of our cutting edge and pioneering work in the Annual SNMMI meetings and research publications in main stream Journals, the leadership of SNMMI has unanimously consented to declare India as the Highlight country in the Chicago SNMMI meeting, 2023 ! SNM-India delightfully acknowledges this global recognition due to India’s emerging prominence in the field of Nuclear Medicine ! With more than 6,500 attendees expected in Chicago, the SNMMI Annual Meeting attracts leading experts in the field of nuclear medicine from around the world and it is matter for pride for India to be the highlight country at one of the world’s biggest nuclear medicine platform.

Undoubtedly, India has today evolved to the era of theranostics with not just beta- but alpha therapy as well, in prostate cancer, neuroendocrine tumors and several other refractory malignancies. The SNM-India ensures that India gets to the forefront of the clinical and research theranostics. We had been signing MOUs periodically between SNM-India and SNMMI through which we are facilitating effective collaborations between interested Nuclear Medicine Physicians, Radiochemists, physicists as well experts from other domains from both the Countries!

As part of this highlight country event, for the first time at SNMMI; SNM-India will organize four CE sessions with eminent speakers from India will showcase the cutting edge research done in this part of the world. The four CE sessions are on :

Radiopharmaceutical Therapies paving the way to Nuclear Oncology,
Infection and Inflammation Imaging,
Oncologic Imaging & Therapies – What is new
Translational theranostics research and AI.

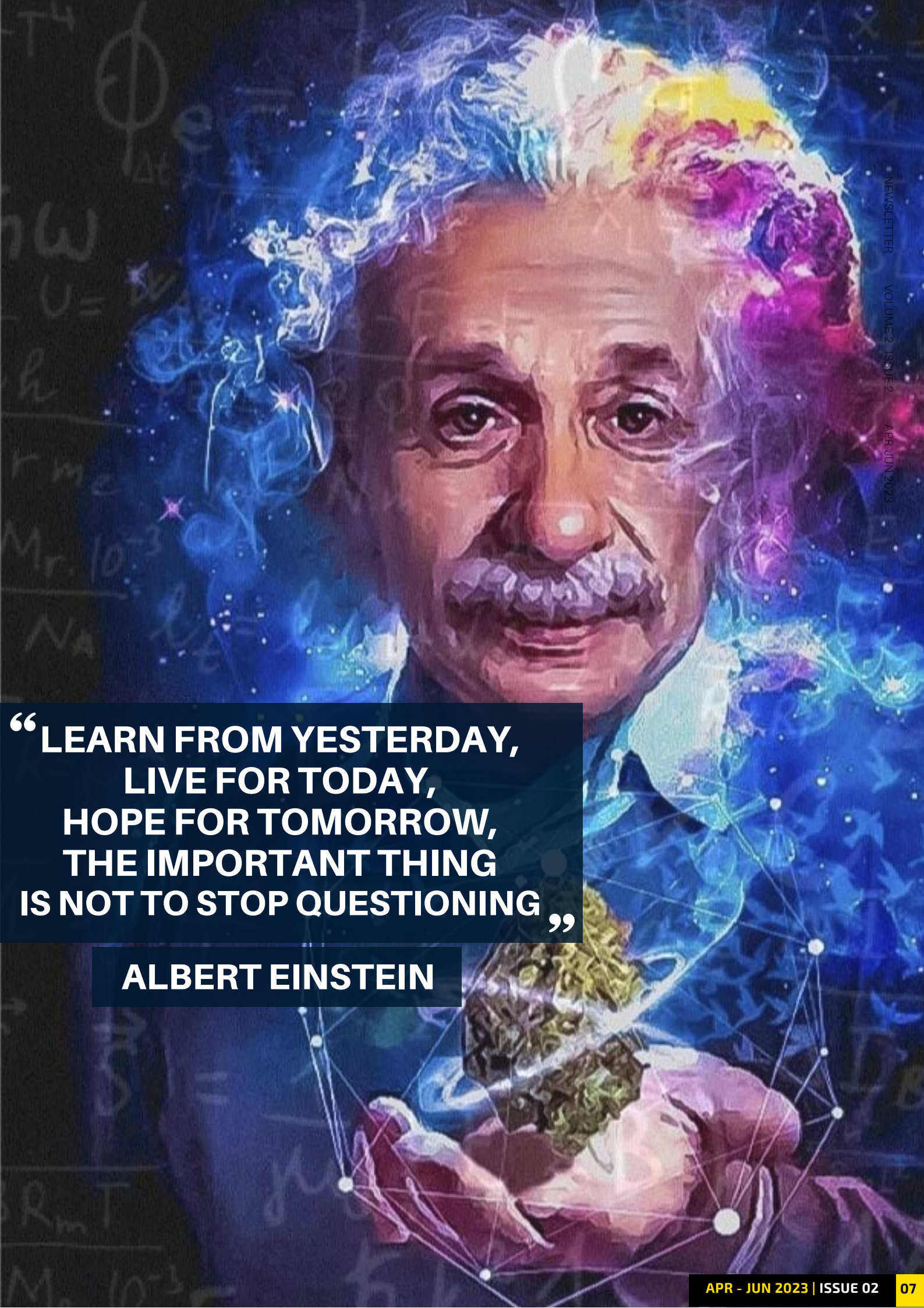
We on behalf of India, cordially invite you to join us at the opening gala reception to witness through the Highlight country Video showing the transformation of the World's oldest civilization catching up with the most advanced countries in medicine and technologies! Enjoy typical Indian dance & music, food and beverages showcasing diverse and rich heritage and culture of India !

Delegates attending this SNMMI meeting in Chicago kindly visit the Highlight country Lounge (# 6043) and be a part of this rare honour bestowed upon India.

India beacons you at SNMMI-23 at Chicago !

Jai Hind !

Dr. Ankit Watts
Secretary HQ
SNM India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NEWSLETTER

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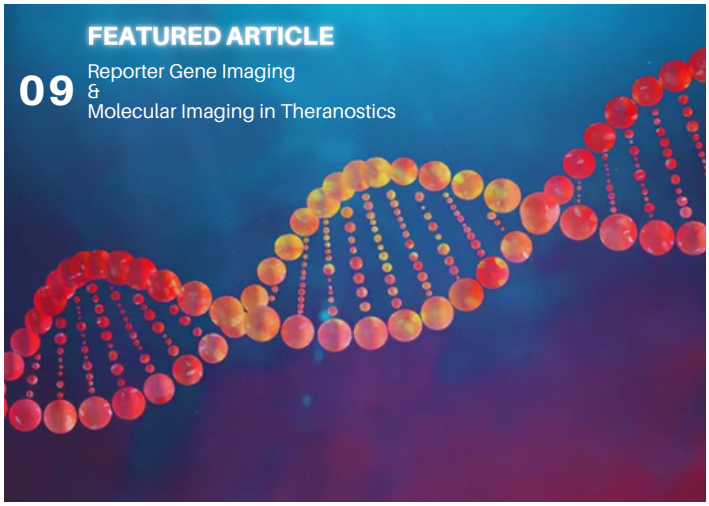

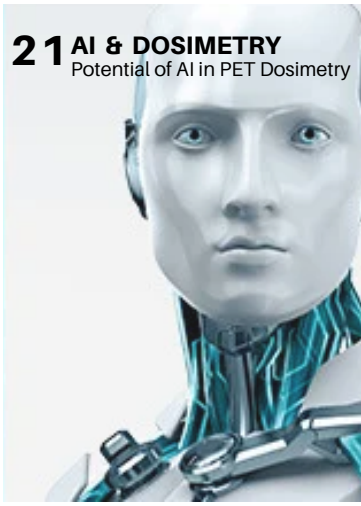

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REPORTER GENE IMAGING AND MOLECULAR IMAGING IN THERANOSTICS

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Theranostics is emerging as a crucial approach, aiming for better treatment outcomes and paving the path towards personalised medicine, considering the diverse presentation of disease among the patient population. It conceptualises the discovery of new radio-tracers, or delivery vectors and chemical agents that have selective receptivity for target molecules or receptors, which helps in strategically designing and delivering therapy regimens at cellular and molecular levels [1]. Exploratory preclinical research in the science of theranostics has led to the introduction and amalgamation of recombinant DNA technology, which involves the insertion of particular genes of interest in the cellular DNA, providing access to imaging and therapy at the gene level [2].

REPORTER GENE IMAGING IN CELL THERAPY

Reporter gene imaging uses a 'Reporter Gene', a DNA fragment that encodes specific protein molecules which can be easily assayed or is part of a particular gene of interest. Hence, this serves as a diagnostic tool to study the expression level of a therapeutic gene of interest and its location in the cell [3]. It is sometimes called a 'Transgene' when it is externally transferred into the cells of an organ system and into the genes that are present naturally. It can then assess the delivery and magnitude of gene expression, interactions between cellular proteins, and cellular or proteomic trafficking in live animals or clinical models. Various reporter genes have been investigated for in-vivo imaging exploiting multiple modalities. Efforts are being made to demonstrate their utility in enhancing stem cell and immune cell-mediated cell therapy, gene therapy, and viral therapy [4].

Conventional drug therapy has many adverse implications. Hence, immune cell and stem cell therapy have emerged as highly anticipated therapy for treating cancer and other major disorders. However, they need detail-oriented pre-planning and process validation to obtain ethical clearance before clinical use, as they are still under research. Imaging using reporter genes can also help to track various parameters related to stem cell survival, their potential for tumour formation, interaction with the immune cells, overall bio-distribution and movement of the different types of stem cells [5]. Reporter gene imaging can also help to monitor the efficacy of immune cell therapies by recognising the physiological pathways through which the treatment manipulates the function of different innate and adaptive immune cells harnessed in the immunogenic response to fight tumour cells [2].

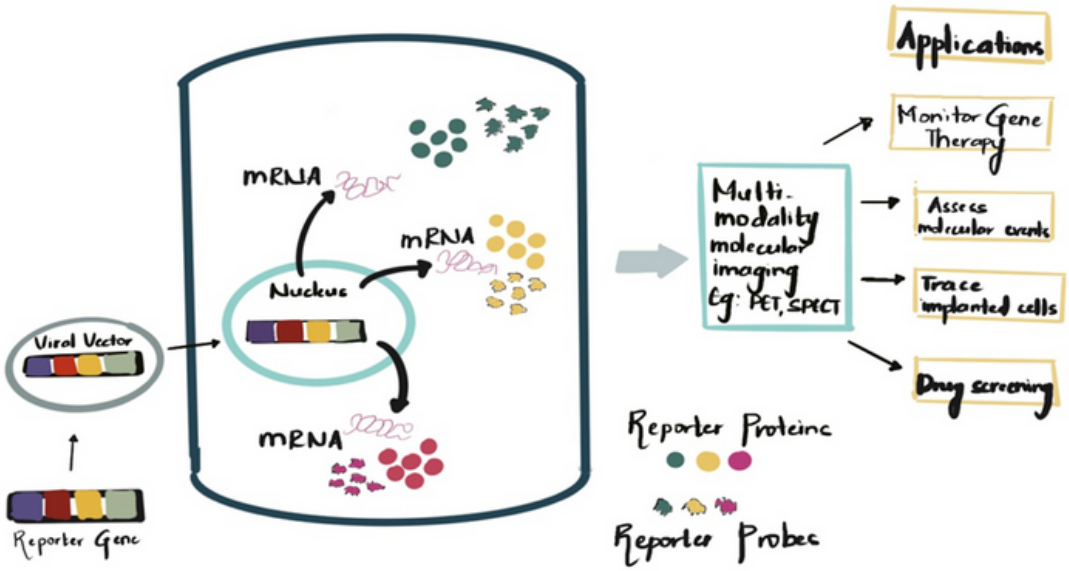

Figure 1: Formation of Reporter Proteins or Probes in the cell used in multi-modality molecular imaging.

IMPORTANCE OF VIRAL VECTORS IN REPORTER GENE IMAGING

One of the essential requirements in reporter gene imaging is using viral vectors or plasmids that selectively replicate in tumour cells. They aid in the transfection of the therapeutic gene of interest consisting the reporter gene. Once transferred into the cell, the reporter gene causes genetic alterations in the cell that lead to the production of a reporter protein or can lead to the synthesis of specific molecules that are entrapped in the cell (reporter probe), which can be used as indicators to elucidate various molecular events within the cell [6]. Herpes simplex virus type 1 thymidine kinase gene (HSV1-tk) obtained from the HSV1 viral vector, is the most popular reporter gene for Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) imaging. Expression of HSV1-tk gene results in the synthesis of Herpes Thymidine Kinase enzyme which phosphorylates two primary classes of exogenously administered reporter probes: pyrimidine analog derivatives such as 2′-fluoro-2′-deoxy-β-D-arabinofuranosyl-5-iodouracil (FIAU), and acyclo-guanosine derivatives such as 9-(4-fluoro-3-hydroxy-methyl-butyl) guanine (FHBG), or Ganciclovir [7].

RADIOTRACERS IN THERANOSTIC IMAGING

Some commonly used radio-pharmaceuticals in nuclear medicine have been found to be useful in evaluating certain vital parameters associated with stem cell therapy. Many studies have demonstrated using F-18 FDG to facilitate the tracking and bio-distribution of bone marrow and peripheral hematopoietic stem cells in the coronary vasculature of animal subjects [8]. F-18 FLT, a well-known tumour proliferation marker, has been used to observe the migration of neural stem cells in the hippocampus of mice [9]. Cu-64, a PET radio-isotope having a half-life of 12.7 hours, can be linked to a tetramer consisting of the amino acids arginine-glycine-aspartic (RGD), and further undergo conjugation with the macrocyclic chelator 1,4,7,10-tetraazacyclododecane-N, N',N", N"'-tetra-acetic acid (DOTA) resulting in the formation of Cu-64-DOTA-RGD4. This radiopharmaceutical can be potentially used to image αvβ3 integrin (a specific marker for neo-vessels). It can be used in the in-vivo evaluation of the post-therapeutic status of Human Embryonic Stem Cells (hESCs) [10].

Pyruvaldehyde-bis (N4-methylthiosemicarbazone) [PTSM] is another carrier molecule, lipophilic and redox-active in nature, which can be radio-labelled with Cu-64. Cu-64 PTSM has demonstrated utility in studying hESCs specific for differentiated renal cell lineages in rhesus monkeys [11].

The SPECT radionuclides, Technetium-99m (Tc-99m) and Indium-111 (In-111) can also be employed to monitor the overall behaviour of Stem Cells. In-111 Oxine and Tc-99m Hexamethylpropleneamineoxime (HMPAO) are helpful in the estimation of stem cell mobilisation to myocardial infarct tissue in the clinical studies conducted [12]. Numerous studies are reporting the use of In-111 for visualising the behaviour of Mesenchymal Stem Cells (MSCs) concerning cases of stem cell-mediated heart transplant in porcine and canine models [13].

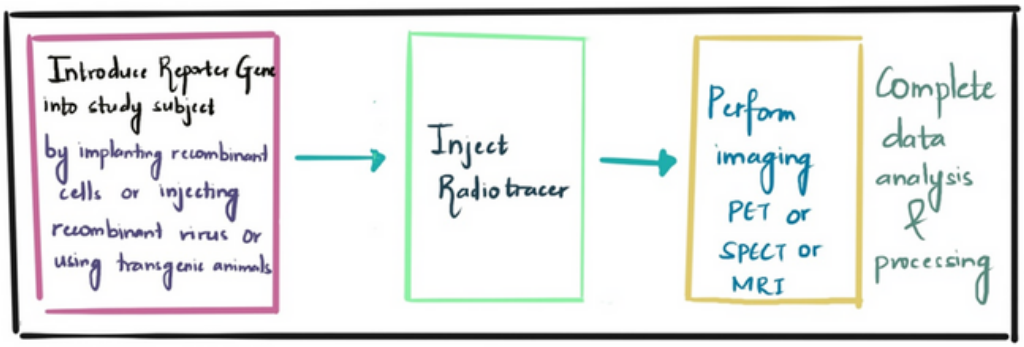

Figure 2: Process of Radio-nuclide based Reporter Gene Imaging in Thera-nostics.

NIS AND NUCLEAR MOLECULAR IMAGING

Many studies have emphasised the dual diagnostic and therapeutic use of Sodium Iodide Symporter (NIS) and its emergence as a reporter gene. NIS is a transmembrane protein facilitating iodine uptake in thyroid tissue [14]. PET imaging with I-124 and SPECT imaging with I-123 or Tc-99m can be made possible through the transfection of NIS gene in non-thyroid cells. NIS imaging provides the possibility to monitor the success of stem cell transplantation in myocardial infarction and track the movement of MSCs in targeted therapy for treating breast cancer [15]. It can prove highly beneficial with the prospective treatment augmentation by performing its radio-labelling with I-131. NIS radionuclide gene therapy and gene-mediated molecular imaging are among the most up-and-coming research areas in the spectrum of theranostic genes explored yet [16].

PET AND SPECT BASED REPORTER GENE IMAGING

Iodine-124, Iodine-125, and Iodine-123 isotopes have been used to radio-label FIAU for PET and SPECT imaging. I-125 FIAU-based SPECT imaging has been used to monitor the outcome of stem cell therapy in mice [6]. Fluorine-18 isotope can be used to radio-label FHBG or Ganciclovir for performing PET imaging. F-18 FHBG or F-18 fluoroganciclovir find their use in the localisation and monitoring of the retention of Mesenchymal Stem Cells (MSCs) in porcine myocardium in cases of stem cell-mediated heart transplant and also to trace the movement of MSCs to targeted tumour tissue. 18F-FHBG is also used for demonstrating transfection of HSV1-tk during suicide gene therapy for the treatment of hepatocellular carcinoma (HCC) and in localisation of cytolytic T-cells expressing HSV1-tk during cell therapy for treating glioblastoma [17].

PET REPORTER GENES DERIVED FROM VIRUSES AND OTHER NON-HUMAN SOURCES

Radionuclide-based PET imaging reporter genes (IRGs) can be used as imaging probes that help localise the transgene of interest and study its in-vivo behaviour by exhibiting increased accumulation intracellularly or on the surface of the cells that have incorporated the transgene, spontaneously having rapid clearance from non-target cells. PET Reporter Probes (PRPs) thus help evaluate the PET IRGs expression and facilitate the imaging of the transgene expression [6]. PET IRG/PRP combinations have three mechanisms of action: A) An enzyme encoded by the reporter gene aids in the catalytic chemical transformation of the reporter probe, as a consequence of which there is intracellular entrapment of the reporter probe in the cells expressing the reporter gene. B) A radioligand-based reporter probe is attached to a membrane protein receptor encoded by the IRG. C) The reporter gene encodes cell-membrane protein transporters that facilitate the flow and accumulation of the radionuclide reporter probe into the cells expressing the reporter gene [18].

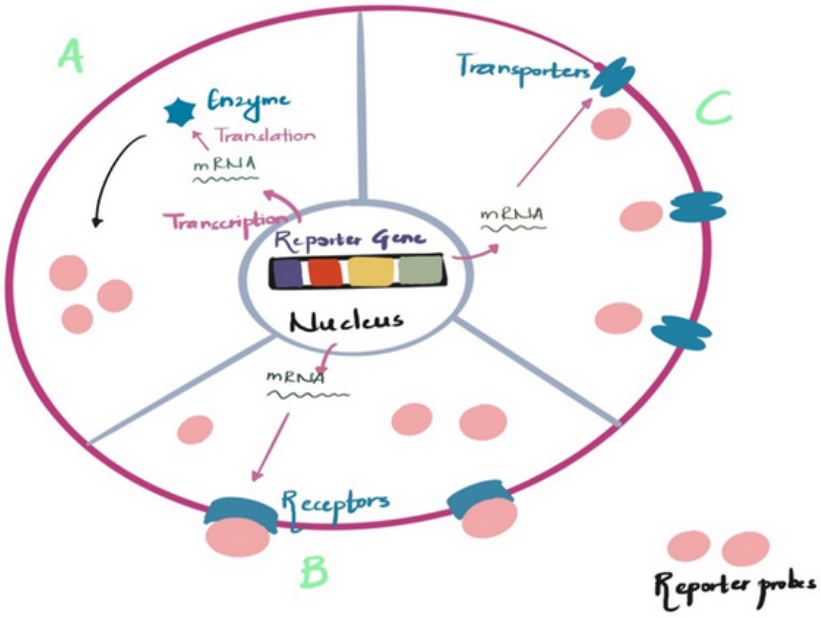

Figure 3: Three different mechanisms of action for PET IRG/PRP systems.

The most exhaustively investigated and utilised among the PET reporter genes until now is HSV1-tk and its mutant derivatives, which cause trapping of the PRPs within the cell. Other reporter genes include modified human mitochondrial thymidine kinase (hmTK2), and truncated mutant deoxycytidine kinase (hΔdCKDM), which are reporter genes that encode protein transporters [19]. Subsequently, in various trials, their corresponding PET reporter probes such as 18F-FHBG, 2'-[18F]fluoro-5-ethyl-1-beta-D-arabinofuranosyluracil (18F-FEAU), 2'-Deoxy-2'-fluoro-5-methyl-1-β-L-arabino-furanosyl-uracil (18F-L-FMAU) and 124I-FIAU have proved as successful candidates in different cancers for monitoring of transgene expression in gene therapy [20].

Table 1: PET Reporter Gene/Probe systems for reporter gene imaging that have been studied to date [6].

Reporter Gene	**Reporter Probe**
Dopamine 2 Receptor (D_2R) Mutant D_2R	^{18}F-fluoro-ethyl-spiperone(FESP) Also potentially: [^{11}C]Raclopride [^{11}C]N-methyl-spiperone
Human estrogen receptor α ligand binding domain (hERL)	[^{18}F]-16 alpha-fluoro-estradiol(FES)
Human somatostatin receptor subtype 2 (hSSTr2)	[^{68}Ga]-DOTATOC
Recombinant human carcinoembryonic antigen (CEA)	[^{124}I] labelled Anti-CEA scFv-Fc H310A antibody fragment
Humanized membrane anchored anti-polyethylene glycol (PEG)	[^{124}I]-PEG-SHPP[N-succinimidyl-3-(4-hydroxyphenyl) propionate]
Sodium Iodide Symporter (NIS)	[^{124}I]-NIS
Human norepinephrine transporter (hNET)	[^{124}I]-MIBG (meta-iodo-benzyl-guanidine)

FUTURE PROSPECTIVE

The efficacy and safety of stem cell therapy should be thoroughly investigated before clinical applications. Despite recent research providing significant insights into the overall characteristics of different kinds of stem cells, it has yet to scratch the surface. The use and optimisation of gene therapeutic agents and their administration protocols require sophisticated assay techniques for obtaining more profound knowledge regarding their kinetics and in-vivo behaviour. Incorporating PET reporter gene imaging in designing drug screening protocols for cell or gene therapy would revolutionise disease management. Effective delivery of PET reporter transgenes during translational research requires large-scale development to ensure widespread utility. It can be paid heed to when molecular imaging and gene therapy researchers come together. In present times, the success of stem cell therapy considering both cell survival and effective localisation in animal models is sparse. PET IRG-based cell and transgene imaging will have greater utility when PRPs have superior pharmacokinetics, better target-to-non-target uptake, and enhanced bioavailability. Since cell survival has been less than 1% and significantly fewer cells demonstrate appropriate localisation in the tissue of interest, there is a necessity for leaps of improvement before its implementation in clinical trials. The long-term survival of these cells must be assured with multiple in-vivo molecular imaging studies. NIS gene therapy is only conducted in the preclinical setting as of now, with clinical trials of the treatment starting to take shape [6,14]

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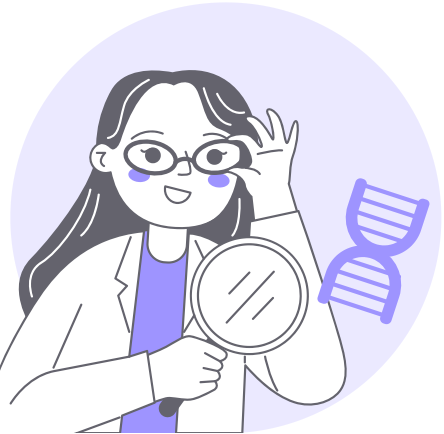

ALPHA EMITTERS IN RADIONUCLIDE THERAPY

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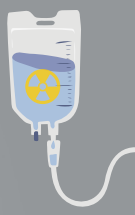

Targeted Alpha Therapy (TAT) is currently an active area of academic and commercial research worldwide, owing to its physical properties of being a particle of high charge and mass with a high kinetic energy of 5 – 9 MeV. The primary target of this high-LET radiation is DNA and can cause irreparable double-strand breaks. The alpha emitters can be labelled with antibodies, antibody fragments, peptides, affibodies and nanocarriers or nanoconstructs for intra-cavity or Intra-tumoral administration, adjuvant treatment for large tumor groups and palliative treatment. Commonly used alpha emitters in field of nuclear medicine therapy are Ac-225, Bi-213, Ra-223, Pb-212 and At-211 (Table 1).

Table 1: Alpha emitters in Nuclear Medicine Therapy

Radionuclide	Half life	Energy α	Energy β	Energy γ
At -211	7.2 hrs	5.9, 7.5 MeV	-	70 , 80, keV
Bi-213	46 mins	5.9 MeV	444 keV	440 keV
Ra-223	11.4 days	7.02 MeV	-	80 keV, 270 keV
Ac-225	10.0 days	5.9 MeV	-	218 keV
Pb-212	10.64 hrs	5 – 6 MeV	570 keV	238 keV

Ra-223 is an alkaline earth metal ion, mixed alpha/beta emitter with a half life of 11.4 days. It emits four α-, two β- particles and γ-rays and decays to stable isotope Pb-207 (Figure 1). It targets the hydoxyapatite [Ca10(P04)6(OH)2] matrix, similarly to calcium ions and accumulates in the bone.
Ra-223-dichloride was developed and was the first FDA-approved alpha emitter for bone metastases in castration-resistant prostate cancer. For treatment of metastatic prostate cancer, Ra-223 is used in a free ionic form without the need of ancillary ligands and is being marketed as Xofigo (formerly Alpharadin) for treatment of metastatic prostate cancer. The results of Phase 3 ALSYMCA trial render Radium-223 to be effective and well tolerated in patients with castration-resistant prostate cancer and symptomatic bone metastases, irrespective of previous docetaxel use.

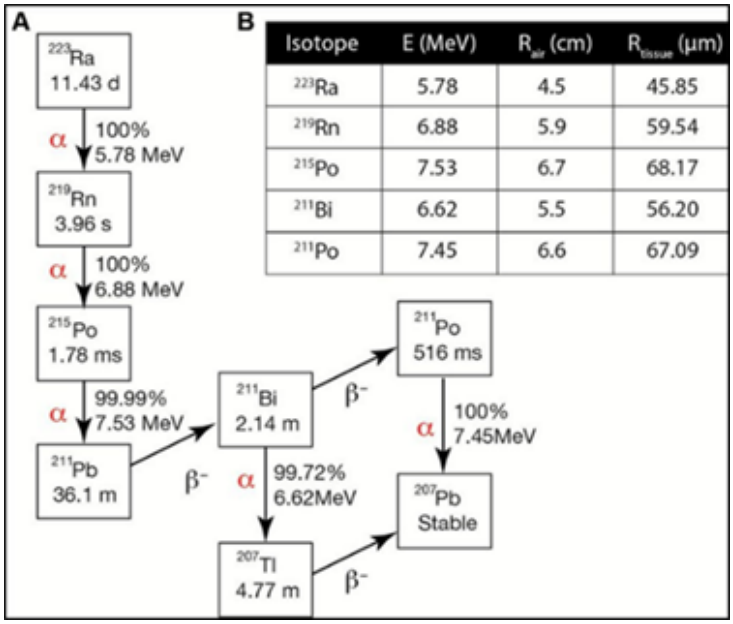

Figure 1 : Decay Scheme of Radium-223

Bi-213 is a mixed alpha/beta emitter with a half-life of 46 mins and decays into Bi-209(stable). α-particle released by Po-213 produces 98% of alpha energy released per disintegration of Bi-213. γ-radiation (Eγ -440keV) (emission probability of 26.1%) allows the monitoring of 213Bi biodistribution and the conduction of pharmacokinetic and dosimetric studies (Figure 2). It is obtained from Ac-225-Bi-213 generator based on cation anion exchange. Generator is eluted every 2-3 hrs to obtain Bi-213 which is further labelled to DOTATOC/PSMA/SubsP. The generator is produced by the Oak Ridge National Laboratory in USA, Institute for Transuranium Elements in Karlsruhe, Germany and Institute of Physics and Power Engineering (IPPE) in Obninsk. Its major limitation is its short half life which creates high demand on the logistics for radiochemistry and treatment as the labelling is to be performed on-site immediately before application. There is ample evidence that targeted therapy with Bi-213 is feasible and safe and can have anti-tumour efficacy with minimal toxicity. Bi-213 has still been the most used TAT nuclide in clinical trials so far. Kratchowil et al. reported the first-in-human experience with Bi-213-DOTATOC targeted alpha therapy (TAT) in patients pretreated with beta emitters [1]. Seven patients with progressive advanced neuroendocrine liver metastases refractory to treatment with Y-90/Lu-177-DOTATOC were treated with an intraarterial infusion of Bi-213-DOTATOC, and one patient was treated with a systemic infusion of Bi-213-DOTATOC. TAT can induce remission of tumours refractory to beta radiation with favourable acute and mid-term toxicity at therapeutic effective doses. Limitation is that large amounts are needed to attain an effective treatment due to the short half-life.

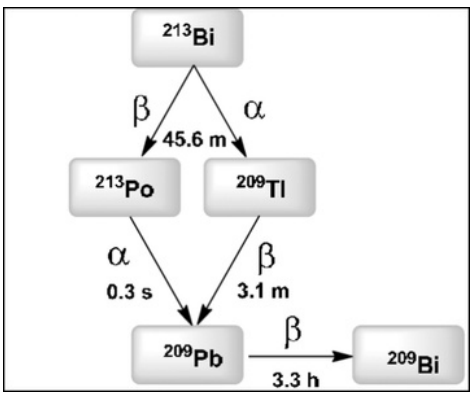

Figure 2 : Decay Scheme of Bismuth-213

Ac-225 is a pure alpha emitter with a half life of 10 days. It decays via a cascade of six relatively short-lived radionuclide daughters to stable Bi-209 and yields - four alpha particles (28MeV) and two beta particles (Emax-1.6 & 0.6 MeV) and its decay chain render Ac-225 a highly cytotoxic radionuclide (Figure 3). It is also associated with gamma emissions of Fr-221 (218 keV, 11.6% emission probability) and 213Bi (440 keV, 26.1% emission probability). Its availability is adequate for clinical trials, however, low yield poses problem. Chelate used is DOTA, but the conditions for labelling require a 2-step approach to be used. Methods to increase yields by use of one-step labelling techniques are underway and production methods are being evaluated.

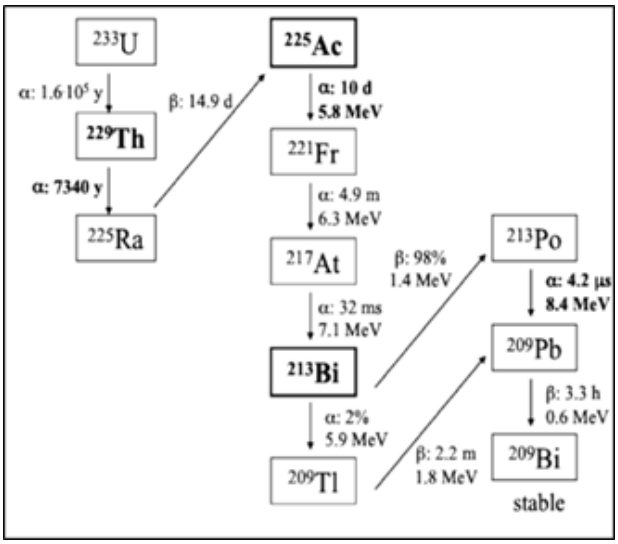

Figure 3 : Decay Scheme of Actinium-225

Pb-212 belongs to a radioactive series of long-lived parent Th-228 (T1/2 = 1.9 year). It is a beta emitter with a half life of 10.6 hrs, but is a parent radionuclide of the α-emitting Bi-212. It emits two α-, three β- particles and γ-rays and decays to stable isotope Pb-208 (Figure 4). Decay of Pb-212 includes the emission of a gamma ray with of 238 keV energy, that has the potential to enable direct imaging via SPECT of [Pb-212]-labeled peptides. It can be produced from Th-228 or Ra-224 based generators. However, Th-228 based generators experienced radiolytic damage to the support resin, consequent diminished yield, serious radiation safety problem and it was difficult to provide practical quantities of Pb-212. Ra-224 based generators, however, facilitated on-site production of Bi-212 or Pb-212 which were suitable for radiolabeling mAbs, peptides, or other vectors and have practical quantities of Pb-212.

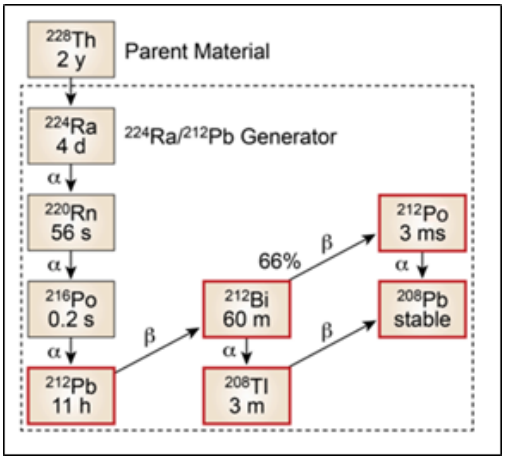

Figure 4 : Decay Scheme of Lead-212

At-211 has a half life of 7.2hrs. It is a halogen having similar chemical properties to iodine. It decays by two pathways (Figure 5). The result of these decay pathways is 100% α-particle emission. It also emits K x-rays with its α-decay to Po-211, which allow sample counting and scintigraphic imaging of At-211 in vivo.

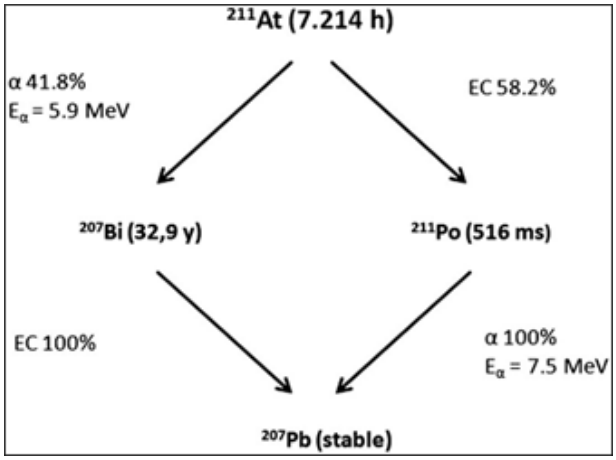

Figure 4 : Decay Scheme of Astatine-211

Several clinical and preclinical studies have been done using these alpha emitters against numerous tumors and have resulted in reasonable outcomes. However, there are several limitations associated with the alpha emitters such as high cost of the alpha-emitting radionuclides, availability of the radionuclides, nuclear recoil effect and the release of daughter nuclei, labelling chemistry, specific activity, dosimetric issues, radiation safety aspects and regulatory approvals. Ra-223 supply is presumed adequate for approved therapy use in USA and clinical evaluations in Europe. Bismuth-213 is obtained from Actinium-225. Large amounts are needed to attain an effective treatment due to the short half-life. Cost of its use in cancer therapy is a major concern. Ac-225 availability is adequate only for early clinical development. Efforts for alternative production methods are being evaluated. At-211 availability is currently low. Medium energy cyclotrons (28-29 MeV) around world to make At-211, is a concern.

Radionuclides decaying by a series of several α decays release radioactive daughter nuclei from the radiopharmaceutical preparations due to the nuclear recoil effect. This complicates the labelling strategies and successful dose targeting. The amount of energy that the recoil atom reaches is not negligible and is sufficient to break some 10,000 chemical bonds which results in direct impact on radiopharmaceutical stability and purity and on dosimetry.

The dosimetry for the labeled alpha particle is challenging owing to a) Short path length of α-particles - The amounts of energy deposited vary greatly from target to target, leading to a wide frequency distribution, b) Small target volume- Given the energy delivered along an alpha-particle track and its potential cytotoxicity, the dosimetry for estimating mean absorbed dose may not always yield physically or biologically meaningful information of radiation energy deposition in biological cells and c) Non-uniform distribution of radioisotopes- When the distribution of radio-labeled antibody is non-uniform, techniques of dose averaging over volumes greater in size than the individual target volumes can become inadequate predictors of the biological effect. Characteristic gamma rays could give an estimate of the macroscopic alpha dose but this is not the dose of interest. Currently available dosimetry methods are not used to guide clinical implementation of alpha-emitter therapy as there are no currently accepted alpha-emitter dosimetry for patient studies as pharmacokinetics are required at an anatomical scale which are not measurable with current patient imaging technology.

Due to the unfamiliarity in dealing with alpha-emitting radionuclides, radiation safety aspects are of concern. Because alpha emitters are limited in their ability to penetrate matter, the dead outer layers of the skin will absorb all alpha radiation from external radioactive sources and does not pose an external radiation hazard. Due to the internalization risk, allowable removable contamination levels for alpha-emitting radionuclides are significantly less than for beta/gamma-emitting radionuclides. Special monitoring equipment and facilities may be needed to limit or prevent contamination or airborne release of alpha emitting radionuclides during handling and/or storage.

So, there is an urgent need to stimulate fundamental research in the field of alpha therapy, particularly radionuclide production, and chemistry of alpha-emitting radioelements. Preclinical studies are required to identify new targets and disease settings and coordinated research projects (CRP) involving basic research institutes would help to identify potential targets for alpha particle therapy.

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POTENTIAL OF ARTIFICIAL INTELLIGENCE IN CALCULATION OF PET DOSIMETRY

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Artificial intelligence (AI) has emerged as a promising tool in various medical fields, including nuclear medicine. In the context of dosimetry in positron emission tomography (PET), AI can play a vital role in improving the accuracy, efficiency, and personalized dose estimation. The present article describes how AI is helpful in these new PET dosimetry algorithms and how it can benefit nuclear medicine post-graduation students.

Dosimetry in PET is a critical aspect of nuclear medicine that involves estimating the radiation dose delivered to a patient's organs and tissues during a PET scan. Accurate and personalized radiation dose estimation is essential for optimizing the diagnostic and therapeutic outcomes of PET imaging. In recent years, there has been significant research and development in PET dosimetry, focusing on developing new algorithms to improve the accuracy, efficiency, and personalized nature of dosimetry estimation. These new algorithms include deep learning-based dosimetry, Bayesian inference-based dosimetry, kinetic modelling-based dosimetry, and Monte Carlo-based dosimetry.

One example of AI-based dosimetry PET is deep learning-based dosimetry. Deep learning algorithms, such as convolutional neural networks (CNNs) and recurrent neural networks (RNNs), can learn complex features from PET images and predict radiation doses. This approach can improve dosimetry accuracy by incorporating temporal information and capturing subtle elements that are difficult to detect by conventional methods. Moreover, deep learning-based dosimetry can be trained on large datasets, allowing improved generalization and transferability across different patient populations.

Another example of AI-based dosimetry PET is Bayesian inference-based dosimetry. Bayesian inference is a statistical method that estimates probability distributions based on prior knowledge and observed data. In PET dosimetry, Bayesian inference can provide a more robust and probabilistic estimate of the radiation dose than obtained from point estimates. Moreover, Bayesian inference can be combined with machine learning algorithms, such as Gaussian processes, to provide a more personalized estimate of the radiation dose based on patient-specific information.

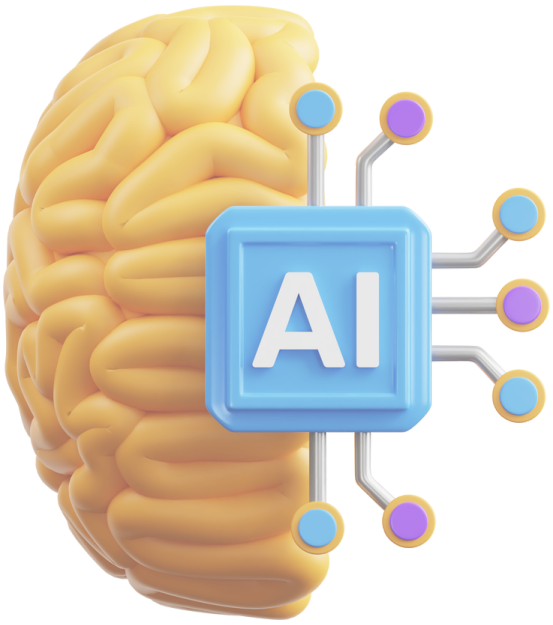
Kinetic modelling-based dosimetry provides a more detailed and mechanistic understanding of radiopharmaceutical behaviour, which can improve the accuracy of dosimetry estimation.

Monte Carlo-based dosimetry simulates the radiation transport and interaction with matter, providing a more accurate and realistic radiation dose estimate.

AI-based dosimetry PET can benefit nuclear medicine post-graduation students in several ways. By working with AI-based dosimetry algorithms, students can better understand the complex relationships between radiopharmaceutical distribution, radiation transport, and tissue response.

It can improve their understanding of the underlying physics and biology of radiation dose estimation. Moreover, working with AI-based dosimetry can provide students with practical experience in machine learning and data analysis, essential skills in the modern medical field.

Despite the potential benefits of these new algorithms, further research and validation are necessary before they can be implemented in clinical practice. The development of software based on these algorithms can significantly improve the ease of use for doctors and allow them to optimize treatment plans for their patients.



METHODS FOR ATTENUATION CORRECTION AND IMAGE OPTIMIZATION IN PET/CT

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WHAT IS ATTENUATION CORRECTION ?

Imaging's foremost goal is to produce an image in which each voxel value represents the true tissue activity concentration. It is desirable to know the actual activity concentration to accurately compare the activity levels in different organs or diseased versus normal tissues. Several corrections need to be applied to raw sinogram data to achieve this goal. These corrections are typically applied to sinograms before image reconstruction. Data correction methods include normalization, correction for random coincidence, correction for scattered radiation, and attenuation correction (AC) [1].

Attenuation is caused either by the loss of detection of true coincidence events due to their inherent absorption within the body or by scattering [2]. The parameter μ is the linear attenuation coefficient, which defines the probability that the photon will undergo an interaction while passing through a unit thickness of tissue. It measures the fraction of primary photons that interact while traversing an absorber. It is expressed in units of inverse centimetres (cm-1) [1]. Attenuation causes less count density generating artifacts, particularly at the center of the image. The degree of attenuation depends on the photon energy, the thickness of the tissue, and the linear attenuation coefficient of the photons in the tissue [3]. As shown in Figure 1, attenuation correction needs to be applied by considering I(a) and I(b) counts, calculating their geometric means of 2 counts, and using total thickness D of tissue [1]. Attenuation due to Compton scatter is related to object density only, but photoelectric absorption is related to density and atomic number [5].

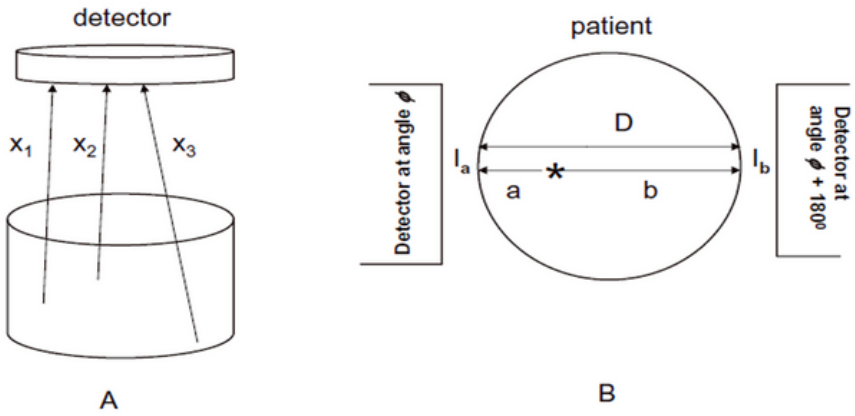

Figure 1 : Showing two 511keV photons detected by two detectors after traversing different tissue thicknesses, a and b. D is equal to the sum of a and b (*) shows point of photon interaction in patient's body [4].

IMPORTANCE OF ATTENUATION CORRECTION

Consider two lesions, superficial and deeply located in a patient's body. Deep lesion produce a highly attenuated signal then superficial lesion. Similarly, suppose a region lies beneath a tissue having a variable thickness, contains a uniform activity distribution, and will produce an image with variable count density [1]. Whereby reconstruction of tomographic images without attenuation corrections or alterations can cause erroneously high-count densities and reduced image contrast in low-attenuation regions such as the lung. Consider situations such as myocardial perfusion imaging or metabolic imaging where soft tissue attenuation might be caused by the diaphragm or breast tissue leading to false-positive defects, obscuring subjective and qualitative interpretation of images [6]. Also, inaccuracies during the quantitative assessment of PET images might arise. Thus, AC in PET is a crucial part of data correction procedures that prove necessary for its application to produce artifacts-free, quantitative PET data.

ATTENUATION MAP DELINEATION IN PET-CT

An exciting feature is an efficient match between energy and spatial resolution. As a result, measured transmission-based AC is the most used technique, as it yields the best attenuation maps [7]. The various transmission sources include rotating positron-emitting (Ge-68/Ga-68) rods measuring transmission in coincidence mode, and X-ray CT units combining x-ray tube and detector on the opposite side are nowadays used on modern combined PET/CT scanners [1]. X-ray CT produces optimal diagnostic image quality of anatomical images. However, possible limiting factors include the high cost of dual-modality PET/CT systems and the potential inclusion of artifacts with CT-based attenuation correction (CT-AC).

A. Radionuclide-Based Transmission Scanning For AC

Radionuclide-based transmission sources were the most accurate means of determining a patient-specific attenuation map before the advent of PET/CT, which could be acquired before (pre-injection), during (simultaneous), or after (post-injection) the PET scan [1,7].

The first-generation PET scanners used transmission ring sources of (Ge-68/Ga-68), 2nd generation scanners used one or more rod sources of the same radionuclide (approximately 400 MBq activity) [6]. The sources rotated around the edge of the field of view (FOV) underneath the detector ring, recording coincidences between detectors. A Blank scan is performed without the patient in FOV with rotating sources around the edge of FOV. The coincidences recorded during the blank (without the object in FOV) scan are divided by those acquired during the transmission scan (with the object in FOV) to give the ACFs (Figure 2) for each line of response [1]:

$$ACF = \frac{blank}{transmission} = \frac{I_0}{I_0 \exp\left(-\int_{L(s,\theta)} \mu(x)dx\right)} = \exp\left(\int_{L(s,\theta)} \mu(x)dx\right)$$

Where I0 is the blank count rate, m(x) is the linear attenuation coefficient at position x in the body, and L(s,q) is the integration path along the LOR.

This operation is carried on every element (i.e., line of response) of sinogram.

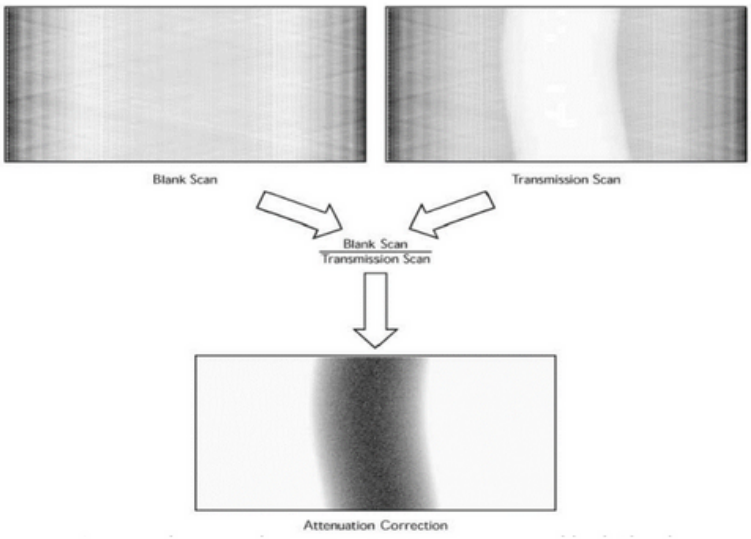

Figure 2 : Showing the attenuation correction matrix which is obtained by dividing the blank scan sinogram (acquired without the subject in the scanner) by the transmission scan sinogram (acquired with the subject in scanner) [8].

Limitations of radionuclide-based AC [9]:

1). The decayed radionuclide source, needs to be replaced.

2). An adverse effect on transmission images can be observed if enhanced emission activity within within patient co-exists leading to inaccurate matrix of attenuation maps.

3). The resolution of transmission scans is limited.

B. Low mA CT-based Scanning For AC

The procedure involves the principle of low mA CT transmission scan for imaging, where the radiation emitted from a rotating X-ray tube is transmitted through the patient's body, which is further recorded by an array of detector elements arranged on the opposite side [1]. A tomographic reconstruction algorithm is used to calculate the spatial distribution of the attenuation coefficients. Reconstructed intensities are expressed in CT numbers or Hounsfield units (HU). The pixel values are related directly to the linear attenuation coefficient (m) calculated for the effective energy of the poly-energetic beam of photons used to create the CT image:

$$CT\ number = \frac{\mu - \mu_{H_2O}}{\mu_{H_2O}} \times 1000$$

As a result, using low-noise, low mA CT images for creating patient-specific attenuation maps for undergoing photon attenuation is relatively easier [1,10,11]. X-ray-based CT inherently provides a patient-specific measurement of electron density. The energy dependence of the attenuation coefficient is considered by calculating scaling factors to convert the linear attenuation coefficient at the x-ray effective energy to the 511 KeV energy of annihilation photons [1].

Pitfalls in CT-based attenuation correction

1. Artifacts due to polychromatic X-Ray Beam: A precise conversion of CT numbers derived from low-energy polychromatic x-ray beam to linear attenuation coefficients at 511 keV is essential to calculate the linear attenuation coefficient as measured with CT. It can be found from the effective energy of the X-ray beam [1].

2. Artifacts due to Beam hardening: Due to the polychromatic behavior of the X-ray beam, there is preferential absorption of lower energy photons than higher energy photons. Hence, the beam gets hardened, resulting in characteristic artifacts as they pass through the patient's body [12, 13]. As a result, the mean energy or the linear attenuation coefficient calculated for thick-body regions is lower than for thin regions [1].

3. Artifacts resulting from misregistration between emission and transmission data: Certain challenges of misregistration occur in dual-modality imaging in the presence of motion [1]. Due to anatomic dislocations of the diaphragm and chest wall during a PET/CT scan acquisition, the appearance of a cold artifact at the lung base occurs as an outcome. Other motion-induced artifacts also may affect the appearance of upper abdomen lesions and result in the false-negative interpretation of liver dome lesions [1]. Possible causes for patient motion may be respiration, cardiac motion, peristalsis, and bladder filling that may lead to motion blurring or inaccurate registration between PET and CT data [14, 15].

4. Artifacts resulting from misregistration between emission and transmission data: A contrast medium may also serve as a source of errors and artifacts when the CT data is used for attenuation correction of PET images. The route of administration also decides its impact [16].

5. Truncation artifact: Truncation artifacts occur due to the disparity between PET and CT gantry FOV in a combined PET/CT scanner. Majorly the FOV of the CT gantry is usually 50 cm, whereas the PET gantry remains up to 70 cm [1]. Therefore, whenever acquisition extends beyond the CT FOV, which mainly occurs while scanning obese patients, truncation errors arise, leading to quantitative and qualitative distortions of CT datasets and attenuation-corrected PET images in the area of truncation.

6. Artifacts arising from metallic objects: The metallic objects generate severe artifacts in reconstructed CT images due to the presence of strongly attenuating objects in the field of view (FOV) [1]. The presence of metallic dental implants [17] or electroencephalogram (EEG) electrodes [18] used for monitoring epilepsy patients may introduce an artifactual appearance in brain images. The same happens for metallic hip prosthetic materials and pacemakers. As a result, metallic objects are assigned maximum value, which underestimates their true HU. Thus, line of responses (LORs) passing through metallic objects might get the wrong assigned ACFs [18].

PROPOSED REMEDIAL MEASURES

1. Various strategies for calibrating CT images for AC of PET image datasets include scaling [19], segmentation [20], hybrid segmentation/scaling [21], piece-wise linear scaling [22,23], and dual-energy decomposition methods [24,25].

Dual-energy X-ray method: Two CT scans of the same regions are acquired involving different energies, which are further combined to generate accurate attenuation coefficients at any photon energy. This method is more encouraging in dual- source X-ray CT scanners [1].

2. Cupping artifact presence induced by nonlinearities in the projection data due to beam hardening are corrected generally in the calibration software. More sophisticated beam hardening correction strategies have been open for further development [26-28].

3. (i) Certain software-based registration methods have been advocated when using hybrid PET/CT to offset inherent patient motion [29].

(ii) By incorporating other solid state detector materials like LSO panel detectors to achieve faster scan times for further improvement in patient comfort, minimizing chances of patient motion, increasing patient throughput, boosting system use, and improving cost-effectiveness. [1,30].

(iii) Other alternatives use of retrospective AC using free-breathing CT, optimized use of CT acquisition protocol, respiratory averaged CT dataset, phase-by-phase CT acquisition, cine CT acquisition, respiration correlation CT acquisitions, and use of respiratory-gated PET/CT acquisitions to accommodate differences between breathing patterns [1].

4. (i) A possible remedy may be acquiring a pre-contrast or post-contrast CT scan acquisition that may minimize possible artifacts contributed by the presence of contrast media [1].

(ii) The segmented contrast correction (SCC) method initially proposed by Nehmeh and colleagues involves identifying regions containing contrast medium through manual segmentation. Corresponding CT numbers or pixels falling into these regions can be substituted with their equivalent effective bone CT number. [1, 31].

5. Truncation correction algorithms can achieve artifact-free images in the FOV by extending the images beyond the field of view [32, 33].

6. Metal artifact reduction (MAR) algorithms must be used during CT-based acquisitions to counter-balance the effect of highly attenuating objects like metals [34-37].

CONCLUSION

Attenuation correction in image processing continues to be one of the most important factors critical to optimizing images in terms of resolution and delineation of clinical-diagnostic information. Of the methods suggested for attenuation correction, the most precise and handy method relates to using CT-based AC. In this paper, the issues relating to the limitations and pitfalls associated with various methods have also been addressed. Therefore, it can be concluded and suggested that CT-based AC is mostly used and adopted for appropriate image optimization.

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EFFECT OF DEEP LEARNING-BASED DENOISING ON LOW COUNTS/REDUCED TIME PROTOCOL IN LOW DOSE F-18 FDG SCANS WITH DIGITAL PET/CT

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PURPOSE

To investigate the effect of deep learning (DL) based denoising method on the image quality and semi-quantitative parameters of low dose F-18 FDG positron emission tomography (PET) images acquired with digital PET/CT, reconstructed with different time per bed position/percentage count protocols.

METHODS

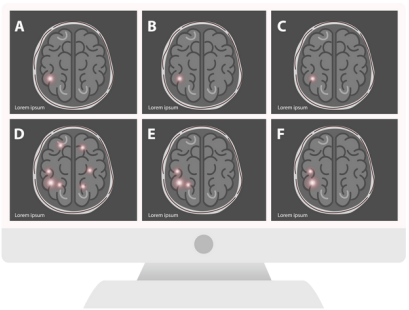
The study retrospectively included 90 patients who underwent F-18 FDG PET/CT imaging on a digital PET/CT scanner (United Imaging 550uM) with an acquisition of 120 s bed position. The list-mode data was rebinned into five datasets: 120 s (reference), 90 s, 60 s, 45 s, and 30s, corresponding to 100%, 75%, 50%, 37.5% and 25% of the total counts, respectively. All images were reconstructed by the OSEM algorithm and post-processed with the DL and Gaussian filter (GS). Standardized uptake values (SUVs) in the liver, mediastinum, and liver-to-mediastinal were compared among different subsets. The background noise, lesion contrast, and contrast-to-noise ratio (CNR) were assessed using a 5-point Likert scale for representative lesions.

RESULTS

The average injected F-18FDG dose was 3±0.5 MBq/kg body weight. The mean uptake time was 60±10 minutes. Overall, there was a significant difference between SUVmax of the liver and mediastinum between all subsets of DL-based and GS-based denoising methods. However, the difference in SUVmean was non-significant. SNR of the liver was significantly higher in the DL group in comparison to the GS cohort. Image noise was considerably less in the DL group than in the GS group ($p<0.05$) in all the subsets. However, a significant difference in lesion contrast was only observed in the 45s and 30s image cohorts. In the DL group, SUV values, SNR, background noise, and lesion contrast showed no significant difference between the reference (120s) and the 90s cohorts.

CONCLUSION

The deep learning-based denoising method results in a better reduction in image noise and signal-to-noise ratio than the GS method at low-dose FDG PET scans. Image acquisition time per bed position can be reduced to 90s without compromising image quality and semi-quantitative data.



JUSTIFICATION: IS BENEFIT GREATER THAN THE RISK?

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Every step taken in a radioactive procedure should have and solve a purpose. Nothing should be nonsense or unnecessary, as that step can be taken as unjust exposure to radiation. The logical reasoning behind every radioactive step or application is based on an assessment of maximum benefit to minimum risk, that is, the benefit: risk ratio needs to be greater than 1.

This concept should not only be applied to patient procedures but also to the steps performed by radiation workers. This will minimize his or her occupational exposure, getting back to the principle of ALARA.

During the appointment itself, an assessment must be made about the correct application and readiness of the patient for the radioactive procedure. For example:

1. If there is a note of a liver scan sent by the referring doctor, a clarifying inquiry of the purpose should be made to avoid a wrong nuclear scan. Even a hepatobiliary scan requisition is sometimes sent as a liver scan.

2. The controlled state of the glucose level of the patients to be appointed for F-18-FDG PET CT scans, especially the diabetic cases, must be assessed. The attempt to control the glucose level in situ on the scan day may be futile, along with the prolonged uptake period to reduce the inhibition of 18FDG uptake. Despite the wait, one may still acquire images with poor interpretable value.

If such radioactive procedures are performed, the benefit: risk ratio reduces to zero, and the scan needs to be repeated.

The time spent on patient preparation for counselling and educating every step of the procedure as per the requirement, especially the fresh case, making him or her cooperative or doubt-free, is completely justified. This can lead to the successful completion of the radioactive procedure without any repetition. The humane and empathetic nature of the patient should not be underestimated or ignored beyond his or her sensitivity.

Consequently, the clarification that the staff cannot be proximal to the patient constantly after administration of radioactivity to follow ALARA, or radiation protection principles, can make the patient cooperative without getting offended. This deduction has been drawn from personal experience. The logical workflow should be that maximum conversation should be done before the patient is radioactive to minimize or avoid conversation or proximity with the radioactive patient.

When a pregnant woman has to undergo a radioactive procedure, justification needs a lot of discussion with the patient and her family, even up to the level of termination of pregnancy, only if "justified" as the "nest" should be strong (a healthy mother) enough to bear the nurturing of the "egg" (foetus).

Judicious application of the radioisotopes is of prime importance. Optimizing the radioactivity to get the maximum information for diagnostic procedures and therapeutic value aims to justify the application. For example, the diagnostic dose as per body weight is more justified than giving the dose by thumb rule and giving a higher dose for the patient with poor cooperative ability. Administration of a higher dose only because of availability is not justified. It may reduce the scanning time, but it also gives extra exposure to all those who handle the patient, apart from the unwanted exposure to the patient.

Extracting the best possible amount of information with a lower dose by increasing scanning time is still justified, especially from the radiation safety point of view (as the distance factor can be maintained during current whole-body acquisition as opposed to the spot views of earlier times).

“When less is sufficient, don’t go for more amount of radioactivity” is a justified rule for both:

1. Safe radiation practice
2. Management economy

Securing an IV line for dynamic scans, PET injections, and all the patients with tender veins is perfectly justified to avoid the wastage of time, handling radioactivity, or extravasation of radioactivity in multiple pricks, which in turn reduces the benefit: risk ratio by

1. Degrading the image quality and
2. Giving unwanted local exposure to the patient

Quality control of the imaging system just before injecting the first patient may cause decay of short-lived radionuclides if there is not sufficient activity or time to spare. However, it is justified to wait until the results are known instead of injecting the patient prior to the QC results. In the event that the QC does not pass, the benefit: risk ratio of the exposure to the already injected patients will be "zero". Ideally, QC of the imaging systems should be completed before the radioactivity is made available (especially PET radiopharmaceuticals) to avoid the loss of the "precious tool" by decay during the waiting period for the QC results.

The presence of a patient attendant or a staff member in the vicinity when a radioactive patient is ambulatory and emotionally strong (not vulnerable) cannot be justified, and keeping the attendant away from the patient will reduce the unwanted exposure. However, the attendant, who plays a supportive role in helping a vulnerable patient improve his or her cooperation, is justified. When the time spent with the radioactive patient is too long, one attendant can be replaced by another.

When an adult co-operative patient does not need the proximity of a bystander during the dynamic scan acquisition, the distance rule can be safely applied but cannot be intrapolated to paediatric cases or a non-co-operative vulnerable adult patient, with the risk of getting hurt due to mobility even after

immobilisation restraints have been used. The attendants of paediatric patients, only after being well educated, become better and more justified supporters than the auxiliary staff during the positioning of the paediatric cases for the following two reasons:

1. Emotionally, both the child and the attendant become relaxed.

2. The daily exposure of the staff can be minimised, and the attendants' rare exposure is justified for the benefit of the report being obtained for their dear one.

Justification for radioactive spillage management or handling has to consider the risk to which the housekeeping staff will be exposed. The decontamination can be delayed if the immediate use of the contaminated area can be avoided. An immediate containment and locking of the contaminated room can be sufficient as the primary management during a major radioactive spillage (to reduce the strength by decay).

The benefit to risk ratio, or the calculated risk taken by the radiation professional (radiation hazard), is hypothetical and not proven or distinct from the risk of nosocomial infections (biohazard) faced by every healthcare professional [1].

Every radiation worker faces the challenge of blending patient care and radiation protection so that they can give the best service to the patient without compromising on safeguarding themselves from radiation exposure. This is the reason why patients administered with radioactivity in the waiting area are monitored through CCTV, which serves both purposes.

Getting maximum benefit and minimizing the risk as much as possible through the "ALARA" principle demands extreme vigilance for the radiation professional to constantly apply the three golden rules of minimum time with, maximum possible distance, and optimum shielding from radioactive sources.

Finally, as it is said, one must "respect" and not "fear" the power of nuclear radiation. It is the awareness of the nature and type of radiation being handled by the qualified radiation worker that can make him/her strong, fearless, and vigilant enough to judiciously apply ALARA as against the psychological undue fear of the unknown by the unqualified, who may be ignorant of the professional satisfaction and better perks obtained as a benefit over the calculated risk taken from this precious and powerful tool: "Nuclear Radiation".

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AWARENESS ABOUT NUCLEAR MEDICINE AMONG PATIENTS AND MEDICAL PRACTITIONER

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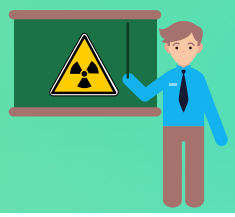


Nuclear Medicine is one of the fastest-growing specialities in the world of healthcare and has been playing an efficient role in diagnostic, therapeutic, and research-based applications.

In India, many companies, diagnostic centres, and hospitals have started investing and opening nuclear medicine departments nationwide, intending to gain financial output while providing the necessary patient services. The availability of short-lived radionuclides such as Fluorine-18 (F-18), Gallium-68 (Ga-68), and Technetium-99m (Tc-99m) etc., along with various other therapeutic and theranostic radionuclides, has revolutionized this branch of medicine. Though various nuclear medicine departments are opening up across the country, “many are unaware of the nitty-gritty of it”. Thus, there are three main talking points among the people:

1.Radiation safety

2.Affordability

3.Awareness among clinicians about the effective use of the services provided.

1. RADIATION SAFETY

The amount of radiation exposure a patient gets is comparable to what they get from a conventional chest X-ray or CT scan. The radiation risk involved in these procedures is generally very low compared with the high potential benefits. There are no known long-term adverse side effects from diagnostic nuclear medicine procedures, which have been performed for over 50 years. Though large doses of radiopharmaceuticals are also used in nuclear medicine therapy, the higher amount may impact the patient and may have some side effects. However, because radionuclide therapy mainly treats fatal conditions, “the benefits usually outweigh the hazards.” Most of the high-dose radionuclide therapies offered are for soothing and non-curative purposes. Along with patients, radiation safety among those professionals working with radionuclides is an essential factor to consider in all nuclear medicine procedures, which is often ignored/neglected in some places. Thus, before performing any procedure, nuclear medicine professionals must follow three basic principles, i.e., Justification of practice, optimization of practice and dose limitations.

2. AFFORDABILITY

It is a significant factor every patient considers before proceeding with the procedures. In the current economic scenario, patients with a poor financial background need help to meet the expenses of various nuclear medicine procedures. In a country like ours, another hardship that patients face is to travel long distances to get the procedure done at relatively affordable centres. Many clinicians, therefore, avoid referring these patients for a nuclear medicine procedure in the first place, thus causing them to miss out on the potential benefit, as they lose out on the vital information about the disease process and settle for conventional diagnostic modalities which may be less sensitive and can eventually lead to suboptimal treatment.

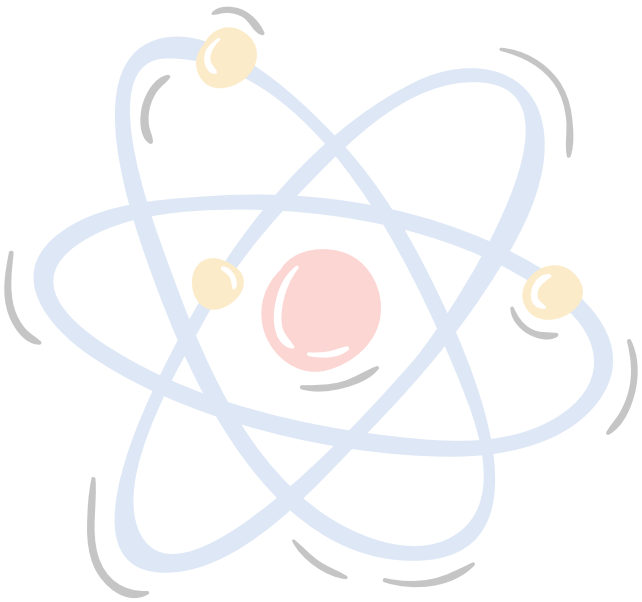
The following problem leads to the last point, where most doctors are unaware of the various nuclear medicine procedures or their alternatives, whether these procedures are available or affordable to the patients.

3. AWARENESS AMONG CLINICIANS

Nuclear medicine is a relatively new branch of medicine and is limited to only a few of the apex teaching institutes in the country. Most other teaching institutes with undergraduate courses do not have nuclear medicine facilities. It is also overlooked in the mainstream MBBS curriculum. These are the main reasons for the lack of awareness among most medical practitioners, which leads to under-utilization of this branch.

As nuclear medicine physicians, radiation safety officers, and technologists, we must educate our fellow clinicians in our circle about this field. Many times, the overall financial burden on the patient can be reduced along with getting the best possible results if the treating clinician prescribing the investigations is well-informed about the nuclear medicine services and their significance. For example, a contrast-enhanced CT scan can be performed in the same sitting as F-18-FDG PET/CT, avoiding a separate standalone CT scan that may be required for surgical planning. Also, cheaper alternatives of expensive PET/CT studies on gamma camera can be performed, such as Tc-99m-HYNIC-TOC or PSMA instead of a Ga-68-DOTANOC or PSMA PET/CT. Although comparatively less sensitive and more time-consuming than PET/CT, they provide a fair amount of information in advanced neuroendocrine tumor and prostate cancer cases.

In conclusion, several factors still need to improve for the complete utilization of benefits offered by modalities under nuclear medicine. Thus, efforts have to be put in terms of awareness about it and its affordability, keeping in mind the interest of the public and the hospitals, leading to a win-win situation for both. Effective communication of the advantages and knowledge about the technical and logistical challenges involved in the medical fraternity is the way forward.



IN-HOUSE PRODUCTION OF [Lu-177]Lu-DOTA-PERTUZUMAB USING MEDIUM SPECIFIC ACTIVITY [Lu-177]LuCl3 FOR RADIOIMMUNOTHERAPY OF BREAST AND EPITHELIAL OVARIAN CANCERS, WITH HER2 RECEPTOR OVEREXPRESSION FOR PATIENT USE

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INTRODUCTION

Radioimmunotherapy (RIT) is a therapeutic modality that uses radiolabeled monoclonal antibodies (MoAbs) to target antigen receptor overexpression in a specific tumor. The strategy utilizes particulate-emitting radioisotopes tagged in the radioimmunotherapeutic agent to target the ionizing radiation to tumor cells, affecting the desired therapeutic outcome. RIT was first carried out with I-131 labeled antibodies [1,2]. With the advancement of chelation chemistry, attempts were made to radiolabel MoAbs with other suitable beta emitters such as Y-90, Lu-177, and Re-188 [1]. The Food and Drug Administration (FDA)-approved MoAbs used in RIT are the ones that use I-131 (Bexaar) and Y-90 (Zevalin) [3,4].

In recent times, Lutetium-177, with favorable decay characteristics (T1/2: 6.65 d, Eβmax: 498keV [78.6%] and 176keV [12.2%]), was conceived as a promising radionuclide for RIT [5-8]. The additional advantage offered by Lu-177 is the emission of imageable gamma photons, which enables post-therapy scintigraphy studies as well as dosimetry analyses. The development of Lu-177-based MoAbs gained momentum, and several clinical trials were initiated [5,9].

Targeting human epidermal growth factor receptor 2 (HER2) using MoAbs is well-established in immunotherapy. The overexpression of HER2 is observed in ~30% of breast cancers. Besides breast cancers, HER2 proteins are also overexpressed in certain pancreatic, epithelial ovarian, and gastric cancers involving gastroesophageal junction adenocarcinoma [10,11]. Among all the cancer types mentioned above, the molecular mechanism for the overexpression of HER2 proteins has been thoroughly investigated and reported in breast and ovarian cancers [12,13].

Unlike conventional immunotherapy (drug monotherapy), where the pharmacological effect is achieved with the MoAbs, in RIT, the MoAbs serve only as the targeting vector for carrying the radionuclide to the cancerous lesion. In RIT, the increased cytotoxicity to the cancerous lesion, even with a lesser amount of antibody, offers a distinct advantage in reducing side effects over conventional immunotherapy, where significantly higher amounts of MoAbs are required [4]. In RIT, a patient receives only 3 mg of pertuzumab per cycle of therapy, which amounts to 12 mg of pertuzumab in three or four cycles of treatment. This is significantly less than targeted drug monotherapy, where 60–600 mg of the MoAb is administered. These tiny amounts of pertuzumab (targeting HER2 protein) neither induce cardiotoxicity nor produce excess chloride secretion [14,15].

MATERIALS AND METHODS

The MoAb pertuzumab (148kDa, Perjeta, concentration 30mg/mL) was purchased from Roche (India). p-NCSbenzyl-DOTA was procured from Macrocyclics, Inc. Lutetium-177 in the form [177Lu] LuCl3 solution with specific activity varying in the range of 0.67–0.81 GBq/μg (1822 mCi/μg) was produced in the DHRUVA research reactor of BARC, by 2-week irradiation of the enriched (84%, 176Lu) Lutetium target (Isoflex, Russia) at a thermal neutron flux ~1014 n/cm2/s. The [177Lu] LuCl3 was supplied by the Board of Radiation in Isotope Technology (India). Amicon ultra-centrifugal filtration devices (30 kD molecular weight cutoff) were procured from Millipore (Ireland). Ultrapure-grade chemicals, viz. sodium acetate, acetic acid, ascorbic acid, sodium carbonate, and sodium bicarbonate, were purchased from Sigma-Aldrich.

Reagents were prepared using ultrapure water (Trace SELECT; Fluka, Switzerland). PD-10 desalting columns procured from GE Healthcare were used for the purification of immunoconjugate as well as radioimmunoconjugate (RIC). The lead-shielded biosafety cabinet (ISO class 5) was used to perform the manual radiolabeling procedures.

Conjugation of pertuzumab with p-NCS-benzyl-DOTA

The MoAb (pertuzumab of γ-DNA origin, 200 μL, concentration: 30 mg/mL) was diluted to 10mg/mL using ultra-pure water. Pertuzumab (167 μL of a 30mg/mL solution) was diluted with 333 μL of ultra-pure water so that the concentration of resultant pertuzumab was 10 mg/mL (5.0 mg in 500 μL). It was pre-concentrated to 75 μL using a 30kDa molecular weight cutoff ultra-centrifugal filtration device (Amicon; Millipore) under a relative centrifugal force at 3000 g for 17min. Pertuzumab was recovered under a relative centrifugal force at 1000 g for 2 min. Here the bifunctional chelating agent (BFCA) is p-SCN-Benzyl-DOTA. Pertuzumab (5 mg in 75 μL, 33.78 nM) was conjugated with p-NCSBenzyl-DOTA at a molar ratio of 1:10 (MoAb: BFCA).

The concentration of p-SCN-Benzyl-DOTA for coupling with pertuzumab was 337 nmoles (14.56mM of ultrapure water). The pH of the conjugation reaction mixture was maintained at 8.0, using 200 μL of freshly prepared 0.2 M Na2CO3 –NaHCO3 buffer (pH ~9.2). The reaction mixture was then incubated at 24°C for 2 h, followed by incubation at 4°C for 18 h. The BFCA-MoAb conjugate thus obtained was purified using a PD-10 column preconditioned with 25 mL of 0.2 M CH3COONa buffer (pH 5.5). Fractions (1 mL) were collected, and the concentration of pertuzumab (protein) in the major fraction of conjugate was estimated using standard protein Bradford's assay (595 nm) as described in the reported literature [16,17].

Radiolabeling of DOTA-benzyl-pertuzumab conjugate with [Lu-177]LuCl3

Post incubation at 37°C for 90 min, the reaction mixture of [Lu-177] Lu-DOTA-pertuzumab was brought to room temperature (22°C–25°C) and purified using preconditioned PD-10 desalting column. [Lu-177] Lu-DOTA-pertuzumab was eluted from the PD-10 column using a freshly prepared 0.2 M CH3COONa solution of pH ~8 (Aldrich). Four fractions of 2 mL each were collected, and the maximum radioactivity of the purified [Lu-177] Lu-DOTA-pertuzumab was obtained in the third fraction. Post purification, 60mg of l-ascorbic acid (Aldrich) per 0.5mL of 0.2 M CH3COONa solution (pH 8.0) was added in the third fraction of [Lu-177]Lu-DOTA-pertuzumab (concentration: 240 μg/37 MBq). [Lu-177]Lu-DOTA-pertuzumab was diluted with sterile, pyrogen-free saline (Nirlife, India) to maintain the radioactive concentration (RAC) between 0.3 and 0.37 GBq/mL (8–10 mCi/mL). The product is filtered using sterile 0.22 μm polyethersulfone membrane syringe filter (Merck).

Physicochemical and biological quality control analysis

The pH of [Lu-177]Lu-DOTA-pertuzumab was measured by observing the color change of a narrow-range pH strip after spotting 0.5–1lL of the final product. RCP of [Lu-177]Lu-DOTA-pertuzumab was estimated by thin layer chromatography (TLC; Ray Test, Germany) using 60 A˚ silica gel plastic TLC plates (Merck, Germany) and 0.1M sodium citrate buffer (pH:5.0) as eluent. The radiochemical purity of the radio-conjugate estimated by TLC was >98%, and the retention factor (Rf) was 0.04 (Figure 1). The radio conjugate was clear and colourless. The yield of [Lu-177]Lu-DOTA-pertuzumab obtained is 86% using carrier-added [Lu-177]LuCl3 with medium-specific activity of 0.81 GBq/kg (22 mCi/microgram). The radioactive concentration typically varied between 0.33 and 0.38 GBq/mL (0.36–0.01 GBq/mL).

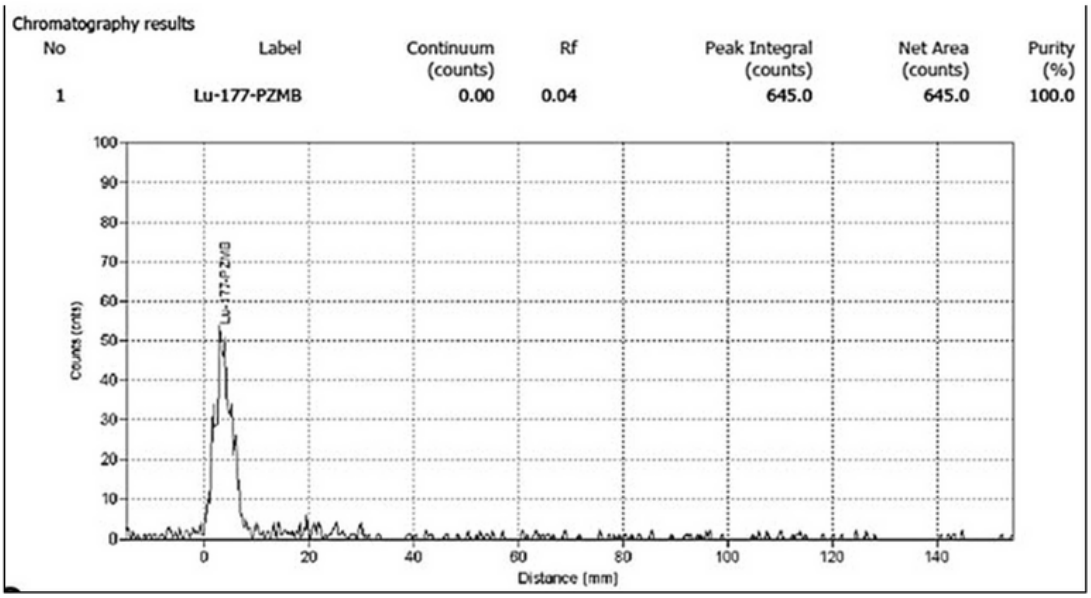

Figure 1 : The radiochemical purity of the radioconjugate [Lu-177]Lu-DOTA-pertuzumab estimated by thin layer chromatography.

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RECENT ADVANCEMENTS IN TECHNOLOGICAL ASPECTS OF NUCLEAR CARDIOLOGY

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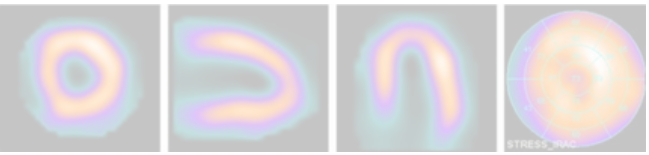
INTRODUCTION

The area of nuclear medicine that focuses on cardiovascular diseases is termed as nuclear cardiology. Nuclear cardiology deals with non-invasive techniques to assess myocardial blood flow, to evaluate the heart's pumping function and the cardiac infarction's size and location. Among them, Myocardial Perfusion Imaging (MPI) is the most widely used [1]. Earlier, planar imaging was the first attempt to evaluate regional myocardial perfusion and function. Advantages of planar imaging include bedside imaging of acutely ill patients or instrumented patients using portable gamma cameras, easy to repeat in case of motional artifacts and easy for imaging obese patients who are too bulky to fit into SPECT/CT gantry bore. It is also beneficial in claustrophobic patients [2]. Traditional gamma-camera (Anger-type gamma cameras) comprises scintillator detectors [thallium-doped sodium iodide, NaI(Tl)] as the gamma-photon absorber, photomultiplier tubes for electric signal generation, and Anger-logic for the mathematical computation of signals [3].

The next step towards improvement includes gated SPECT, which is a well-established diagnostic and prognostic method for evaluating patients with suspected and known coronary artery disease. It allows the evaluation of myocardial perfusion and global and regional left ventricular function analysis. [4]. The modifications to the SPECT include the utilisation of multiple heads instead of the single head, which allows fast acquisition (especially radiopharmaceuticals having rapid washout), high count images resulting in reduced noise without increasing imaging time, permits the use of high-resolution collimators or ECG gating with no loss of significant counts [5]. Despite all these advantages, cardiac SPECT has some limitations, including low photon sensitivity, poor image resolution (~15 mm) compared to planar imaging (5-7 mm), inefficient use of the detector, and high radiation dose. Several commercially available solid-state digital cardiac dedicated scanners were recently introduced, including Spectrum Dynamics D-SPECT, GE Discovery NM 530c and NM/CT 570c, Digirad Cardius, and CardiArc. In Digirad Cardius, CsI (Tl) crystals and avalanche photodiodes were used in a one to three-headed configuration. Each detector is pixelated with 21 x16cm. There are 768 pixels in each head, and each pixel (voxel) has a 6.1 x 6.1cm dimension. The uniqueness of this camera is that they did not use a PMT tube for pulse formation and used a silicon diode instead. Various Digirad camera model includes Cardius X-ACT, Cardius 3XPO (three-head) and Cardius 2 XPO (two-head). In order to concentrate on the heart region, the CardiArc scanner uses a slit-slat collimator with a stationary curved NaI(Tl) detector. A curved lead sheet with six vertical slits rotates back and forth to cover a 180-degree imaging arc. The latest advancement in cardiac imaging includes the use of a semiconductor detector named cadmium zinc telluride (CZT) avalanche Si photodiode, which results in compact system design for dedicated cardiac imaging (DSPECT and GE 530c/570c), the modular detectors in both cameras are positioned towards the heart to increase the detection efficiency of photons emitted from the heart.



The D-SPECT system consists of nine arrays of CZT detectors with parallel-hole collimators. Each of the nine detectors rotates around the central axis independently during the data acquisition to cover the whole field of view (FOV). All the detectors are inclined towards the heart, leading to higher detection efficiency of photons. Additionally, the size of the square-shaped holes of the tungsten parallel-hole collimators is larger. In contrast, the hole length is shorter than those of typical parallel hole collimators, leading to increased sensitivity. Another dedicated cardiac system includes GE 530c/570c, which can be a SPECT-only system (GE 530c) or a SPECT incorporated with a CT system (GE 570c). This system comprises 19 detector modules, each with a tungsten pinhole collimator. It has 4 cm by 4 cm CZT detector modules as the D-SPECT, with four modules per detector in a 2 by 2 array instead of a 1 by 4 array in D-SPECT. All 19 detectors focus on the heart specifically, leading to high sensitivity [6].

CONCLUSION

New solid-state dedicated (CZT) cardiac cameras provide excellent spatial and energy resolution and allow for markedly reduced SPECT acquisition times or injected radiopharmaceutical activity and reduction in radiation dose [7]. Studies have shown that cardiac CZT has higher sensitivity and specificity for detecting myocardial ischemia and infarction than traditional SPECT. Additionally, CZT imaging allows for more accurate quantification of myocardial perfusion, which can aid in diagnosing and managing coronary artery disease.

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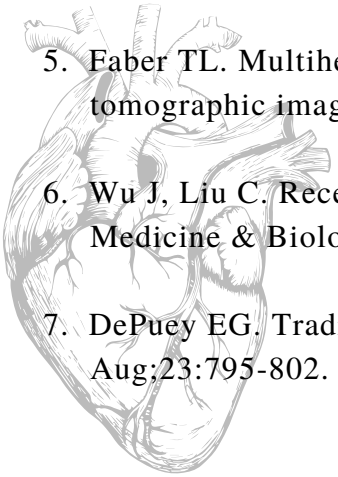
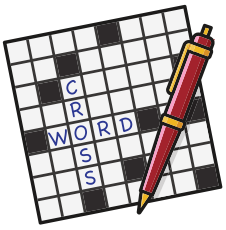
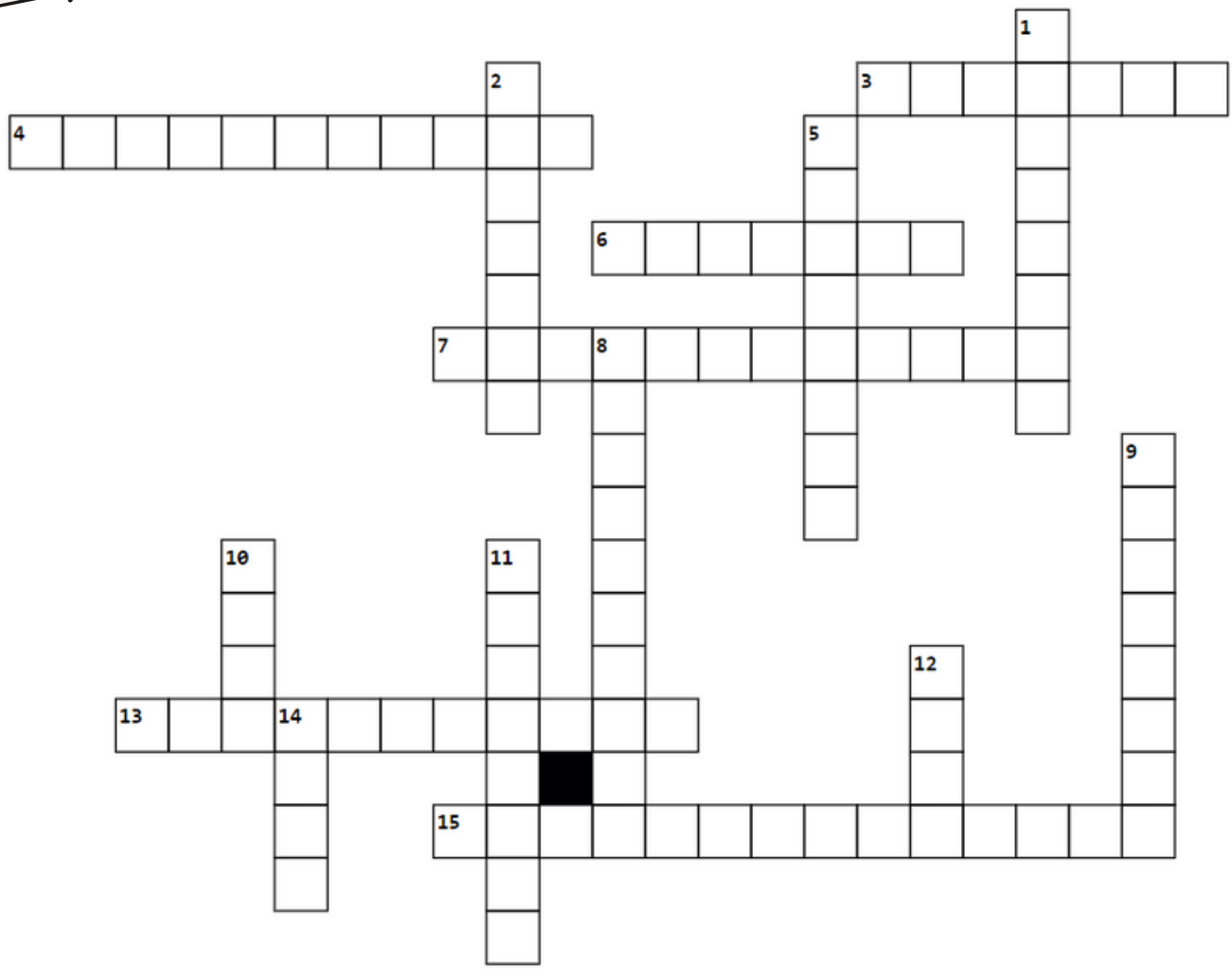




CROSSWORDS



ACROSS

3. Equilibrium attained when the parent half-life is much longer than that of the daughter nuclide

4. Electromagnetic radiation of wavelength 190 nm falls in which region

6. Force of attraction between the nucleus and the orbital electrons

7. Scintillating crystal used in NM imaging(6,6)

13. C-8 and C-18 cartridges are based on which type of interactions

15. TRODAT is labeled with Tc-99m through this mechanism

DOWN

1. High z material used for shielding and collimation

2. Mode of production of I-131

5. Atoms having nuclei with the same number of protons but different number of neutrons

8. Dose Calibrator principle is based on which region of voltage response curve

9. Particle emitted in competitive process with electron capture

10. Chelating agent used in radiolabelling of PSMA-11

11. Data representation in PET is done using

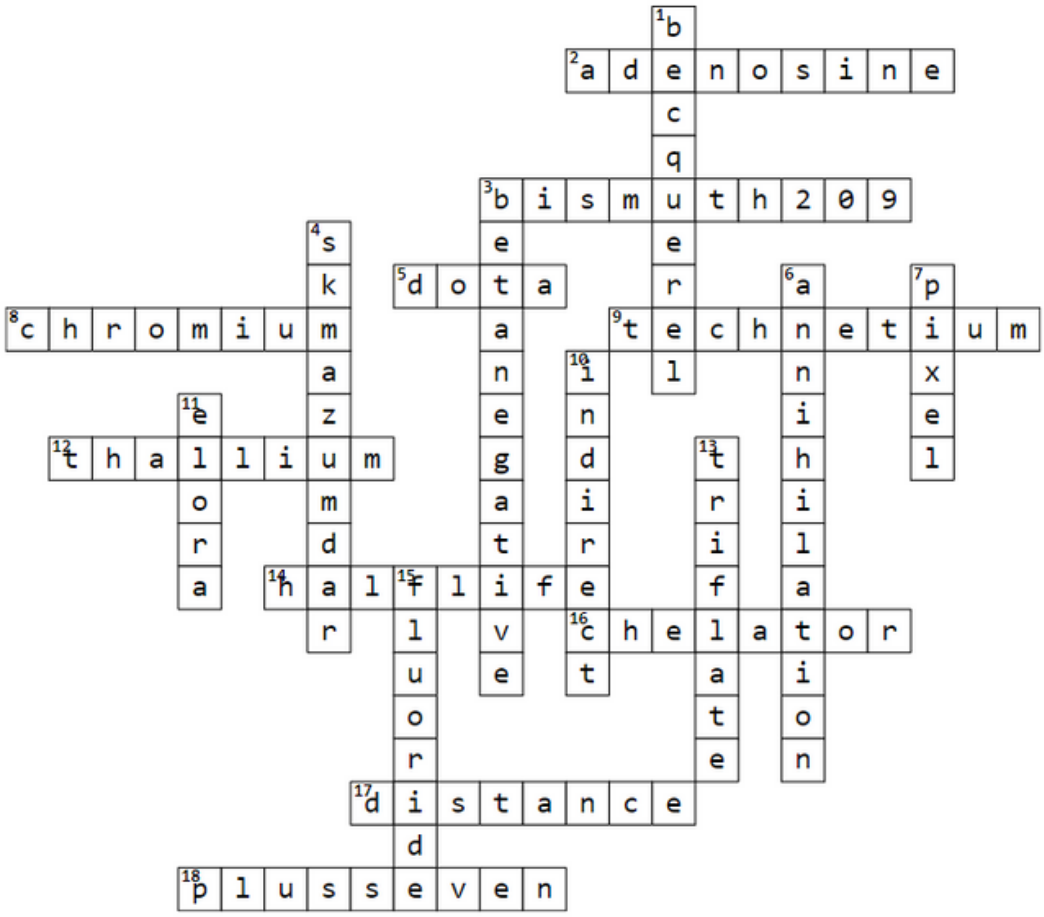
12. Main circulatory metabolite of N-13 NH3 is

14. Example of high pass filter

ANSWERS IN NEXT ISSUE

CROSSWORDS

ANSWERS OF JAN-MAR 2023 ISSUE



ACROSS

2. Stress agent in cardiac studies
3. Stable daughter product of Actinium-225 decay
5. Commonly used chelating agent
8. Nuclide used for splenic sequestration studies
9. Lightest element with all radioactive isotopes
12. Doping element/Impurity in NaI scintillator
14. Characteristic of Radionuclide
16. For better in-vivo stability of Ga-68 is labelled using which agent
17. Radiation exposure varies as Inverse Square of this factor
18. Most stable oxidation state for Technetium (2 Words)

DOWN

1. SI unit of activity
3. Decay mode which results in increase in Z (2 Words)
4. Father of Indian Nuclear Medicine Program is
6. Process of conversion of masses into energy
7. Basic unit of image
10. Water radiolysis is an example of which effect radiation
11. Web-based application established by AERB used by Radiation Professionals for Registration
13. Commonly used leaving group in FDG synthesis
15. Bone seeking nuclide

Schedule

NATIONAL

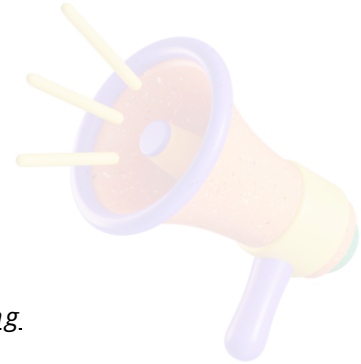
21st Annual Conference of Association of Nuclear Medicine Physicians of India
29 September - 1 October, 2023
Sarvodaya Health Care, Faridabad
Last date for Abstract Submission: 31st August, 2023

CME on Current Trends in Pediatric Nuclear Medicine
21-22 October, 2023
PGIMER, Chandigarh

3rd Indian Cancer Congress
2-5 November, 2023
Jio World Convention Center, Mumbai

55th Annual Conference of Society of Nuclear Medicine India
16-19 November, 2023
AIIMS, Jodhpur
Last date for Abstract Submission: Yet to be announced

Schedule



INTERNATIONAL

Annual meeting of Society of Nuclear Medicine and Molecular Imaging
24-27 June, 2023
Chicago, Illinois, USA

8th International Conference on Education and Training in Radiation Protection (organized in cooperation with the IAEA)
27-30 June, 2023
Groningen, Netherlands

11th International Conference on Isotopes
23-27 July, 2023
Saskatoon, Canada

Targeted Radiopharmaceuticals Summit
25-27 July, 2023
Boston, USA

World Molecular Imaging Congress
5-9 September, 2023
Prague, Czech Republic
Last date for Abstract Submission: 30th June, 2023.

36th Annual Congress of the European Association of Nuclear Medicine
9-13 September, 2023
Vienna, Austria
Last date for Abstract Submission: 25th April, 2023.

International Symposium on Artificial Intelligence and Informatics in Nuclear Medicine and Molecular Imaging
9-11 September, 2023
Groningen, Netherlands
Last date for Abstract Submission: 15th August,2023

ICRP 2023, the 7th International Symposium on the System of Radiological Protection
6-9 November, 2023
Tokyo, Japana
Last date for Abstract Submission: 4th August,2023

Upcoming Events

FROM EDITORIAL TEAM

Dear NMPAI members and readers,

Being part of the editorial team of this electronic Newsletter has been an enlightening and rewarding experience. I am honoured to have had the privilege to contribute to a platform dedicated to propagating Nuclear Medicine knowledge, research-based articles, and recent advancements among the Nuclear Medicine fraternity.

This editorial team comprises vibrant and supportive members, headed by two dynamic chief editors, each passionate about literature in Nuclear Medicine. The team is committed to excellence and dedicated to bringing out the best issue every single time. Engaging in brainstorming sessions, reviewing articles, meeting deadlines, and emphasising innovation is an integral part of the team as we strive to explore new ways to engage our readership. Whether it is incorporating articles from renowned experts in the field, encouraging students to write more, or engaging readers with a crossword puzzle, we always aim to deliver a dynamic reading experience.

Working alongside accomplished professionals and researchers has significantly expanded my knowledge base. The opportunity to review and edit a wide range of topics has been instrumental in broadening my understanding of the field. One of the most fulfilling aspects of being an editorial team member has been witnessing the impact our work has on the Nuclear Medicine community. The positive feedback we receive from readers serves as a testament to the collective effort we put in as a team. Receiving a physical hard copy of the newsletter during NMPAICON 2023 was rewarding. Beyond the technical skills gained, being an editorial team member has helped me develop soft skills like attention to detail and adaptability.

I am thankful to the editors of the newsletter, Dr. Priyanka Gupta and Dr. Rakhee Vatsa, for giving me this opportunity. I am grateful to all the editorial team members for their invaluable support. I take this opportunity to thank Mr. Navneet Kumar for designing every single issue to release the most visually enthralling newsletter. My journey as an editorial team member has been brimming with personal growth, and as I look forward, I am excited to continue playing my part in advancing the field with excellence and innovation, one issue at a time.

Regards,

Lavanya K

Nuclear Medicine Technologist,
Yenepoya Medical College Hospital,
Mangaluru, Karnataka.

FROM EDITORIAL TEAM

Dear Readers,

We are very excited to deliver the third edition of the newsletter!

And with that being said, I would like to thank an amazing multidisciplinary team including members from all around India for allowing me to contribute to the newsletter. I was assigned to design the magazine and the editorial team has been encouraging and supportive throughout the process whenever I needed it.

Design as we say, starts with the thought process of an individual. The challenge that comes with designing is when you're asked to align your design ideas with literature. Sometimes you get great ideas that complement perfectly with the write-up but sometimes you run out of ideas. The mesmerizing as well as daunting thing about designing is that a dilemma of design placement a few centimeters to the left or right can change the entire visual presentation. I would like to thank Dr. Priyanka Gupta and Dr. Rakhee Vatsa for saving me from this dilemma while designing. Also, I am thankful to, Ms. Lavanya K for ensuring every piece of literature free from the slightest of publication errors.

As I said earlier, Designing is a daunting task and you'll need positive reinforcements. Mr. Naresh Kumar and other team members have been encouraging and supporting me with their valuable feedback and guidance throughout the process of production and design.

During the entire design process, we have come across brilliant write-ups sent by our contributors which we design wholeheartedly for the best visual treat for our readers. We would love to see your inputs which will enable us to present articles even more visually engaging. Also for delivering a dynamic reading experience, we would be introducing new sections in the newsletter which we are thrilled about. We introduced a quote section & a crossword puzzle section as a part of this effort. Other exciting ideas are in the pipeline and we are constantly working for bringing them to upcoming issues.

Thanking our readers and contributors,

Navneet Kumar

Technical Assistant,
All India Institute Of Medical Sciences,
Bhubaneswar, Odisha

NMPAICON - 2024

8th Annual Conference of Nuclear Medicine Physicists Association of India

Venue :

Shri Mata Vaishno Devi Narayana
Superspeciality Hospital
Katra, Jammu

24th - 25th February, 2024