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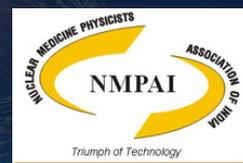Yenepoya Medical College Hospital,
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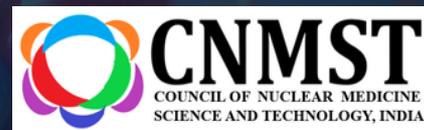
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पधारो म्हारे देस

> " My success will not depend on what A or B thinks of me.
>
> My success will be what I make of my work. "

HOMI J. BHABHA

NEWSLETTER

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ALPHA EMITTERS IN TARGETTED THERAPY : A NEW ERA FOR NUCLEAR MEDICINE

Ravi Ranjan Kumar

Molecular Imaging Specialist, United Kingdom

Radiation therapy uses ionizing radiation to kill cancer cells by targeting DNA, thereby preventing them from growing and dividing. External radiation therapy is the most common way of exposing cancer patients to radiation [1,2]. This approach irradiates only a limited body area by delivering a beam of high-energy X-rays to the tumor site. On the other hand, like chemotherapy, targeted radionuclide therapy is also a systemic treatment; however, it utilizes a molecule labelled with a radionuclide to target tumor sites.

In targeted radionuclide therapy, the biological effect is obtained by energy absorbed from the radiation. The radionuclides used for targeted radionuclide therapy must emit radiation with a relatively short path length. Three types of particulate radiation of consequence for targeted radionuclide therapy, beta particles, alpha particles, and Auger electrons, can irradiate tissue volumes with multi-cellular, cellular, and sub-cellular dimensions, respectively [2,3].

Alpha particles are helium nuclei emitted from radionuclides which decay via an alpha decay pathway explained in Figure 1 [4].

Several alpha-particle emitters with suitable half-lives are currently in use or being investigated for use in human trials, for instance, Astatine-211 (At-211, t1/2= 7.2 h), Bismuth-212 (Bi-212, t1/2= 1 h), Bismuth-213 (Bi-213, t1/2= 45.6 mins), Radium-223 (Ra-223, t1/2= 11.4 day), Actinium-225 (Ac-225, t1/2= 10.0 days) and Thorium-227 (Th-227, t1/2= 18.7 days) [Table 1].
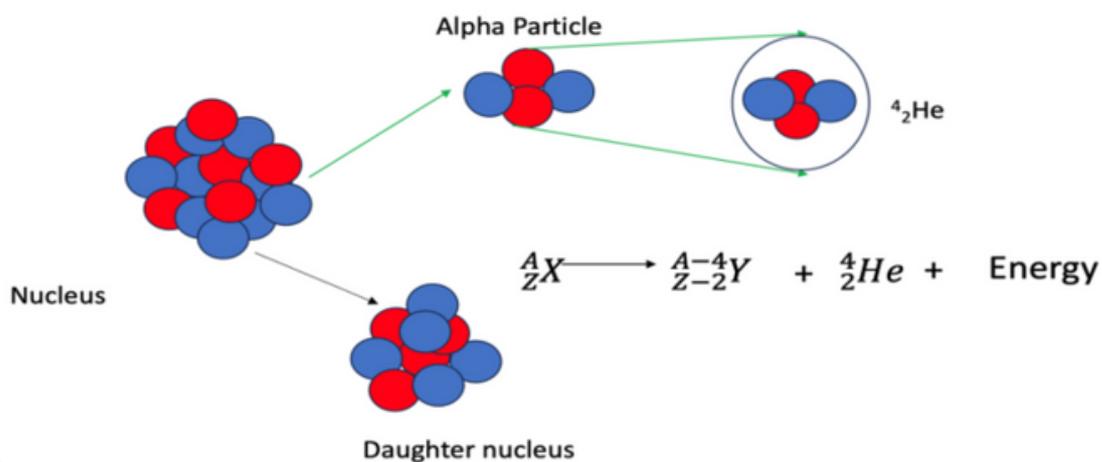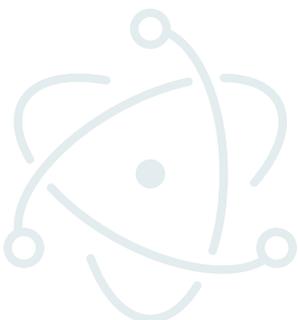

$$_{Z}^{A}X \longrightarrow _{Z-2}^{A-4}Y + _{2}^{4}He + \text{Energy}$$

Figure 1 : Typical example of Alpha decay

Radionuclide	Daughters	Half Life	Emission	Energy (MeV)	Production
Ac-225	Fr-221, At-217, Bi-213, Po-213, Tl-209, Pb-209	10 days	5 α, 3β-	5.8	U-233 natural decay Cyclotron
At-211	Po-211, Bi-207	7.2 h	2α, 2EC	5.9	Cyclotron
Bi-212	Po-212, Tl-208	60.6 mins	2α, 2β-	6.05	Th-228 natural decay Ra-224 Generator
Bi-213	Po-213, Tl-209, Pb-209	45.6 mins	2α, 3β-	5.8	Ac-225 Generator
Pb-212	Bi-212, Po-212, Tl-208	10.6 h	2α, 3β-	6.05	Ra-224 Generator
Ra-223	Rn-219, Po-215, Pb-211, Bi-211, Po-211, Tl-207	11.4 days	5 α, 3β-	5.7	Ac-227 Generator
Th-227	Ra-223, Rn-219, Po-215, Pb-211, Bi-211 Po-211, Tl-207	18.7 days	56α, 3β-	5.9	Ac-227 Generator

Table 1 : Characteristics of alpha emitting radioisotopes for treatment of targeted cancer therapy In-vivo.
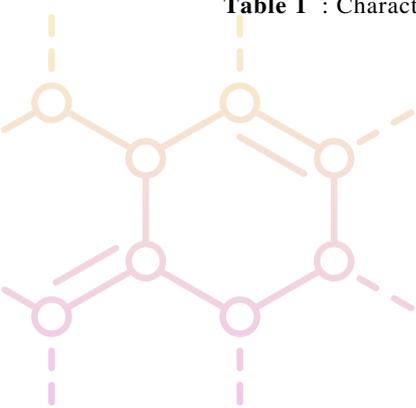
The main principle of alpha radiations reaching to specific tumor is based on tumor biology. The characteristics of tumor cells is defined in terms of overexpression of characteristics molecule (example protein) on cell membrane. However, these overexpressed characteristics molecules are absent in healthy cells [5,6].

Classical example, in prostate cancer, prostate specific membrane antigen (PSMA) is over-expressed on cell surface of prostate cancer cell with minimal expression on healthy cells. Therefore, alpha emitter radionuclide is linked to a peptide having strong affinity for the PSMA (E.g.: 217Ac-PSMA-617).

Dealing with alpha therapy, radio-conjugate must bestable in-vivo to reach the tumor specific cells. Figure 2 clearly demonstrate the mechanism targeted PSMA therapy with alpha emitter radionuclide.
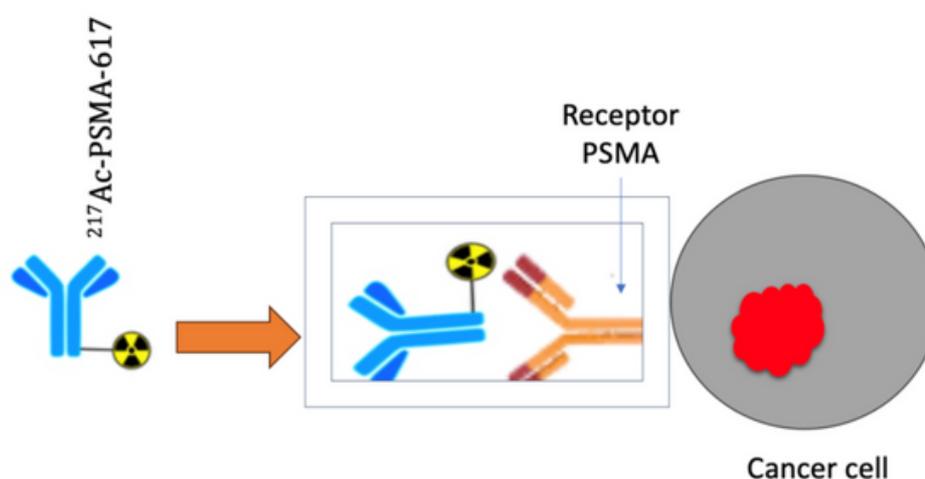

Figure 2 : Typical mechanistic understanding of Alpha Therapy

Several commercial radiopharmaceuticals have been introduced as targeted alpha therapy for treating the cancer diseases. Table 2 represent the active and recruiting clinical trials with commercially available drug using targeted alpha therapy.

The major challenge of targeted alpha therapy is dosimetry and tumor necrosis syndrome. Another in-vivo challenge, antibodies, or albumin-binding small molecules may mitigate renal clearance [6,7]. Recent research advocates the interaction between alpha particles and immune system is complex process.

Some of the recent data shows that such interactions may damage the immune system. However, some research shows synergistic interactions that could be exploited for therapeutic gain. Therefore, clearly challenges and opportunities are always coming in the picture while exploring targeted alpha therapy.
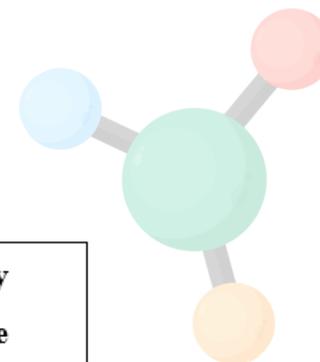
Trial Studies	Radionuclide	Target	Agent	Primary outcome
NCT03276572	Ac-225	PSMA	^{225}Ac-J591 (Cornell)	DLT,MDT
NCT03746431	Ac-225	IGF-IR	^{225}Ac -FPI-1434 (Fusion Pharmaceuticals)	AE,DLT
NCT04147819	Th-227	HER2	BAY2701439 (Bayer)	AE,ORR
NCT05720130	Pb-212	PSMA	^{212}Pb -ADVC001 AdvnCell	RP2D
NCT03466216	Pb-212	SSTR2	^{212}Pb-DOTAMTATE (Radiomedix)	ORR

Table 2 : Ongoing clinical trials of targeted alpha therapy.

Abbreviations

AE: Adverse Events
DLT: Dose-limiting toxicities
MTD: Maximum tolerated dose
CEA: Carcinoembryonic antigen

REFERENCES

1. Nelson BJB, Andersson JD, Wuest F. Targeted alpha therapy: progress in radionuclide production, radiochemistry, and applications. Pharmaceutics. 2020; 13:49.

2. Sgouros G, Ballangrud AM, Jurcic JG, McDevitt MR, Humm JL, Erdi YE, et al. Pharmacokinetics and dosimetry of an α-particle emitter antibody: 213Bi-HuM195 (anti-CD33) in patients with leukemia. J Nucl Med. 1999; 40:1935–1946.

3. McDevitt MR, Sgouros G, Finn RD, Humm JL, Jurcic JG, Larson SM, et al. Radioimmunotherapy with alpha-emitting nuclides. Eur J Nucl Med. 1998; 25:1341–1351.

4. Miederer M, McDevitt MR, Sgouros G, Kramer K, Cheung NKV, Scheinberg DA. Pharmacokinetics, dosimetry, and toxicity of the targetable atomic generator, 225Ac-HuM195, in nonhuman primates. J Nucl Med. 2004; 45:129–137.

5. Zalutsky MR, Reardon DA, Pozzi OR, Vaidyanathan G, Bigner DD. Targeted α-particle radiotherapy with 211At-labeled monoclonal antibodies. Nucl Med Biol. 2007; 34:779–785.

6. Raja C, Graham P, Rizvi SMA, Song E, Goldsmith H, Thompson J, et al. Interim analysis of toxicity and response in phase I trial of systemic targeted alpha therapy for metastatic melanoma. Cancer Biol Ther. 2007; 6:846–852.

7. Zechmann CM, Afshar-Oromieh A, Armor T, Stubbs JB, Mier W, Hadaschik B, et al. Radiation dosimetry and first therapy results with a (124)I/(131)I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. Eur J Nucl Med Mol Imaging. 2014; 41:1280–1292.

THE EVOLUTION OF ARTIFICIAL INTELLIGENCE IN MEDICAL IMAGE RECONSTRUCTION TECHNIQUE: HISTORY AND FUTURE PERSPECTIVES

Viraj Sawant

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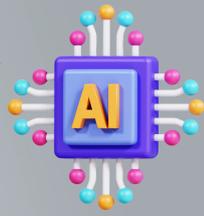
In recent years, the field of medical imaging has seen remarkable advancements with the integration of artificial intelligence (AI) techniques. One such application of AI is in medical image reconstruction techniques, which has revolutionized the field of diagnostic imaging.

Evolution of Medical Image Reconstruction: A Brief Background

The history of medical image reconstruction can be traced back to the introduction of Computed Tomography (CT) in the 1970s. Initially, traditional reconstruction methods were employed to reconstruct images from raw data acquired by CT scanners. Earlier CT image reconstruction was based on simple analytical algorithms that pieced together the data collected from X-ray scans to create cross-sectional images of the body [1]. These methods were time-consuming and often resulted in images with limited quality.

In the 1990s, iterative reconstruction algorithms emerged, which improved image quality by iteratively refining the image until convergence [2]. These techniques utilized mathematical models and prior knowledge about the imaging process to enhance image accuracy and reduce artifacts. More computationally intensive, iterative methods yielded significant improvements in image quality and became widely adopted in medical imaging modalities such as CT and Positron Emission Tomography (PET).

Fast forward to the 21st century, where AI has made significant progress. The application of AI algorithms, particularly deep learning techniques, has accelerated the development of advanced medical image reconstruction methods.

AI in Medical Image Reconstruction: History

Over the past decade, AI has played a significant role in enhancing the quality and efficiency of medical image reconstruction techniques. In 2012, the ground breaking development of Convolutional Neural Networks (CNNs) paved the way for deep learning algorithms in medical imaging [3]. Since then, various AI-based image reconstruction techniques have emerged, each with its own unique approach. For instance, Generative Adversarial Networks (GANs) have been utilized to generate high-quality medical images by training a generator network to reconstruct images from noise [4]. GANs have proven to be highly effective in improving image resolution and reducing noise artifacts.

Another notable technique is iterative reconstruction, where AI algorithms iteratively refine the image by incorporating prior knowledge and regularization strategies. These iterative approaches have shown significant potential in reducing radiation dose and improving image quality simultaneously.

Future Perspectives and Potential Applications

The integration of AI in medical image reconstruction holds immense potential for future applications in healthcare. Here are a few perspectives that can shape the future of this field:

1. Enhanced diagnostic accuracy

With the aid of AI algorithms, medical image reconstruction can significantly enhance diagnostic accuracy. By improving image resolution, reducing artifacts, and enhancing subtle details, AI can contribute to more accurate diagnoses and better patient outcomes.

2. Reduced radiation exposure

Traditional medical imaging techniques often involve high radiation doses, which can pose risks to patients. AI-based image reconstruction techniques can help mitigate this issue by reducing the required radiation dose without compromising image quality. This has the potential to improve patient safety and reduce long-term health risks.

3. Personalized medicine

AI algorithms can leverage the vast amount of patient data available to personalize image reconstruction methods according to an individual's unique characteristics. By tailoring image reconstructions to specific patient conditions, AI can contribute to personalized medicine, leading to more effective treatment plans and better patient care.

4. Streamlined workflow

Through faster and more efficient reconstruction methods, AI can significantly improve the workflow in medical imaging departments. This can reduce waiting times, increase throughput, and enhance overall operational efficiency, allowing healthcare professionals to focus more on patient care.

The Road Ahead: AI-Powered Personalized Medicine

The integration of AI in nuclear medicine image reconstruction opens up exciting possibilities for personalized medicine. As AI algorithms learn from vast datasets and patient information, they can tailor image reconstructions to individual patients' specific needs, optimizing diagnostic accuracy and treatment planning. Additionally, AI's real-time capabilities in reconstructing nuclear medicine images can significantly reduce scanning time and enhance patient comfort during imaging procedures, making healthcare more efficient and accessible.

Conflict of Interest : None
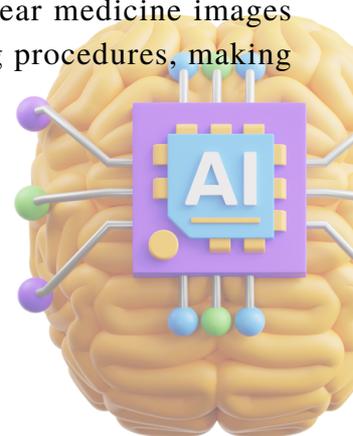
REFERENCES

1. Kalender WA. Computed Tomography: Fundamentals, System Technology, Image quality. Applications. Erlangen: Publics Corporate Publishing. 2005.

2. Fessler JA. Statistical Image Reconstruction Methods for Transmission Tomography. In Sonka M & Fitzpatrick JM, editors. Handbook of Medical Imaging: Medical Image Processing and Analysis (Vol. 2). SPIE Press. 2000.

3. Litjens G, Kooi T, Bejnordi BE, Setio AA, Ciompi F, Ghafoorian M, et al. A survey on deep learning in medical image analysis. Med Image Anal. 2017; 42:60-88.

4. Goodfellow I, Pouget-Abadie J, Mirza M, Xu B, Warde-Farley D, Ozair S, et al. Generative Adversarial Networks. Commun ACM. 2020; 63:139–144.
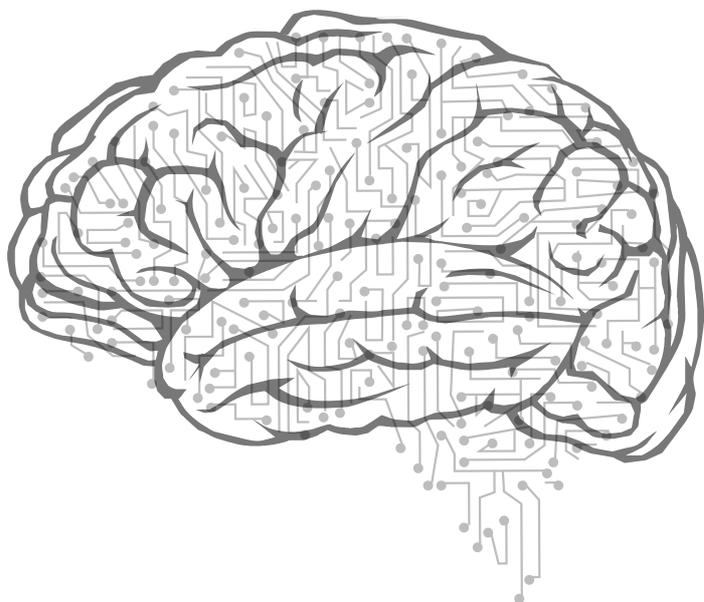
IMAGE BASED DOSIMETRY: SIMPLIFYING THE INTERNAL ABSORBED DOSE ESTIMATION

Komalpreet Kaur

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Targeted radionuclide therapy (TRT) is gaining momentum as a treatment of choice for cancer patients. Radionuclide therapy targets cancer cells on molecular levels, minimising the undesired effect of radiation on healthy cells. Personalised dosimetry should be performed on every patient to increase the efficacy of the therapeutic regime. Internal dosimetry is a very bulky process that is usually difficult to execute. Due to this complexity, image-based dosimetry is gaining popularity. For the accurate estimation of absorbed doses in organs imaged, precise activity quantification is an important step that requires proper calibrations and standardisation of the imaging instrument.

Some basic steps need to be followed to perform image-based dosimetry, from the radiopharmaceutical administration to dose estimation using mathematical medical internal radiation dosimetry (MIRD) formulism. The steps are discussed in brief as follows:

1. Administration of Radiopharmaceutical

Image-based dosimetry can be performed post-therapy after the uptake period of the radiopharmaceutical. It can also be performed pre-therapy with a diagnostic dose of the radiopharmaceutical in concern to estimate the absorbed dose to the critical as well as the target organs.

2. Sequential Imaging

Sequential whole-body imaging is often required to generate a time-activity curve (TAC) and calculate the residence time of the radiopharmaceutical in the organ of interest. Image-based dosimetry can be done in three ways. First: a planar scenario where only wholebody imaging is done over a time period to generate TAC for the organ of interest; Second: Multiple single photon emission computed tomography-computed tomography (SPECT-CT) scenario where SPECT-CT is acquired at multiple time points and used for generation of TAC; Third: The hybrid scenario which is a combination of planar imaging and SPECT imaging.

3. Registration of SPECT and CT images

Co-registration of SPECT and CT images is an essential step in reconstruction and pre-processing as it will help determine the volume of interest in organs in the acquired images and can be used in dedicated dosimetry software.
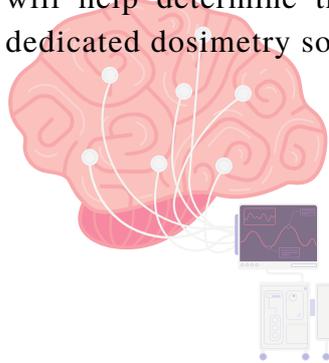
4. Image Quantification

Image-based dosimetry depends upon accurate activity quantification in the acquired images. Various commercial softwares are now available for activity quantification and image-based dose estimations. Image quantification is possible due to the availability of correction algorithms for scatter, attenuation, collimator-detector-response, partial volume, etc., which can be incorporated into the reconstruction algorithm. Activity is quantified in different volumes of interest created on the acquired images. Calibration of the acquisition system and standardisation of acquisition protocols is a necessary step in activity quantification.

5. Time-activity-curve fitting per volume of interest

The activity quantified in the different volume of interest (VOI) is plotted against time to obtain the time-integrated activity, i.e., the accumulated activity. The residence time can be calculated and further used for dose estimation with the help of dedicated dosimetry software.

6. Dose Calculation

The image-based input parameters, such as accumulated activity and residence time, are calculated and used in dose estimation using the MIRD formula. Standalone software like OLINDA/EXM or MIRDOSE can be used for dose calculations for diagnostic and therapeutic radiopharmaceuticals. Standardisation of protocols and calibration of the acquisition system plays a vital role in image-based dosimetry. It needs to be established in the department to perform dosimetry in the clinical evaluation of patients receiving diagnostic or therapeutic doses.

FLUENCY IN THE F-18 FDG PET-CT WORKFLOW

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Every Nuclear Medicine (NM) professional faces the challenge of placing the correct order of F-18 FDG tracer for the appointed cases to optimize the dose used in the PET-CT unit. It is well known that the regulatory limit of dose permitted for a workplace should not be crossed. The regulatory dose limit for the week is laid down with due consideration to the shielding facilities available in the unit and the number of radiation workers who can share the radioactive work. The daily dose to be ordered depends on the number of appointments for the day and the amount of accepted dose for the week that has already been ordered until the lapsed days of the week. This marks the upper limit for the dose that can be ordered. The optimum dose should:

- Suffice the need for interpretable quality images for each patient. An interpretable image is an output that can yield the best quality report through accurate reporting without ambiguity.
- Be appropriate for the patient's weight; for example, a 60 kg patient will need a lesser dose than a 90 kg patient.
- Be sufficient to get cooperation throughout the scanning period from the patient, depending on their health condition.

The requisites mentioned above indicate the lower dose limit that needs to be ordered.

As said, "well begun is half done", and the optimum dose ordered per the weight, age, and health condition of the appointed PET-CT cases can lay a sound foundation for fluent workflow in the PET-CT unit.

The equipment's sensitivity also determines the minimum dose to be administered to get good-quality images within the scanning time of the patient's tolerance. For highly sensitive TOF imaging systems, one can administer as low as 0.1 times the patient's weight (for example, a 60 kg patient needs to be given 6 mCi, while a 90 kg patient needs 9 mCi). If given a lesser dose, one must increase the corresponding scanning time. This may challenge a non-cooperative patient or dilute the efficiency of time management. Considering all the points mentioned earlier, one must optimize the dose to be ordered and administered to the patient.

Every teammate of the NM department must be educated about the exponential decay of the radioactivity, especially fast decaying Fluorine-18, and consequently train them to be on their toes, not wasting any time with unwanted activity, and nullify communication gaps as soon as the dose is received, in the initial 2 hours. Once the workflow is streamlined, the steps can be taken in the format of patients getting promoted from one step to another.

A gap of half an hour (approximate scanning time for each patient, as per the speed of the imaging system) can be kept between two consecutive patients to be administered. This can also maintain the biodistribution/uptake time at one hour.
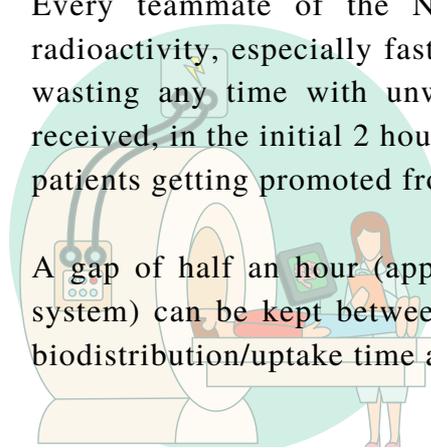
The scan time also depends on the cooperation, health, or ambulatory status of the patient. The efficiency of an optimum workflow depends on coordinated teamwork and the prediction of the time needed in advance. Time saved in each step saves the dose for the upcoming cases.

The waiting area with CCTV should be filled with the number of patients as much as the number of sitting areas as per the approved plan. It is always convenient to have one place assigned for non-ambulatory cases in one of the waiting areas.

It is always helpful to plan very well for the next case, like extra activities needed (for example, rectal contrast to be given) to be taken during the current scan to avoid wastage of time when the patient is on the imaging bed.

One should also have a "back-up" plan for diabetic cases with uncontrolled sugar levels. Insulin control on the same day before dose administration has been questionable for optimum F-18 FDG uptake and should be avoided. In such a condition, there should be a tentative waiting list of local cases that have been appointed. This leads to optimum application of the precious tool as well as appealing to the management for having applied the resource for the beneficiary.

It is preferable to start the dose administration with heavier cases, if possible, when the dose is maximum initially to match the use of exponentially fast decaying radioactivity. The critical or non-ambulatory cases that need to be completed in the shortest acquisition times have to be administered an equivalent dose too.

Overall, each appointed case should cover every step of the PET-CT procedure, like:

- Patient history-taking and consenting
- Patient changes into a hospital gown
- IV cannula fixation
- F-18 FDG administration
- Waiting for optimum biodistribution
- Patient scanning
- Observation post-scanning

It is judicious to start the first two steps for two patients to prevent wastage of time due to an inadvertent delay in
- Counselling non-cooperative patients
- Difficulty in securing a patent IV line

Predicting the causes of delay and taking corrective measures throughout the PET-CT work for the day will definitely improve the fluency of the workflow. A senior technical staff member who applies his or her substantial experience to prevent delay at every step proves to be an asset to the team.

Finally, one should not underestimate the peaceful and well-coordinated communication between teammates along with the empathetic attitude towards the patients, having the singular goal of serving to the best of their abilities for an accurate diagnosis and consequently the right line of treatment for the patients.

BIFUNCTIONAL CHELATORS FOR Ga-68-RADIOPHARMACEUTICALS : INSIGHTS INTO CHEMISTRY AND CHALLENGES

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INTRODUCTION

Nuclear medicine represents a pivotal discipline employing biological pathways for disease management. This can be achieved by utilising biomolecules labeled with radiometals of interest, including α, β, and γ emitters. By localising ionising radiation at specific regions of interest, imaging instruments like positron emission tomography (PET) and single photon emission computed tomography (SPECT) can detect and precisely map the radiation within the body. Consequently, these methods are crucial in disease localisation, therapy, and therapeutic interventions. To optimise the effectiveness of such procedures, it is highly desirable to employ the same biomolecule (peptides, proteins, and small molecules) for both diagnostic ($\beta+$ and γ) and therapeutic (α and β-) radiometals. These theranostic radiopharmaceuticals ensure consistent pharmacokinetics, thereby enhancing the overall efficacy of the approach. However, direct chelation of radiometals with biomolecules proves impractical due to structural changes in biomolecules, necessitating the introduction of bifunctional chelators (BFCs) to protect biomolecules from alteration. It serves as a molecular link between the biomolecule and the radiometal. BFCs enable the stable and efficient formation of radio complexes. This article presents an overview of desirable BFCs tailored explicitly for the chelation of commonly used trivalent radiometal gallium-68 (^{68}Ga), focusing on its chemistry that makes it well-suited for chelation.

Chemistry of trivalent radiometal (Ga-68)

Gallium (Ga), an element denoted by the chemical symbol Ga and possessing atomic number 31, is in group IIIB of the periodic table. It was first discovered by Lecoq de Boisbaudran in 1875. The electronic configuration of gallium is $[Ar]3d^{10}4s^{2}4p^{1}$ with an atomic radius of 1.245 Å, while its ionic radius measures 0.62 Å. Gallium's electron affinity, electronegativity, and ionisation energy are measured as 0.32 eV, 1.81 on the Pauling scale, and 6.0 eV, respectively. Given its low ionisation energy and electron affinity, gallium demonstrates a thermodynamically favored tendency for electron removal rather than addition. It readily attains an oxidation state of +3 (represented by Ga(III)) by releasing two 4s-electrons and one 4p-electron, a characteristic that influences its chemical reactivity. However, gallium can also exist in lower valency states with oxidation numbers of +1 and +2, resulting in compounds such as GaCl, GaOH, $Ga_{2}O$, $GaCl_{2}$, $Ga(OH)_{2}$, and GaS [1, 2]. Gallium-69 is the most abundant natural isotope, constituting 60% of gallium's isotopic composition. Gallium-68, a radioactive isotope of Ga(III), is highly useful for nuclear medicine applications due to its relatively short half-life of 68 minutes and a positron energy of 1.9 MeV. The predominant source of Ga-68(III) in numerous nuclear medicine establishments is the ^{68}Ge/^{68}Ga generator. In conjunction with this generator, the production of ^{68}Ga can also be accomplished via cyclotron, employing two distinct methodologies: the ^{68}Zn(p,n)^{68}Ga and ^{65}Cu(α,n)^{68}Ga reactions [3].
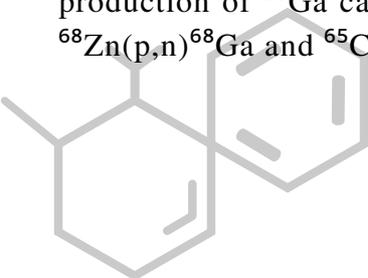
The combination of a high charge (+3) and a small ionic radius (0.62 Å) results in a high charge-to-radius ratio, classifying the Ga(III) ion as a hard Lewis acid [1-2]. This ionic character and the strong electrostatic attraction allow Ga(III) to deprotonate water molecules and form Gallium hydroxide $[Ga(OH)_3]$. Notably, these gallium hydroxides can precipitate even at an acidic pH of 3.5, forming colloidal particles in the solution. This poses a significant challenge in developing radiopharmaceuticals, as the OH- groups (formation constant, log K = 10) compete with ligands for metal bonding. Another obstacle in designing Ga-68-radiopharmaceuticals arises from the strong chelation between Ga(III) and the plasma protein transferrin (log K = 20). Due to the high stability constant of this chelate, a Ga-68-radiopharmaceutical is not kinetically inert and may exchange its metal with transferrin, impacting its effectiveness [2,4]. To overcome these challenges, the role of BFCs has been explored to prepare Ga-68-radiopharmaceuticals. These BFCs can bind more strongly to Ga(III) ions than the OH- group and transferrin, preventing the formation of insoluble hydroxide precipitates and transchelation to transferrin protein, facilitating the successful development of radiopharmaceuticals.
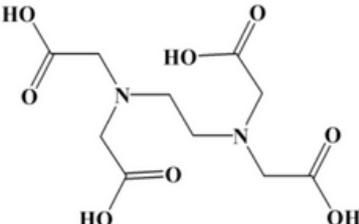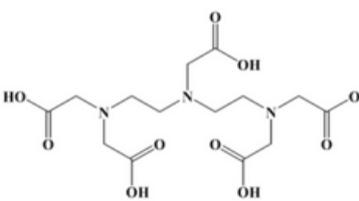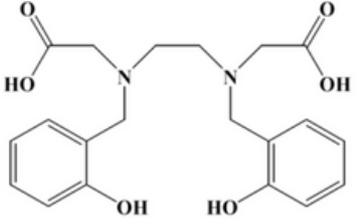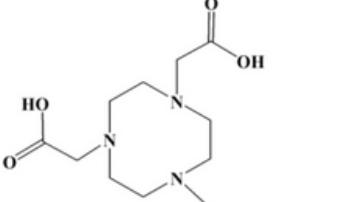
Bifunctional Chelators

An ideal radiopharmaceutical is desired to have good complexation kinetics (incubation time and temperature), thermodynamic stability, and kinetic inertness. BFCs achieve these goals simultaneously. Bifunctional chelators possess two distinct functional sites: one is responsible for biomolecule conjugation, while the other facilitates the chelation of radiometals. The conjugation can be done directly with the reactive functional group present in the BFC, such as carboxylic acid, NHS esters, and NSC. The presence of BFC in the vicinity of biomolecules can alter the pharmacokinetics of the biomolecule and the affinity for specific targets. So, to avoid this, the BFC can be distanced from biomolecules with the help of linker groups such as polyethylene glycol, AHX, and amino acids. [5]. Being the hard acid, Ga-68(III) requires hard donor groups such as nitrogen (N), oxygen (O), and sulfur (S) for the chelation. Ga-68(III) has the coordination number 6, so the kinetically inert and thermodynamically stable radio-complex formation requires a BFC that can provide a large enough coordination cavity to accommodate the six bonds [6, 7]. Among all the studied BFCs, polyaminopolycarboxylic acid-based chelators best suit this trivalent radiometal. These chelators can be acyclic or cyclic, with different denticities having their advantages and disadvantages over each other. The acyclic BFCs show good complexation kinetics at room temperature. However, they are less kinetically inert.

In contrast, cyclic BFCs require heating for the radio-complex formation and are advantageous as they are kinetically inert. However, due to the heat requirement for chelation, cyclic BFC chelators are unsuitable for heat-labile protein. The slow metal-binding kinetics of cyclic chelators is due to the requirement of metal to enter the pre-organised macrocyclic cavity, which is not a problem with acyclic chelators. Hence, acyclic chelators show fast metal-binding kinetics.

31
Ga
Gallium
69.723
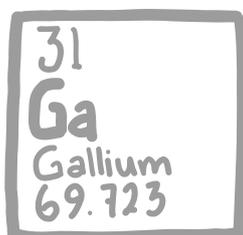
Radiolabeling of Ga-68

Ga-68 is most commonly obtained from the Ge-68/Ga-68 generator in the form of [Ga-68] GaCl3 by utilizing hydrochloric acid (HCl). As determined by the aqueous complex of Ga(III) with a six-coordinated structure, it has an inherent ionic nature, leading to the ionic complex formation with BFC. In this context, Ga(III) establishes six coordination bonds with multi-dentate ligands containing polycarboxylates appended to the nitrogen backbone, ultimately adopting an octahedral geometry. The coordination involves the formation of coordination bonds with N3O3, N4O2, N2O4, and O6 donors. The ionic charge of the Ga(III) ion is balanced through the deprotonated oxygen atom of carboxylic acid. The presence of a high concentration of hydrochloric acid (HCl) can result in the protonation of the carboxylic groups within the BFC, detrimentally affecting the binding of the metal. Hence, it is imperative to maintain a low HCl concentration during the reaction. To achieve this, the elution process of the generator should employ a dilute HCl solution ranging from 0.05 to 0.1 M. The binding affinity of Ga(III) varies for distinct donor atoms, with the order being N > O > Cl [4]. This hierarchy dictates the choice of donor atoms during the formation of coordination bonds in the metal-ligand chelation process. The stability constants of radio complexes were documented for various ligands, both acyclic and cyclic. The Log K values of commonly used BFCs are shown in Table-1 [5-11].

S. No.	Chelators	Structure	Denticity	Donar Type	Log K
1	EDTA		6	N_2O_4	20.3
2	DTPA		8	N_3O_5	25.4
3	HBED		6	N_2O_4	38.5
4	NOTA		6	N_3O_3	31.05
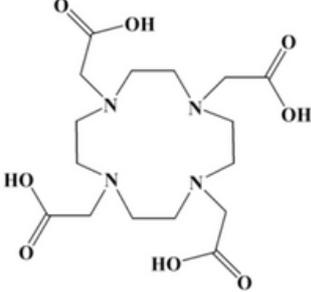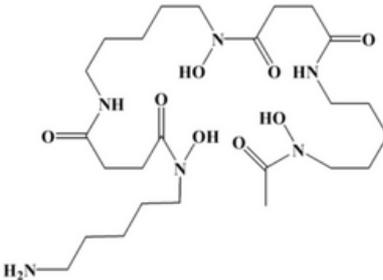
Table 1 : Characteristics of Ga(III) complex with various bifunctional chelators and their stability constants.

The relatively less stability of the Ga-68-DOTA complex than Ga-68-NOTA arises due to the precise match between the ionic radii and the coordination cavity provided by NOTA. The pre-organized larger coordination cavity of DOTA, coupled with the relatively smaller ionic radii of Ga-68(III), culminates in a markedly distorted octahedral Ga-68-DOTA complex and hence a less stable complex. However, short half-life and early imaging often make DOTA-conjugated molecules suitable for preparing Ga-68(III) radio complexes.

Conclusion

Among the BFCs investigated, both acyclic chelators, such as HBED, and cyclic chelators, including NOTA and DFO, exhibited the highest stability constants and favorable formation kinetics for Ga-68(III) radio complexes. However, it is essential to note that biomolecules can influence the stability of Ga-68(III) radio complexes.

Abbreviations

NHS: N-hydroxysuccinamide
NCS: Isothiocyanate
AHX: Aminohexanoic acid
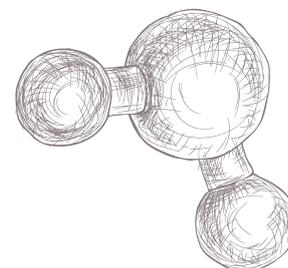EDTA: Ethylenediaminetetraacetic acid
DTPA: Diethylenetriaminepentaacetic acid
HBED: N,N'-Bis(2-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid
NOTA: 1,4,7-Triazacyclononane-N,N',N''-triacetic acid
DOTA: 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid
DFO: Desferrioxamine B

REFERENCES

1. Latimer WM. The oxidation states of the elements and their potentials in aqueous solutions. Prentice-Hall, Englewood Cliffs, N.J. 1952.

2. Greenwood NN. The chemistry of gallium. Advances in Inorganic Chemistry and Radiochemistry. Academic Press. 1963; 5:91-134.

3. Chakravarty R, Chakraborty S, Dash A, Pillai MR. Detailed evaluation on the effect of metal ion impurities on complexation of generator eluted Ga-68 with different bifunctional chelators. Nucl Med Biol. 2013; 40:197-205.

4. Moerlein SM, Welch MJ. The chemistry of gallium and indium as related to radiopharmaceutical production. Nucl Med Biol. 1981; 8:277-287.

5. Lattuada L, Barge A, Cravotto G, Giovenzana GB, Tei L. The synthesis and application of polyamino polycarboxylic bifunctional chelating agents. Chem Soc Rev. 2011; 40:3019-3049.

6. Morfin JF, Tóth É. Kinetics of Ga (NOTA) formation from weak Ga-citrate complexes. Inorg Chem. 2011; 50:10371-10378.

7. Kubicek V, Havlickova J, Kotek J, Tircsó G, Hermann P, Tóth É, et al. Gallium (III) complexes of DOTA and DOTA− monoamide: kinetic and thermodynamic studies. Inorg Chem. 2010; 49: 10960-10969.

8. Clarke ET, Martell AE. Stabilities of trivalent metal ion complexes of the tetraacetate derivatives of 12-, 13-and 14-membered tetraazamacrocycles. Inorganica Chim Acta. 1991;190:37-46.

9. Eplattenier FL, Murase I, Martell AE. New multidentate ligands. VI. Chelating tendencies of N, N′-Di (2-hydroxybenzyl) ethylenediamine-N, N′-diacetic acid. J. Am. Chem. Soc. 1967;89:837-843.

10. Weger HG, Lam J, Wirtz NL, Walker CN, Treble RG. High stability ferric chelates result in decreased iron uptake by the green alga Chlorella kessleri owing to decreased ferric reductase activity and chelation of ferrous iron. Botany. 2009;87:922-931.

11. Evers A, Hancock RD, Martell AE, Motekaitis RJ. Metal ion recognition in ligands with negatively charged oxygen donor groups. Complexation of iron (III), gallium (III), indium (III), aluminum (III), and other highly charged metal ions. Inorg. Chem. 1989;28:2189-2195.
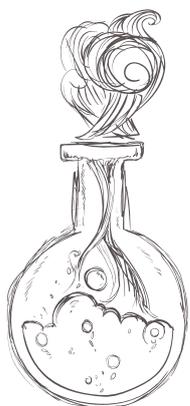
ADVANCEMENTS IN THERAPEUTIC NUCLEAR MEDICINE

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Nuclear Medicine therapy is an approach to treat cancer that might be used with or after other treatment options, such as chemotherapy and surgery. These therapies may lead to a cure for the disease when combined with other therapies. For the last two decades, radiopharmaceutical therapy (RPT) has been important in treating various systemic malignancies [1]. Alternatively, RPT is also referred to as targeted radionuclide therapy (TRT) or molecular radiotherapy (MRT) [2]. It can deliver a highly concentrated absorbed dose to the tumor while sparing the surrounding normal tissues. These therapies are primarily indicated in the treatment of systemic malignancy, such as in bone metastases, where whole-body irradiation using external beam radiotherapy is impossible [1].

The choice of a particular therapeutic radionuclide concerning its emissions, linear energy transfer (LET), and the physical half-life is dictated to a large extent by the character of the disease (i.e. localized or metastatic disease) and by the small molecule (carrier) which is used to selectively transport the radionuclide to the desired site [3]. For the radionuclide therapy, high LET radionuclides emitting beta or alpha, tagged with a suitable targeting molecule, are delivered to the target organ to destroy the malignant and other rapidly proliferating cell populations. The tissue penetration range of alpha, beta, and auger electrons should also match the tumor or cavity size. Particularly for alpha-particles, there is a localized deposition of dose over the tumor that provides the potential to spare organs at risk.

The choice of a therapeutic radionuclide may be based upon two main categories, namely physical characteristics (including the physical half-life, type of emissions, energy of the radiation(s), daughter product(s), method of production, and radionuclide purity) and biochemical characteristics. The biochemical aspects include tissue targeting, retention of radioactivity in the tumor, in-vivo stability, and toxicity [1].

In RPT, radiation is delivered to the target by administering the radiopharmaceuticals, either systemically or locally, that bind preferentially to cancer cells or accumulate by physiological mechanisms. The various routes for radiopharmaceutical administration include oral, intravenous, and loco-regional injection. The activity administered is either fixed or based on a patient's body weight or body surface area (BSA) [2].

This article summarizes and discusses various radionuclide therapies in clinical practices.

Orally administered RPT

I-131 NaI, also called radioiodine, is orally administered as a capsule or solution to the patient for treating thyroid diseases such as hyperthyroidism and thyroid malignancies with metastatic lesions [4]. Its action causes permanent destruction to the thyroid tissue by emitting radiation of two sorts: gamma and beta rays [5, 6]. I-131 has a half-life of 8.04 days, maximum and mean beta particle energies of 0.61 MeV and 0.192 MeV, respectively, and penetration of 2.4 mm. The beta radiation of I-131 is responsible for its therapeutic effects, and a gamma emission of 364 keV (81% abundance) is utilized for imaging purposes.

I-131 NaI administration is indicated in patients with high surgical risk and decreased life expectancy or who have failed to obtain a euthyroid state or cannot tolerate oral anti-thyroid agents. The action mechanism depends on the uptake of iodine from thyroid tissue. Iodine is a natural precursor for thyroid hormones T3 and T4, which is taken up from the blood into the thyroid follicular cell by sodium iodide (Na-I) symporter. Radioactive iodine (RAI) exerts its therapeutic effects once it is taken up by the thyroid follicular cells, emitting beta rays that further cause definitive local damage to the thyroid tissue [7, 8].

The RAI therapy may be administered as an adjuvant to surgery in Ca thyroid and may be given 4-6 weeks post-surgery [9]. The recommended dosage for thyroid carcinoma patients ranges from 3700 to 5550 MBq.

I-131 is produced by two ways [10]: 1) Cyclotron produced by bombardment of tellurium, 2) Reactor produced by irradiating either Tellurium-130 (^{130}Te (n,γ) ^{131}Te$\rightarrow$^{131}I) or uranium-235 (^{235}U (n,f) ^{131}I).

Intravenously Administered RPT

Peptide Receptor Radionuclide Therapy for Neuroendocrine tumors (NETs)

NETs are the heterogeneous group of neoplasms that originate from endocrine glands (pituitary, parathyroid), neuroendocrine (adrenal), endocrine islets within glandular tissue (thyroid, pancreatic) and the cells dispersed between exocrine cells. NETs secrete various metabolically active substances (amines and peptides) and may occur sporadically or as a part of familial syndromes.

Somatostatin-type receptors (SSTR), found on cell surfaces, occur in many places, including the central nervous system, the gastrointestinal tract, and the pancreas. Six different SSTRs (SSTR1, SSTR2A, SSTR2B, SSTR3, SSTR4 and SSTR5) have been identified. SSTR2 and SSTR5 are predominantly overexpressed in NETs, while normal tissue majorly expresses SSTR3 and SSTR5 [3]. These overexpressed SSTRs in NETs can be targeted by a radiolabeled peptide as shown in Figure-1. SSTR, particularly SSTR2a, expressing neuroendocrine tumors (NETs) of the pancreas and midgut can be imaged with gallium-68 (Ga-68) DOTA peptides (DOTATATE [tetraazacyclododecane tetraacetic acid octreotate], DOTANOC [tetraazacyclododecane tetraacetic acid sodium triiodide octreotide], and DOTATOC [tetraazacyclododecane tetraacetic acid D-phenylalanine 1 tyrosine 3 octreotide]) [Table-1, indium-111 (In-111) octreotide, or Technetium-99m (Tc-99m) octreotide and treated with Lu-177 DOTA-peptides or yttrium-90 (Y-90) octreotate as a theranostic pair [11].
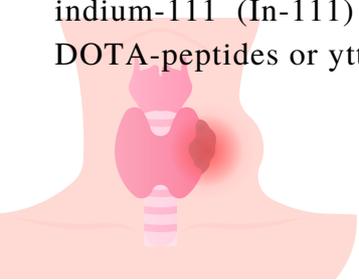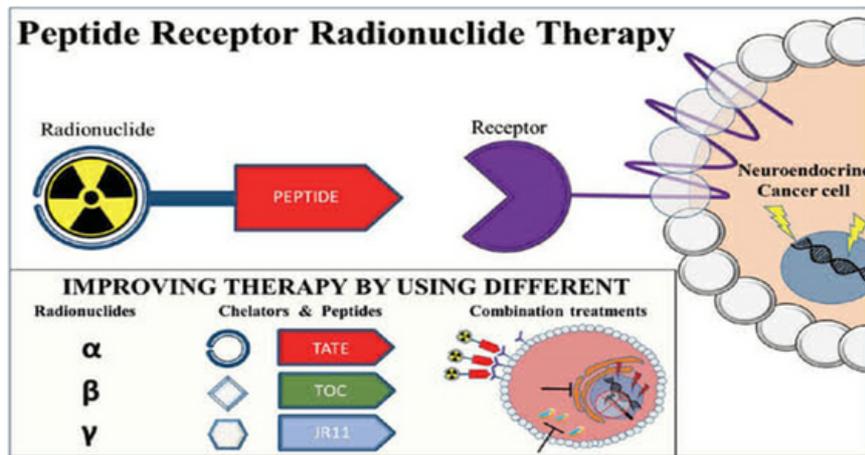
Figure 1: showing the mechanism of interaction of peptide labelled radionuclides with Somatostatin-type receptors (STTR), found on cell surface.

Now a days, many peptide receptors are used for Targeted radionuclide therapy (TRT) [Table 1]. Also different peptides/analogs and their receptors overexpressed on various tumor subtypes [Table 2] [12].

Peptide	Abbreviation	SSTR subtype affinity
DOTA-tyrosine-3-octreotate	DOTATATE	2
DOTA-1-Nal3-octreotide	DOTANOC	2,3,5
DOTA-TyI3-octreotide	DOTATOC	2,5

Table 1: Different peptides showing expression on different SSTR subtypes.

Peptide	Receptor type/ subtype	Tumor expression
Pentixather	CXCR4 (chemokinin-4)	Multiple myeloma, leukemia, and non-Hodgkin lymphoma, and in some solid cancers (e.g., lung cancer, adrenocortical cancer, and high-grade NEN).
DOTA-/DOTAGA-[Thi8, Met(O2) 11]- substance P	NNK1 (neurokinin-1)	Grade II-IV gliomas
DOTA-FAP-Inhibitor	FAP (fibroblast activation protein)	stromal fibroblasts of all melanocytic tumors

Table 2: showing other peptides along with their receptors which showed overexpression on various tumor subtypes.

The pivotal neuroendocrine tumors therapy (NETTER)–1 phase 3 trial of Lu-177 DOTATATE in patients with advanced midgut NETs demonstrated increased progression-free survival at 20 months of 65.2% versus 10.8% in control, as well as a significantly increased tumor response rate with Lu-177 DOTATATE [12]. In 2018, FDA approval of Lu-177 DOTATATE for NETs represented a significant addition to the treatment options for patients with these tumors [11]. Emerging SSR-targeted radionuclide therapies are also under investigation. A recent phase 2 clinical trial investigated using an SSR-targeted α-particle therapy using actinium-225 (Ac-225) DOTATATE, demonstrating promising response and progression-free survival outcomes for gastroenteropancreatic NETs.

PSMA-Targeting Therapy

PSMA is a type-II transmembrane protein with two monomers and corresponding intracellular, transmembrane, and extracellular domains [13]. PSMA, also termed folate hydrolase I or glutamate carboxypeptidase II, is expressed at high levels on prostatic adenocarcinoma cells [14, 15]. The degree of PSMA expression positively correlates with tumor stage [14,16] and early recurrence [17,18]. The mechanism of DNA damage on the surface of prostate cancer cells by radiolabeled PSMA emitting β-particle is given in Figure 2. Normal human tissues, including prostate epithelium, small intestine, renal tubules, and salivary glands, demonstrate considerably lower levels of PSMA expression than prostate cancer [19].
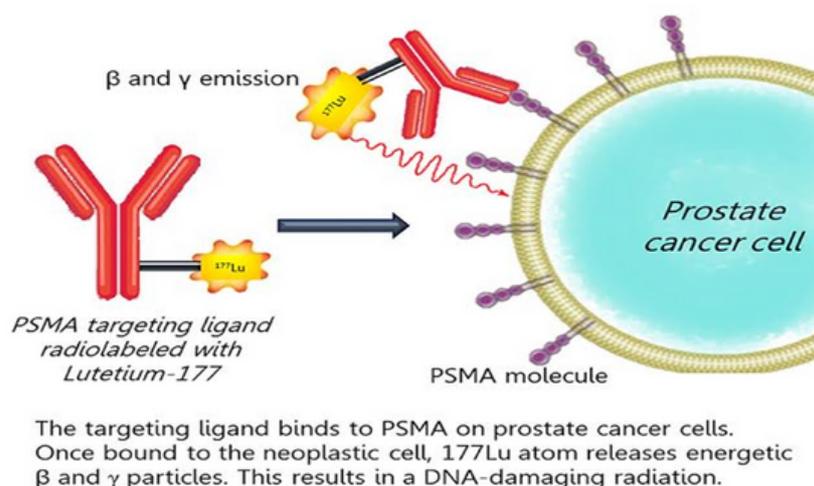

Figure 2: showing the binding of 177Lu-PSMA targeting PSMA molecule present on the cell surface of Prostate cancer cells and DNA damage of the prostate cancer cells.

The phase 2 randomized controlled TheraP trial between Lu-177 PSMA-617 and cabazitaxel demonstrated higher prostate-specific antigen (PSA) response with Lu-177 PSMA-617 therapy than cabazitaxel for progressive, metastatic castration-resistant prostate cancer (mCRPC) [20]. Subsequently, the phase 3 VISION trial showed that the patients treated with Lu-177 PSMA-617 had higher imaging-based progression-free survival and median overall survival than those who received standard treatment alone (15.3 months vs 11.3 months) [21]. Recently, Lu-177 PSMA-617 has been approved by the FDA for mCRPC patient treatment, paired with diagnostic imaging using Ga-68 PSMA-11 PET/CT.

PSMA-based radionuclide therapy is an active area of clinical research and innovation. Recently, the development of targeted α-particle therapy using PSMA-labelled radionuclides has emerged. The literature suggested a good treatment response with Ac-225 labeled PSMA ligands (Ac-225 PSMA-617) in patients with mCRPC [22].

Recently, a systematic review and meta-analysis comprising 256 patients treated with Ac-225 PSMA-617 showed an overall biochemical response in 62.8% of mCRPC patients and a molecular response with Ga-68 PSMA-11 PET/CT in 74% of patients. The median progression-free survival and overall survival in these patients were 9.1 months and 12.8 months, respectively [23]. A randomized controlled trial between Ac-225 PSMA-617 and Lu-177 PSMA-617 is ongoing to prove further the therapeutic efficacy and survival benefit of Ac-225 PSMA-617 compared to Lu-177 PSMA-617. Currently, Ac-225 PSMA-617 is not FDA approved, has a risk of adverse effects such as substantial xerostomia [22], and no phase-3 trial has been investigated till now.

Other than Prostate Cancer

Despite its name, PSMA expression is not truly prostate-specific and is observed in many other neoplasms. PSMA receptors are located in the endothelium and have also shown their correlation with VEGF expression in highly vascular tumors. The PSMA expression is associated with tumor neovasculature rather than the tumor cells [24]. However, non-prostate tumors, such as adenoid cystic carcinoma (AdCC), a salivary gland neoplasm, show high PSMA expression on tumor cells [25]. A phase 2 clinical trial assessing 177Lu-PSMA-617 treatment of advanced salivary gland cancers is currently enrolling patients at AIIMS, New Delhi, and recently a small group of patients targeting tumor neovascular showing high PSMA expression treated with 177Lu-PSMA-617 in glioblastoma, thyroid cancer, and hepatocellular carcinoma (HCC) have been reported.

Locoregionally administered RPT

Radiosynovectomy

This method is used in the treatment of inflammatory synovial diseases such as rheumatoid arthritis, reactive or psoriatic arthritis, and other inflammatory joint conditions (such as Lyme disease), Behcet's disease, persistent synovial effusion, haemophilic arthritis, calcium pyrophosphate dihydrate (CPPD) arthritis, pigmented villonodular synovitis (PVNS), persistent effusion after joint prosthesis, and undifferentiated arthritis (characterized by synovitis, synovial thickening or effusion). The injected radiotracer agents, typically colloids, are assumed to be rapidly phagocytized by synovial cells (synoviocytes) and then distributed within the synovium, primarily at the surface of synovial cells. The most common agents have been radiocolloids or macro-aggregates with high-energy β-emitters (Y-90, Au-198, Dy-165, Re-186, Re-188, and Lu-177) [3]. The choice of radionuclide for radiosynovectomy depends on joint size. Owing to the large range of joint sizes, no single radionuclide is suitable for all joints. Related to joint size, the following radionuclides have gained widespread acceptance for radiosynoviorthesis:
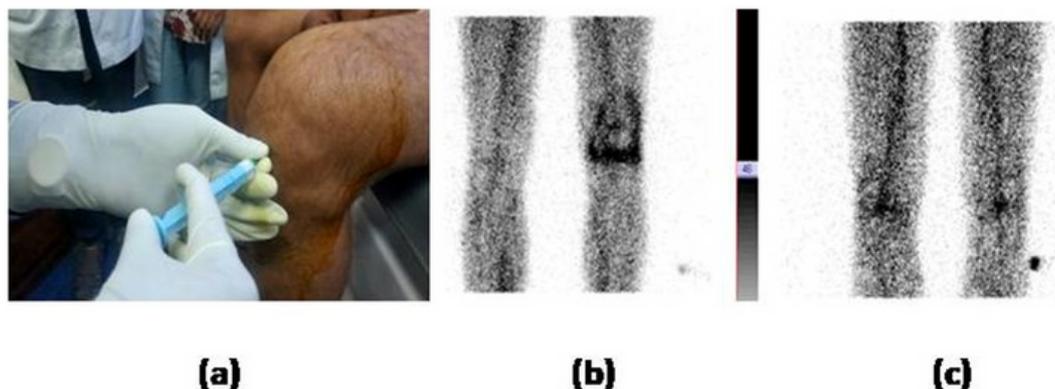

(a) **(b)** **(c)**

Figure 3: Injection of Re-188-tin colloid (a) to the left knee joint showing increased pool activity in pre-therapy image (b). Post-therapy image (c) shows resolution of blood pool activity of left knee joint, suggestive of complete response to therapy.

- Yttrium-90, Rhenium-188: Knee

- Rhenium-186; Lutetium-177: Hip, Shoulder, Wrist, Ankle

- Erbium-169: Metacarpophalangeal, Metatarsophalangeal, Proximal inter-phalangeal

A distribution scan should be acquired in joints treated with the radionuclides mentioned above, except Er-169, to verify successful intra-articular injection and proper distribution within the joint [Figure 3]. A passive joint movement is performed to achieve a homogenous intra-articular distribution of the radionuclide. Absolute immobilization of the treated joint(s) must be performed for 48 h, reducing particles' transport through the lymphatics to the regional lymph nodes. The clinical effect of the treatment, such as pain reduction, typically starts after 1-3 weeks post-injection. Treatment failure is likely if no response is detected by 6 weeks post-injection. The minimal time interval between the repeated treatments in the same joint should be at least 6 months. Subsequent treatments should not follow two failed injections. The gap between arthroscopy or joint surgery and radio-synovectomy should be 2-6 weeks, and between joint puncture and radio synovectomy, 2 weeks.

Skin Keloids and Basal-Cell Carcinomas

Keloids are irregular fibrous tissue formation at any wound, surgery, scar, or injury site. However, basal-cell carcinomas are generally painless skin cancers caused by sunburn. Several procedures are used for their treatment in nuclear medicine, like Re-188 patch therapy [26].

Re-188 is a beta emitter (Eβmax = 2.1 MeV) suitable for keloid treatment due to high LET and low tissue penetration. Re-188 coated patch delivers a high radiation absorbed dose to the keloid lesions from uniformly distributed β-radiation and a minimum dose to the surrounding tissue. Using a customized patch for therapy overcomes the disadvantages of external beam radiation therapy and allows flexibility in delivering the desired radiation dose to the keloid lesion.
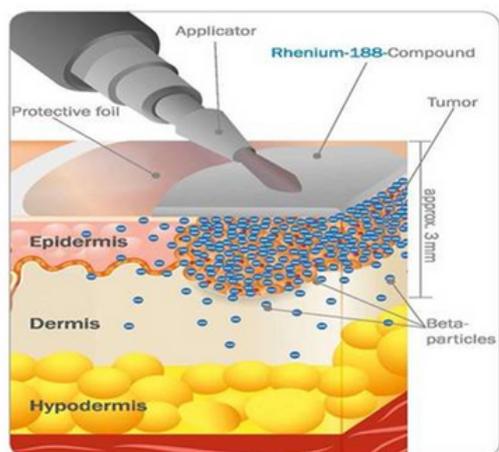

Figure 4: Rhenium-SCT device developed by OncoBeta® GmbH (Garching, Germany) for application of 188Re-patch over keloids or tumor cells.

Skin patches have also been developed using radionuclides like P-32, Y-90, and Ho-166. However, the major disadvantage is the non-availability of these radionuclides due to their production via cyclotron. Thus, the treatment time has to be planned according to the shipment of these radionuclides. On the other hand, the main advantage of Re-188 is its easier availability from the W-188/Re-188 generator that can be eluted daily for the fabrication of radioactive patches.
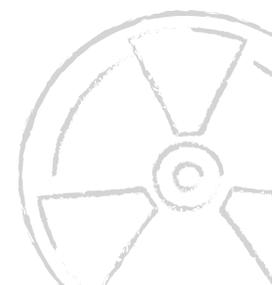
Trans Arterial Radioembolization (TARE)

TARE is an internal targeted radiation therapeutic technique with the use of various β emitting radionuclides (such as Y-90, Ho-166, I-131, and Re-188) for the locoregional treatment for various stages of HCC and was developed long before the evolution of modern targeted radiotherapy techniques using radionuclides [Figure 5] [27].
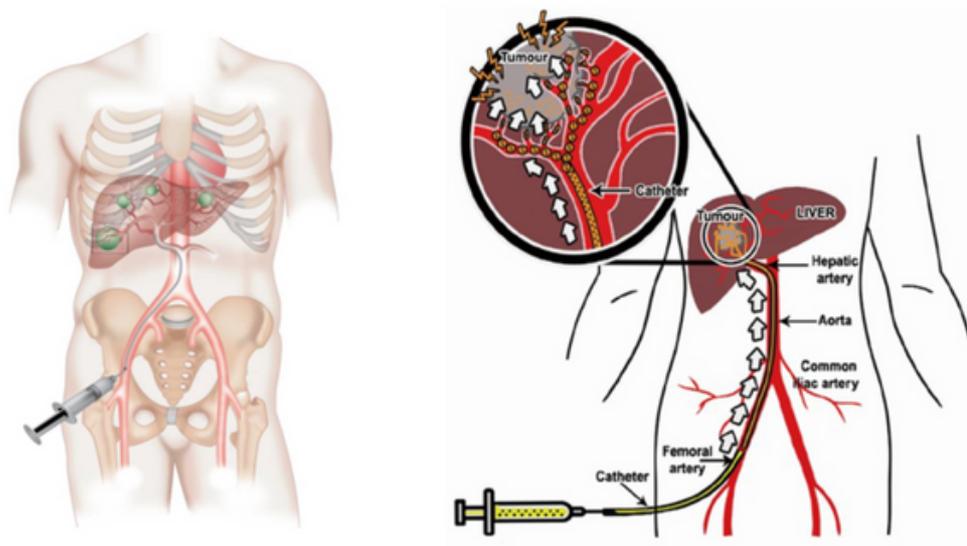

Figure 5: Diagrammatic presentation of TARE. The trans-arterial infusion of therapeutic activity of radiopharmaceutical, close to the feeding artery.

The commonly used TARE agents are :

1. Y-90 microspheres [TherSpheres and SIR (Selective Internal Radiation) spheres]
2. Ho-166 microspheres (Ho-166-PLLA-MS) Currently on Phase-III trial
3. I-131 lipiodol
4. Re-188 labelled-lipiodol agents
   (a) HDD-lipiodol
   (b) SSS-lipiodol
   (c) N-DEDC-lipiodol
   (d) Re-188 Microspheres

TARE with the radiopharmaceuticals, as mentioned earlier, can be used in patients with an intermediate stage (BCLC-B) of HCC who are not good candidates for TACE due to multiple bulky tumors; patients of advanced stage (BCLC C) with solitary HCC tumors and segmental or lobar PVT; and patients with HCC having distant metastasis to downstage the disease as a radical approach [28].
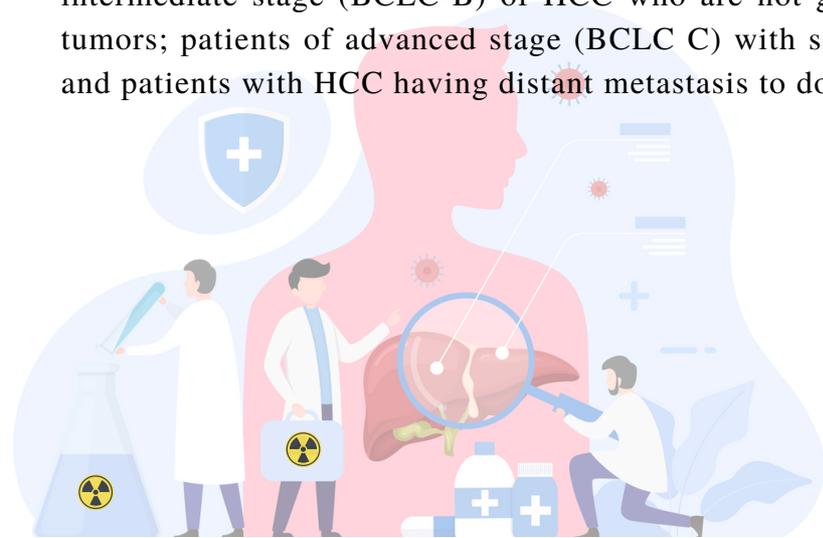
REFERENCES

1. Yeong CH, Cheng MH, Ng KH. Therapeutic radionuclides in nuclear medicine: current and future prospects. J Zhejiang Univ Sci B. 2014 Oct;15(10):845-63. doi: 10.1631/jzus.B1400131. PMID: 25294374; PMCID: PMC4201313.

2. St. James, S., Bednarz, B., Benedict, S., Buchsbaum, J. C., Dewaraja, Y., Frey, E., Hobbs, R., Grudzinski, J., Roncali, E., Sgouros, G., Capala, J., & Xiao, Y.Current Status of Radiopharmaceutical Therapy. International Journal of Radiation Oncology Biology Physics. 2021; 109(4): 891-901. https://doi.org/10.1016/j.ijrobp.2020.08.035.

3. Srivastava S, Dadachova E. Recent advances in radionuclide therapy. Semin Nucl Med. 2001 Oct;31(4):330-41. doi: 10.1053/snuc.2001.27043. PMID: 11710775.

4. Hertz, S., Roberts, A., Means, J. H. & Evans, R. D. Radioactive iodine as an indicator in thyroid physiology - Iodine collection by normal and hyperplastic thyroids in rabbits. Am. J. Physiol. 1940; 128: 565–576.

5. Sawin CT, Becker DV. Radioiodine and the treatment of hyperthyroidism: the early history. Thyroid. 1997 Apr;7(2):163-76.

6. Wyszomirska A. Iodine-131 for therapy of thyroid diseases. Physical and biological basis. Nucl Med Rev Cent East Eur. 2012 Aug 28;15(2):120-3. PMID: 22936505.

7. Mumtaz M, Lin LS, Hui KC, Mohd Khir AS. Radioiodine I-131 for the therapy of graves' disease. Malays J Med Sci. 2009 Jan;16(1):25-33.

8. Ahad F, Ganie SA. Iodine, Iodine metabolism and Iodine deficiency disorders revisited. Indian J Endocrinol Metab. 2010 Jan;14(1):13-7.

9. Limaiem F, Rehman A, Anastasopoulou C, Mazzoni T. Papillary Thyroid Carcinoma.StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL). Jan 1, 2023.

10. Knapp, R. F. F. & Dash, A. Radiopharmaceuticals for Therapy. Springer. 2016.

11. Burkett BJ, Dundar A, Young JR, et al. How we do it: a multidisciplinary approach to 177Lu DOTATATE peptide receptor radionuclide therapy. Radiology 2021;298(2):261–274.

12. Strosberg J, El-Haddad G, Wolin E, et al; NETTER-1 trial investigators.phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med 2017;376(2):125–135.

13. Schülke N, Varlamova OA, Donovan GP,et al . The homodimer of prostate-specific membrane antigen is a functional target for cancer therapy. Proc Natl Acad Sci USA. 2003;100:12590–12595.

14. Perner S, Hofer MD,Kim R, et al. Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. Hum Pathol. 2007;38:696–701.

15. Mannweiler S, Amersdorfer P,Trajanoski S, Terrett JA, King D,,Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. Pathol Oncol Res. 2009;15:167–172.

16. Bostwick DG, Pacelli A, Blute M, Roche P,Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. 1998;82:2256–2261.

17. Minner S, Wittmer C, Graefen M,et al. High level PSMA expression is associated with early PSA recurrence in surgically treated prostate cancer. Prostate. 2011;71:281–288.

18. Ross JS,Sheehan CE,Fisher HA, et al. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–6362.

19. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3:81–85.

20. Hofman MS, Emmett L, Violet J, et al; ANZUP TheraP team. TheraP: a randomized phase 2 trial of 177 Lu-PSMA-617 theranostic treatment vs cabazitaxelin progressive metastatic castration-resistant prostate cancer (ClinicalTrial Protocol ANZUP 1603). BJU Int 2019;124(Suppl 1):5–13.

21. Sartor O, de Bono J, Chi KN, et al; VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N EnglJ Med 2021;385(12):1091–1103.

22. Kratochwil C, Bruchertseifer F, Giesel FL, et al. 225Ac-PSMA-617 for PSMA-targeted α-radiation therapy of metastatic castration-resistant prostate cancer. J Nucl Med 2016;57(12):1941–1944.

23. Satapathy S, Sood A, Das CK, Mittal BR. Evolving role of 225Ac-PSMA radioligand therapy in metastatic castration-resistant prostate cancer-a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2021;24(3):880–890.

24. Van de Wiele C, Sathekge M, de Spiegeleer B, et al. PSMA expression on neovasculature of solid tumors. Histol Histopathol 2020;35(9):919–927.

25. Uijen MJM, Derks YHW, Merkx RIJ, et al. PSMA radioligand therapy for solid tumors other than prostate cancer: background, opportunities, challenges, and first clinical reports. Eur J Nucl Med Mol Imaging 2021;48(13):4350–4368.

26. Shukla, Vandita J, Chhabra A, Pandey S, Vasta R, Mittal BR. Re-188 skin patch for the treatment of keloids at PGIMER CHD. India. Manipal Academy of Higher Education. 2020.

27. Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, Hickey R, Kulik L, Ganger D, Flamm S, Atassi R. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. Hepatology. 2018 Oct;68(4):1429-40.

28. Xing M, Prajapati HJ, Dhanasekaran R, Lawson DH, Kokabi N, Eaton BR, Kim HS. Selective internal yttrium-90 radioembolization therapy (90Y-SIRT) versus best supportive care in patients with unresectable metastatic melanoma to the liver refractory to systemic therapy. American journal of clinical oncology. 2017 Feb 1;40(1):27-34.doi: 10.1097/COC.0000000000000109.
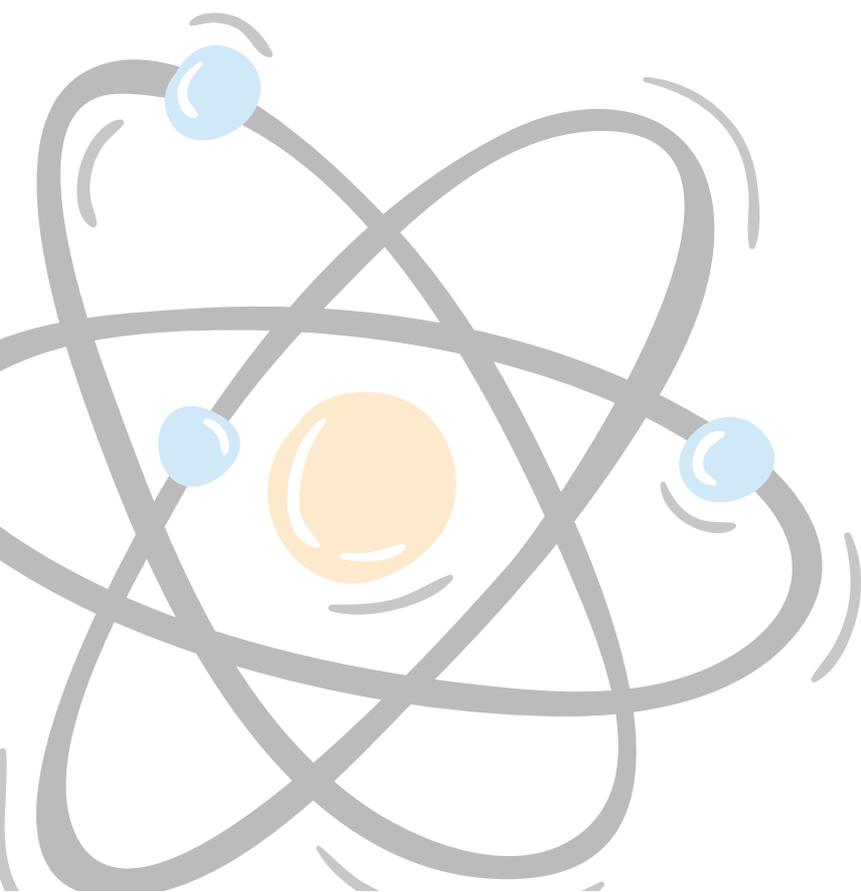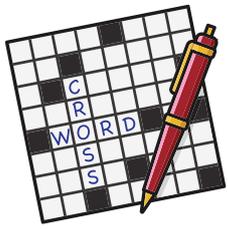
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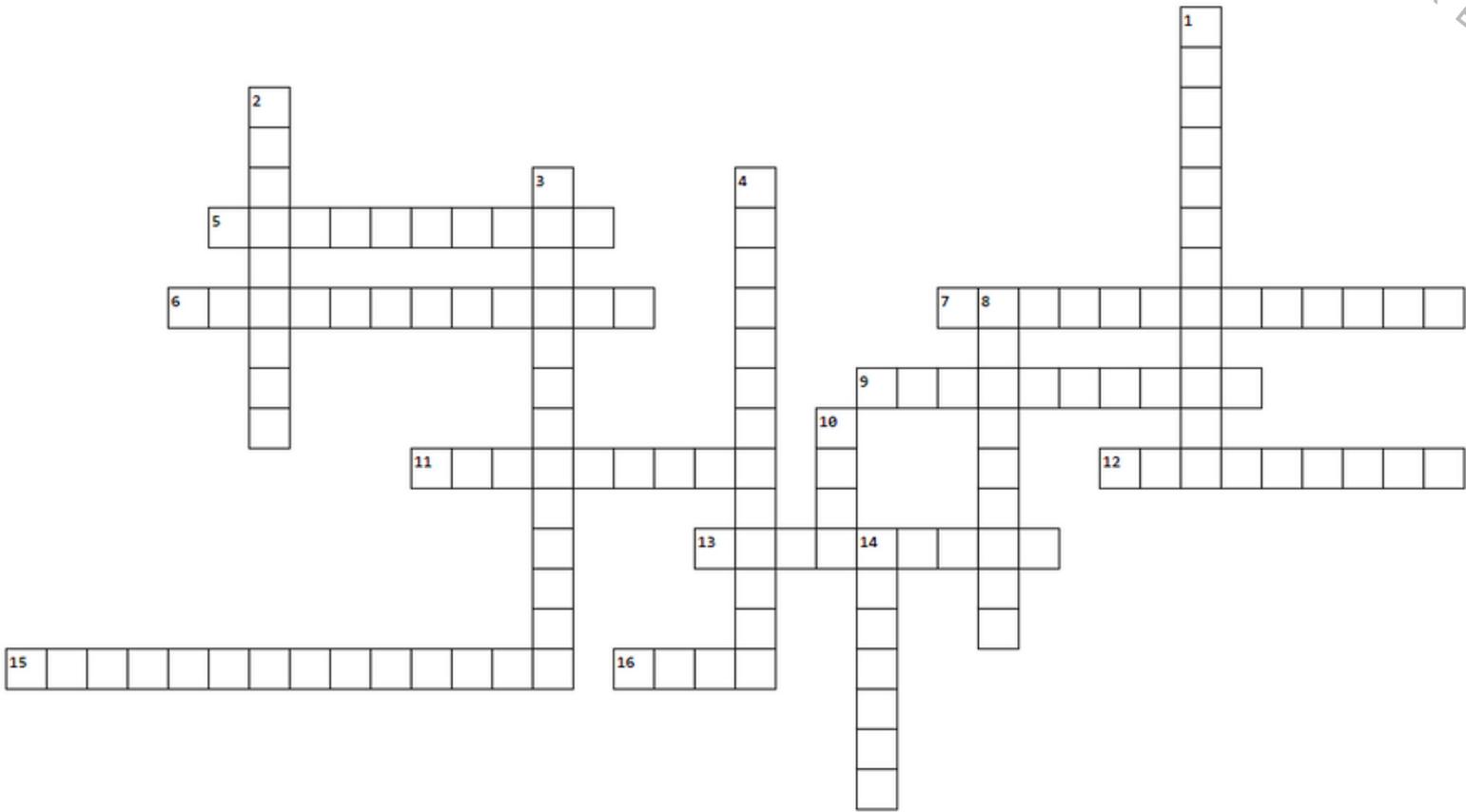
ACROSS

5. What represents Ventricular depolarization on the EKG strip (2words)

6. β Particles exert their therapeutic effects throughDNA damage via which DNA breaks(2 words)

7. One of The "fundamental" effects that limit the spatial resolution in PET cameras

9. Discrepancy between fields of view (FOVs) in a PET/CT scanner when imaging extends beyond the CT FOV causes this artifact

11. Nuclear Medicine procedure for evaluation of RVEF (2 words)

12. Phenomenon of ionizing radiation affecting the non-irradiated neighbours in addition to directly irradiated cells

13. UV radiation causes which nucleotide dimerization

15. Increase in number of chelator molecules attached to peptide results in increased

16. Oxidation state of Tc-99m in Tc-99m-DMSA used for tumour imaging

DOWN

1. Route of administration of Tc-Sulphur colloid in lymphoscintigraphy

2. This prompt emission in BGO scintillators improves coincidence time resolution significantly, enabling use of TOF

3. Catalyst used in ammonium production (2 words)

4. Pharmaceutical labelled with Tc-99m for both bone scintigraphy and cardiac amyloidosis imaging

8. Quality control test that should be performed on a dose calibrator after a power cut

10. It is often used as a measure of Spatial Resolution

14. What are the parent and daughter nuclide to each other incase of beta decay
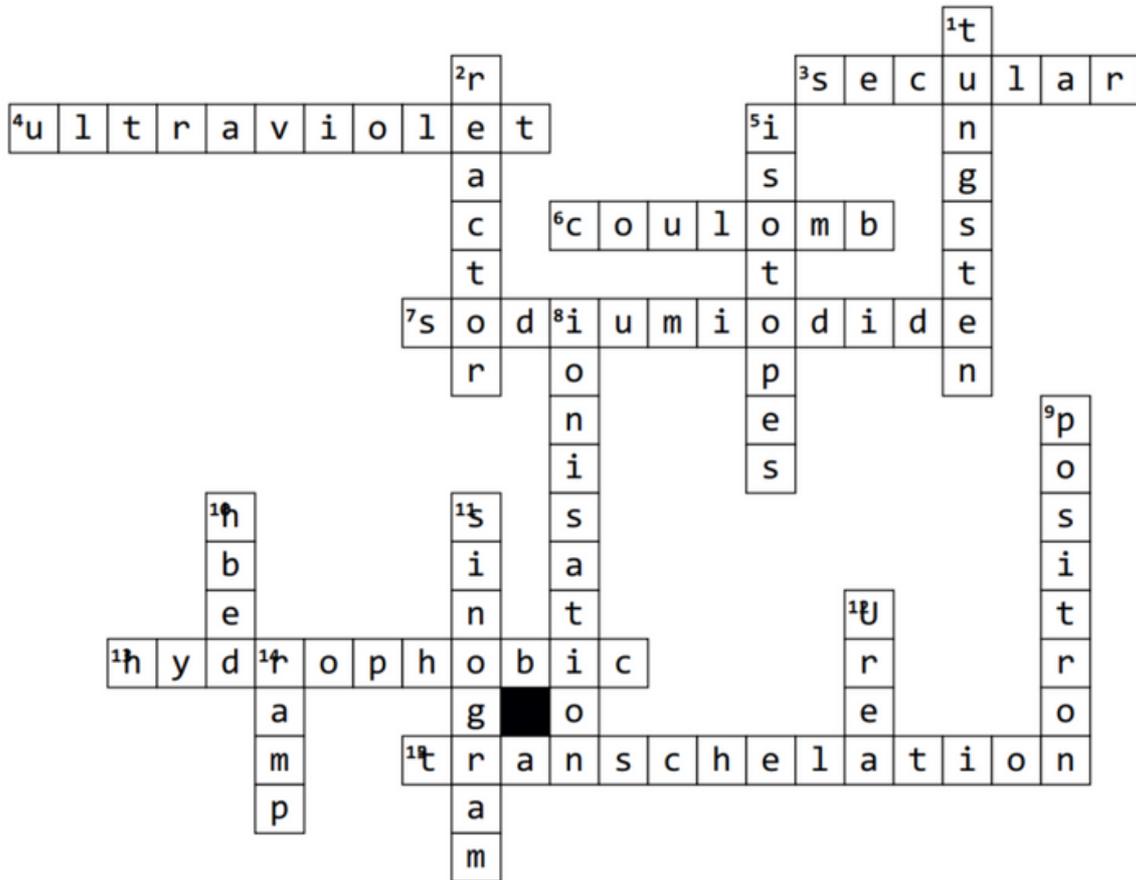
ANSWERS IN NEXT ISSUE

ANSWERS OF APR-JUN 2023 ISSUE

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

Schedule
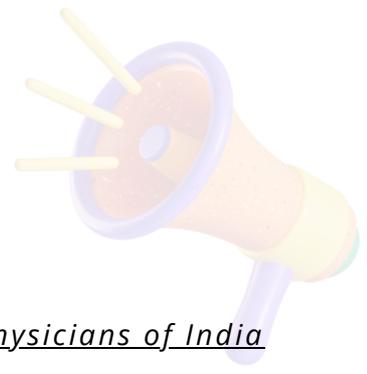
NATIONAL

21st Annual Conference of Association of Nuclear Medicine Physicians of India
29 September - 1 October, 2023
Sarvodaya Health Care, Faridabad

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

NCSICON (Nuclear Cardiological Society of India Conference)
4-5 November, 2023
Jaipur, Rajasthan

55th Annual Conference of Society of Nuclear Medicine India
16-19 November, 2023
AIIMS, Jodhpur
Last date for Abstract Submission: 30th September, 2023

44th Annual Conference of Association of Medical Physicists of India ,
23rd Asia Oceania Congress on Medical Physics and International
South-East Asian Congress on Medical Physics
&
25th International Conference of International Organization for Medical
Physics (IOMP)
6th to 9th December 2023
DAE Convention Centre, Anushaktinagar, Mumbai, India

8th Annual Conference of Nuclear Medicine Physicist Association of India
23rd – 24th February 2024
Shri Mata Vaishno Devi Narayana Superspeciality Hospital (SMVDNSH)
Katra, Jammu & Kashmir
Abstract Submission: 15th December, 2023

Upcoming Events

Schedule

INTERNATIONAL

International Conference on Advances in Nuclear Medicine (ICANM)
07th -08th October, 2023
Tokyo, Japan

15th Asia Oceania Congress of Nuclear Medicine and Biology (AOCNMB 2023),
5th -7th October, 2023
Amman, Jordan

ICRP 2023, 7th International Symposium on the System of Radiological Protection
06th-09th November, 2023
Tokyo, Japan

7th Theranostic World Conference
22nd -24th March, 2024
Santiago, Chile

21st European conference on Radiopharmacy and Radiopharmaceuticals
18th- 21st April, 2024
Venue- Coimbra, Portugal
Last date for Abstract Submission: January 17, 2024

54th Annual Scientific Meeting of the Australian and New Zealand Society of Nuclear
Medicine,
26th -28th April 2024
Christchurch, New Zealand
Abstract Submission: Yet to be announced

BNMS Annual Spring Meeting 2024
13th -15th May 2024
Belfast United Kingdom
Abstract Submission: Yet to be announced

Annual meeting of Society of Nuclear Medicine and Molecular Imaging, 2024
08th -11th June, 2024
Toronto, Canada
Abstract Submission: Yet to be announced

37th Annual Congress of the European Association of Nuclear Medicine
19th– 23rd October, 2024
 Hamburg, Germany
Abstract Submission: Yet to be announced

Upcoming Events

FROM EDITORIAL TEAM

Dear Readers !

So far, I have always been at the reader's end. When I was given the opportunity to be part of this newsletter's editorial team, I realized what it takes to bring the articles and information in a beautiful form as this newsletter.

This newsletter is the brainchild of our very able editors, Dr. Rakhee Vatsa and Dr. Priyanka Gupta, who have done a tremendous job being torchbearers for the propagation of knowledge and advances in the field of Nuclear Medicine. This idea could only be materialized with the contribution of all authors and the untiring efforts of the editorial team. As a team, we have worked diligently and tried to bring something or the other on board to the best of our abilities - Brainstorming innovative ideas, bringing the sponsorships, designing the newsletter for engaging reading, editing and proofreading the articles for content and language, getting updates about the upcoming events and whatnot.

In my experience, editing the write-ups is an excellent way of enhancing knowledge as it develops a critical outlook towards a topic and gives a better insight, which we might miss as readers.

To add some fun element to otherwise informative publication, I was tasked with creating crossword puzzle that was not part of the first issue. With the help of Dr. RakheeVatsa, I have made these crosswords engaging, keeping in view the students (M.Sc., M.D. and others). As our reward, we have received positive feedback from readers eagerly waiting for this section.

The support of contributing authors who have been sending articles in good numbers has left no room for any speculations about the success of this newsletter. Hoping for such support in future as well.

Lastly, I thank the editors and other members of the editorial team, as it has been an enriching experience overall and has added another dimension to my vision, both personally and academically. I will continue to contribute in every possible way to make the reading experience more pleasing to all of you.

Thank you and regards,

Dr. Nivedita Rana

Nuclear Medicine Physicist,
Post Graduate Institute of Medical Education and Research,
Chandigarh

FROM EDITORIAL TEAM

Dear NMPAI Members and Readers,

Greetings from the editorial desk of NMPAI-CNMSTe-Newsletter!

As a member of the editorial team, it is my privilege to bring you another insightful edition of our e-newsletter, a platform that thrives on the spirit of collaboration and the dissemination of knowledge.

In this issue, we've once again gathered a collection of original articles, short reviews, and recent advances in Nuclear Medicine that highlight the multifaceted nature of scientific inquiry. The journey of discovery is not a solitary one; it's a collective effort that spans across disciplines, and across institutions.

Our featured articles encompass a wide spectrum of subjects, from the intricate workings of PET-CT to the implications of recent advances in Nuclear Medicine such as the role of Artificial Intelligence and Internal dosimetry in therapeutic Nuclear Medicine. Our contributors have poured their expertise and passion into these pieces, with the hope that they will ignite conversations, foster debate, and spark new avenues of exploration in Nuclear Medicine.

In this Issue, we shine a light on some of the most intriguing studies and projects that are shaping the scientific landscape and thus, encapsulate the essence of discovery—from the initial spark of an idea to the meticulous process of experimentation and analysis.

As we look to the future, it's imperative that we nurture the next generation of scientists and physicists. This e-newsletter introduces us to the innovative thinking and fresh perspectives of emerging researchers. Their enthusiasm is infectious, reminding us all of the boundless potential that lies ahead.

I extend my heartfelt appreciation to our dedicated contributors who generously share their expertise, insights, and time to make each edition of this e-Newsletter possible. Your passion for advancing human understanding is truly inspiring.

I am thankful to both the editors of this newsletter, Dr. Priyanka Gupta and Dr. RakheeVatsa, for giving me this opportunity. I am grateful to all the editorial team members for their invaluable support. Also, I thank to Mr. Navneet Kumar for designing every single issue to release the most visually enthralling newsletter.

To our readers, we thank you for your continued support. It is your engagement, feedback, and curiosity that drive us to continually improve and deliver content that resonates with your interests.

As we turn the pages of this edition, let's be reminded that scientific progress is a journey, not a destination. It's a journey we embark upon together, as a global community of curious minds, dedicated to unravelling the mysteries of the universe and making the world a better place.

Happy reading and exploring!

Naresh Kumar

PhD Scholar,
Department of Nuclear Medicine
All India Institute of Medical Sciences, New Delhi
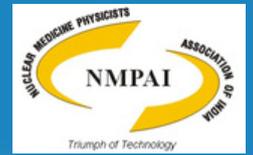
NMPAICON - 2024

8th Annual Conference of Nuclear Medicine Physicists Association of India

Venue :

Shri Mata Vaishno Devi Narayana Superspeciality Hospital
Katra, Jammu

23rd - 24th February, 2024

Abstract Submission
Begins from 1st Oct, 2023
Ends on 15th Dec, 2023

Abstract acceptance
1st January, 2024

Abstract submission at
nmpaiconabstracts2024@gmail.com

REGISTRATION

	ONLY FOR 15th AUGUST, 2023	Early Bird Registration (16/08/2023 - 30/11/2023)	Late Registration (1/12/2023 - 15/02/2024)	SPOT REGISTRATION (AT THE VENUE)
NMPAI members	2500	3500	4500	5500
Non Members	3500	4500	5500	6500
Student (NMPAI members)	1000	1500	1800	2000
Student (Non-Members)	1500	2000	2500	3000
International Delegates	USD 100	USD 150	USD 200	USD 250
Trade Delegates	10000	10000	10000	10000

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