REVIEW ARTICLE

Radiopharmaceuticals: A Brief Overview of Basic Pharmacological Parameters

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Abstract

Radiopharmaceuticals are combinations of two main components including a pharmaceutical ingredient that targets specific moieties, and radionuclide, which acts through spontaneous degradation to create diagnostic or therapeutic effects, as well as both effects simultaneously known as theranostics. By combining diagnostic and therapeutic methods, radiotheranostics play an important role in reducing patient radiation dosages, increasing treatment effectiveness, controlling side effects, improving patient outcomes, and reducing overall treatment costs. Despite the diagnostic and therapeutic roles, radiopharmaceuticals are beneficial for assessing prognosis, disease progression, and the possibility of recurrences, treatment planning strategies, and assessing response to treatment. The most incredible role of radiopharmacy is establishing new radiopharmaceuticals with the aim of better targeting functions and enhanced tolerability for imaging and treatment purposes in a clinic. These approaches are supported by nuclear medicine non-invasive procedures. It is crucial for radiopharmaceuticals that drug delivery occurs in a highly selective and sensitive manner to minimize the potential radiation risk to non-targeted organs of patients. This report will provide an overview of basic pharmacological patterns related to clinical radiopharmaceuticals for diagnosis and therapy, including the latest radiotheranostic tracers, key concerns within the field, and future trends and prospects. Additionally, the available and useful radiopharmaceuticals are categorized into separate tables based on their specific characteristics. Presenting information in table format enhances organization and makes the data more understandable and accessible for users. This structured approach allows users to quickly locate relevant information, compare different radiopharmaceuticals, and grasp essential details at a glance. By utilizing tables, we ensure that critical information is not only easy to read but also effectively highlights the unique attributes of each radiopharmaceutical, ultimately improving the decision-making process for healthcare professionals.

Keywords: Radiopharmaceuticals; Theranostics; Diagnostic; Therapeutic; Radiotracer; Radiation.

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1. Introduction

Radiopharmaceuticals were first reported by the Federal Register in the United States with the discovery of carbon-14 (^{14}C) and potassium-40 (40K). These unstable nuclei decay spontaneously to nuclear particles, which has proven advantageous in medicine for diagnostic purposes [1]. The field of nuclear medicine was revolutionized by the restraint of these radioactive isotopes for innovative approaches to the diagnosis and treatment of patients. Currently, radiopharmaceuticals' usage can be classified into four main purposes, including research, diagnosis, treatment, and environmental applications [2]. This classification highlights the radiopharmaceuticals' integral role and diversity in advancing medical science and patient care.

Due to the critical role of radiopharmaceuticals in research and preclinical studies, they allow scientists to follow the pharmacological parameters of new pharmaceuticals in clarified manners. These tracers help researchers gather crucial data on drug behavior, like absorption, distribution, metabolism, and excretion. The evaluated pharmacokinetics and pharmacodynamics data are essential for understanding how investigational radiopharmaceuticals will act in clinical settings when administrated in non-radioactive forms [2]. Furthermore, radiopharmaceuticals in the field of research make efforts for personalized medicine by identifying how different patients may respond to specific treatments based on their unique biological profiles [3].

In nuclear medicine, radiopharmaceuticals have been mainly used as diagnostic agents. Numerous chemical compounds are designed to specifically and sensitively target considered organs, aiding in the diagnosis and imaging of physiological deficiencies. This specificity is vital for accurate diagnosis and treatment planning. This is achieved through the incorporation of gamma (γ) or positron (β+) emitting radionuclides, which enhance the visibility of targeted areas during imaging procedures [4, 5].

Certain radionuclides, like alpha (α) or beta (β) particle emitters, have therapeutic applications, particularly in oncology. Therapeutic radiopharmaceuticals are developed to emit radiation specifically at cancerous cell sites, effectively targeting and destroying malignant cells [3]. This targeted approach minimizes damage to surrounding healthy tissue, making treatment more effective and reducing side effects. Radiopharmaceutical Therapy (RPT) is defined as a novel therapeutic method with outstanding advantages over the common radiotherapy procedures which are going to be explained in this report. The ongoing research and development in this area have promising effects to expand the range of treatable cancers and improve patient outcomes significantly.

Additionally, radionuclides can serve as references for monitoring waste radioactivity released into the environment, ensuring safety and compliance with regulatory standards [2]. This application highlights the importance of radiopharmaceuticals beyond clinical settings, extending their impact on environmental health and safety. By tracking and managing radioactive waste, we can mitigate potential risks associated with radiation exposure in the community and ensure responsible use of nuclear materials.

We are going to concentrate on the basic characterizations of radiopharmaceuticals in diagnosis and therapy, their recent advancements and future trends will be discussed, and key concerns regarding their use in nuclear medicine will be investigated. Our mission is to provide a comprehensive overview of the evolving landscape of radiopharmaceuticals and their impact on patient care together with medical research. This report's important factor is the classification of radiopharmaceuticals in table format. The presentation of the data in a tabular form enhances accessibility and clarity, allowing healthcare professionals, researchers, and students to reference critical information quickly [6]. Tables are powerful tools to concisely summarize complex data, such as the characteristics, applications, and dosimetry of various radiopharmaceuticals, making it easier to compare and contrast different agents. A structured approach not only helps in retrieving information but also supports informed decision-making in clinical and research settings. By providing a clear and concise overview, we hope to enhance understanding and prompt more research into the helpful and effective use of radiopharmaceuticals in modern healthcare.

1.1. Diagnostic Radiopharmaceuticals

Diagnostic radiopharmaceuticals are essential tools in nuclear medicine, enabling healthcare providers to visualize and assess various physiological processes within the body [7]. These radiolabeled tracers are

typically monitored using collimated external gamma (γ) ray detectors through techniques such as Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET). These modalities detect γ rays emitted by radiopharmaceuticals that are administered to patients, by gamma cameras to produce images of the distribution within the body. Diagnostic radiopharmaceuticals help differentiate abnormalities in anatomy, physiology, and biochemistry, providing critical information for diagnosis and treatment planning [8-10].

SPECT radiopharmaceuticals are generally more accessible and cost-effective compared to their PET counterparts [11]. Common SPECT γ-emitting radionuclides can be include as technetium-99m (^{99m}Tc), iodine-123 (^{123}I), iodine-131(^{131}I), indium-111(^{111}In), gallium-67 (^{67}Ga), thallium-201 (^{201}Tl), krypton-81m (^{81m}Kr), and xenon-133 (^{133}Xe). These radionuclides have specific characteristics that make them suitable for imaging of particular organs or conditions. For example, ^{99m}Tc is favored for its ideal half-life (6 h) and its ability to easily chelate into a variety of pharmaceutical compounds, making it the workhorse of nuclear medicine agents [12, 13].

On the other hand, PET radiopharmaceuticals benefit from higher resolution and sensitivity, making them particularly valuable for detecting metabolic changes such as (fluorine-18-fluorodeoxyglucose ([^{18}F]FDG)) which can be associated with cancer conditions. PET imaging relies on β+ emitting radionuclides, such as carbon-11 (^{11}C), fluorine-18 (^{18}F), and gallium-68 (68Ga). During the annihilation process, the emitted positrons interact with electrons in the body, resulting in the emission of γ rays that are detected to create detailed images of metabolic activity. The development of [^{18}F]FDG has revolutionized oncology, allowing for the detection of tumors based on their increased glucose metabolism [12, 13].

Both SPECT and PET radiopharmaceuticals must meet precise qualifications to be considered effective diagnostic imaging agents. These include high specificity to target tissue, high binding affinity to relevant biological sites, low toxicity to minimize adverse effects, stability against degradation in plasma, rapid clearance from non-targeted tissues to reduce background noise, accessibility at low costs, and regulatory approval for clinical use [14]. Importantly, while diagnostic radiopharmaceuticals are designed to provide imaging information, they exert neither pharmacological effects nor significant side effects in patients. This safety profile is crucial, as the goal of diagnostic imaging is to gather information without causing harm to the patient [4].

Understanding the mechanisms involved in the localization of these radiopharmaceuticals at target sites is crucial for their successful application in clinical practice. Table 1 summarizes the localization mechanisms of the main common diagnostic radiopharmaceuticals.

1.2. Therapeutic Radiopharmaceuticals

Radiopharmaceutical Therapy (RPT) represents a significant advancement in the treatment of various malignancies, utilizing the fact that the applied radionuclide delivers cytotoxic radiation directly to the tumor cells. This approach involves the radiolabeling of tumor-targeting agents, such as antibodies, proteins, small molecules, and Nanoparticles (NPs), which can selectively bind to neoplastic cells [30]. Alternatively, these agents can concentrate in tumors through physiological mechanisms that are predominantly active in cancerous tissues. The effectiveness of therapeutic radiopharmaceuticals depends on the precise calculation of radioactivity that is transferred to the targeted tissue without affecting normal tissues [30]. Therapeutic radiopharmaceuticals may be curative or palliative and can be categorized based on their emission characteristics, including α, and β, as well as auger-electron emitting radionuclides. This classification is crucial for understanding their mechanisms of action in therapeutic application [31].

α-emitting radionuclides, including astatine-211 (^{211}As), bismuth-213 (^{213}Bi), actinium-225 (^{225}Ac), and radium-223 (^{223}Ra), have garnered attention for their potential in targeted α- particle therapy (TAT) (Table 7) [32-34]. The unique properties of α-emitters, including their high Linear Energy Transfer (LET) and short path length in tissue, make them suitable particularly for treating small-volume, homogeneous, disseminated cancers [35]. For instance, [^{223}Ra]Ra chloride has shown significant efficacy in treating Castrate-Resistant Prostate Cancer (CRPC) and bone metastases. Clinical studies have shown that ^{223}Ra can improve overall survival and reduce skeletal-related

Table 1. Localization mechanism of diagnostic radiopharmaceuticals

Radiopharmaceuticals	Mechanism of Localization & Action	References
[^{99m}Tc]Tc-ECD	Diffusion into the brain, and retention in the brain due to conversion to a hydrophilic species and enzymatic metabolism	[15]
[^{99m}Tc]Tc-HMPAO	Once across the blood-brain barrier, it enters the neuron and becomes a polar hydrophilic molecule trapped inside the cell	[16]
[^{99m}Tc]Tc-Sestamibi	Lipophilic diffusion & binding to negative electrical charges of mitochondria	[17]
[^{99m}Tc]Tc-MAA	capillary blockade	[17]
[^{99m}Tc]Tc-MDP	Chemisorption	[17]
[^{99m}Tc]Tc-DMSA	Accumulation in proximal tubular cells of kidneys	[18]
[^{99m}Tc]Tc-Trodat	Binding to dopamine transporters	[19]
[^{99m}Tc]Tc-HYNIC-TOC	Somatostatin receptor subtype 2-mediation	[20]
[^{67}Ga]Ga-Citrate	Binding to transferrin	[21]
[^{201}Tl]thallous chloride	Analogous to potassium ion (K^+)	[22]
[^{123}I]MIBG	Taken up by the postganglionic, presynaptic nerve endings	[23]
[^{18}F]Florbetapir [^{18}F]Flutemetamol [^{18}F]Florbetaben	Binding to β-amyloid in human brain tissue	[17]
[^{18}F]FDG	Analogous to glucose internalization through GLUT1	[24]
[^{68}Ga]Ga-FAPI	Inhibition of FAP which is overexpressed by cancer-associated fibroblasts of several tumor entities	[25]
[^{18}F]Flurpiridaz	The Structural analog of pyridaben binds with high affinity to the mitochondrial complex.	[26]
[^{82}Rb]-RbCl	Analogous to potassium ion (K^+)	[27]
[^{68}Ga]Ga-PSMA	Targeting Prostate-specific membrane antigen (PSMA) which is commonly upregulated in prostate carcinoma (PCa)	[28]
[^{68}Ga]Ga-Pentixafor	Binding to CXCR4 (significantly upregulated under hypoxic conditions)	[29]

ECD: Ethyl Cysteinate Dimer, FAPI: Fibroblast Activation Protein Inhibitor, HMPAO: Hexa-Methyl Propylene Amine Oxime, MAA: Macro-Aggregated Albumin, MDP: Methyl Di-Phosphonate, DMSA: Di-Mercapto Succinic Acid, MIBG: Meta-Iodo Benzyl Guanidine, FDG: Fluoro Deoxy Glucose, PSMA: Prostate-Specific Membrane Antigen

metastasis in patients with advanced prostate cancer [36-38]. This targeted delivery minimizes the exposure of surrounding healthy tissues to radiation, thus reducing potential side effects.

β-emitting radionuclides, like ^{131}I and lutetium-177 (^{177}Lu), are widely used in PRT. ^{131}I has been a longstanding treatment radiopharmaceutical for differentiated thyroid cancer. The β radiation emitted from ^{131}I not only destroys cancerous thyroid tissue but also helps in the ablation of residual thyroid tissue after surgery [38]. ^{177}Lu, often used in Peptide Receptor Radionuclide Therapy (PRRT), targets specific receptors on tumor cells, such as somatostatin receptors in Neuroendocrine Tumors (NETs) [20].

Auger-electron emitting radionuclides, have a high LET, resulting in a high radiotoxicity similar to alpha particles. These radionuclides can cause significant damage to cells at very short ranges, making them suitable for targeting small tumors such as individual cells, micrometastases, or small clusters of tumor cells [39]. While still largely in experimental stages, auger electron therapy holds promise for treating certain types of cancers where conventional therapies have limited efficiency.

The RPT radiopharmaceuticals available in clinical applications are optimistically increasing [30]. The localization mechanisms of the most important therapeutic radiopharmaceuticals are summarized in Table 2.

1.3. Theranostic Radiopharmaceuticals

One of the brilliant concepts in nuclear medicine is radio-theranostics. The backbone of radio-theranostics refers to the simultaneous or sequential accomplishment of therapeutic agents with diagnostic tracers in a single framework [43, 44]. As you can see in Figure 1, there are two main approaches to radio-theranostics. One-pair radio-theranostics utilizes different radioisotopes of the same element or one radioisotope with varying emissions, while the second form (two-pair radio-theranostics) uses the same molecular probe labeled with different radionuclides

Table 2. Localization mechanism of therapeutic radiopharmaceuticals

Radiopharmaceuticals	Mechanism of Localization & Action	References
[^{131}I]- Sodium iodide	Thyroid function (taken up by the sodium iodide symporter as is the case for normal, nonradioactive iodide)	[40]
[^{131}I]-MIBG	Taken up by the postganglionic, presynaptic nerve endings	[23]
^{32}P Colloid	Cell proliferation and protein synthesis	[40]
^{32}P Sodium Phosphate	Cell proliferation and protein synthesis	[40]
[^{225}Ac]Ac/[^{177}Lu]Lu-PSMA	Targeting Prostate-specific membrane antigen (PSMA) which is commonly upregulated in prostate carcinoma (PCa)	[28]
[^{177}Lu]Lu-DOTA-TATE	Somatostatin receptor subtype 2-mediation	[20]
[^{153}Sm]Sm-EDTMP	Binding to hydroxyapatite	[40]
[^{186}Re]Re-HEDP	Binding to hydroxyapatite	[40]
[^{177}Lu]Lu-FAPI	Inhibition of FAP which is overexpressed by cancer-associated fibroblasts of several tumor entities	[25]
[^{223}Ra]RaCl	Localizing to sites of bone (calcium mimetic) turnover apposite to skeletal metastases	[41, 42]
[^{90}Yb]Yb-Ibritomumab	Lymphocyte antigen CD20	[40]

HEDP: Hydroxy Ethylidene Di-Phosphonate, EDTMP: Ethylene Diamine Tetra (Methylene Phosphonic acid)

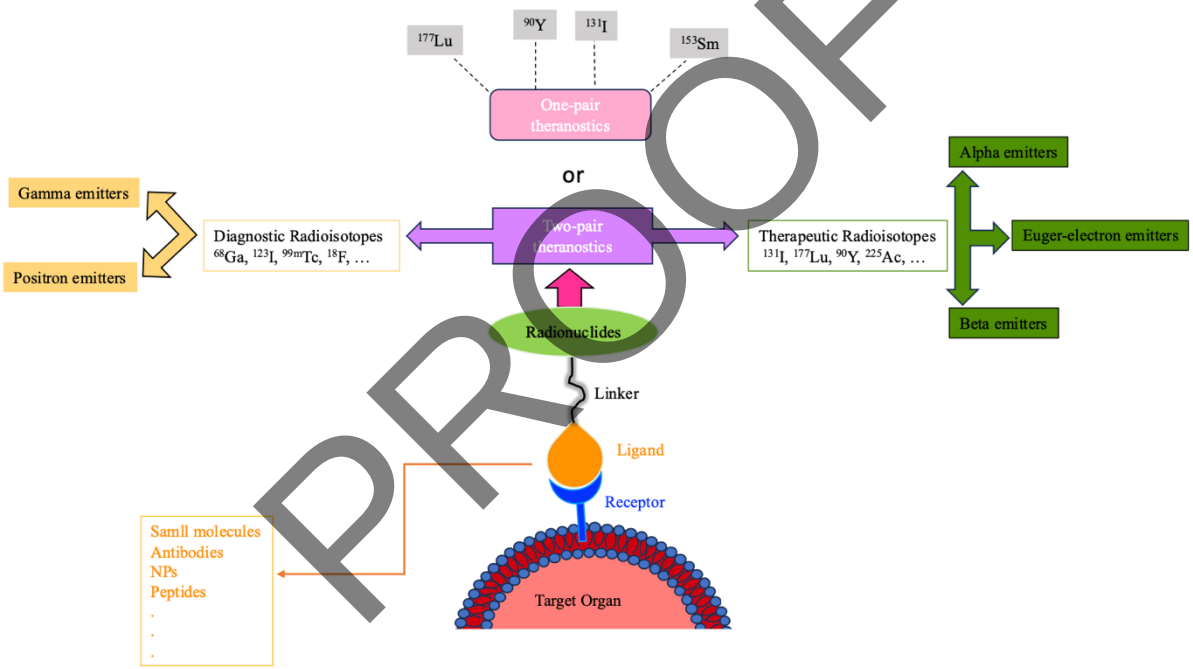

Figure 1. Backbone of radio-theranostics

based on their diagnostic versus therapeutic purposes [45].

Recently, the United States Food and Drug Administration (US FDA) has approved several theranostic radiopharmaceuticals, including ^{177}Lu-labeled anti-somatostatin peptide (Lutathera®) and ^{177}Lu-labeled anti-PSMA antigen (Pluvicto™). These agents are remarkable examples, for treating somatostatin receptor-positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) and PC, respectively [46, 47]. The relevant impressive ligands for imaging and therapy of NET and PC, respectively, are DOTA-Phe1-Tyr3-Octreotide (DOTA-TOC), DOTA-DPhe1,Tyr3-octreotate (DOTA-TATE), and PSMA-617, PSMA-11, and PSMA-I&T, which are used worldwide [48-52].

Finally, the most considerable theranostic "radiopharmaceutical pair" (^{68}Ga/ ^{177}Lu-FAPI) has attracted so much attention in Cancer-Associated Fibroblasts (CAFs) in nuclear medicine [53].

Pharmacologically, there is increased expression of CAFs in damaged cells compared to normal cells [53].

Based on this fact radiolabeled FAPI derivatives can be a better alternative to [^{18}F]-FDG. It was demonstrated that radiolabeled FAPI derivatives showed better Tumor-to-Background Ratios (TBR) in the broad spectrum of cancers [53, 54]. Besides the absence of relevant adverse effects or poor tolerability profiles such as dietary restrictions, makes radiolabeled FAPI derivatives a superior choice compared to [^{18}F]-FDG [54-56]. Figure 2 represents the chemical structures of some of these radiotracers which have demonstrated a role in cancer treatment.

For a clearer perception of one-pair or two-pair theranostic radiopharmaceuticals, the physical characteristics of theranostic radionuclides are shown in Table 3 and the functional mechanisms of the most important ones are summarized in Table 4.

1.4. Recent Advancements and Development of Popular Radiopharmaceuticals

In Table 5, we summarized radiopharmaceuticals are approved for clinical applications in nuclear medicine with diagnostic indications, to have a perspective on the field of radiopharmaceuticals used in nuclear medicine.

The development of novel radio-ligands in corporations with appropriate radionuclides for cancer diagnosis and treatment with optimal characterizations led to considerable advancements in nuclear medicine [3, 58, 59]. For instance, targeting of albumin or immunoglobulin binding sites, Fibroblast Activation Protein (FAP), PSMA, or somatostatin receptors

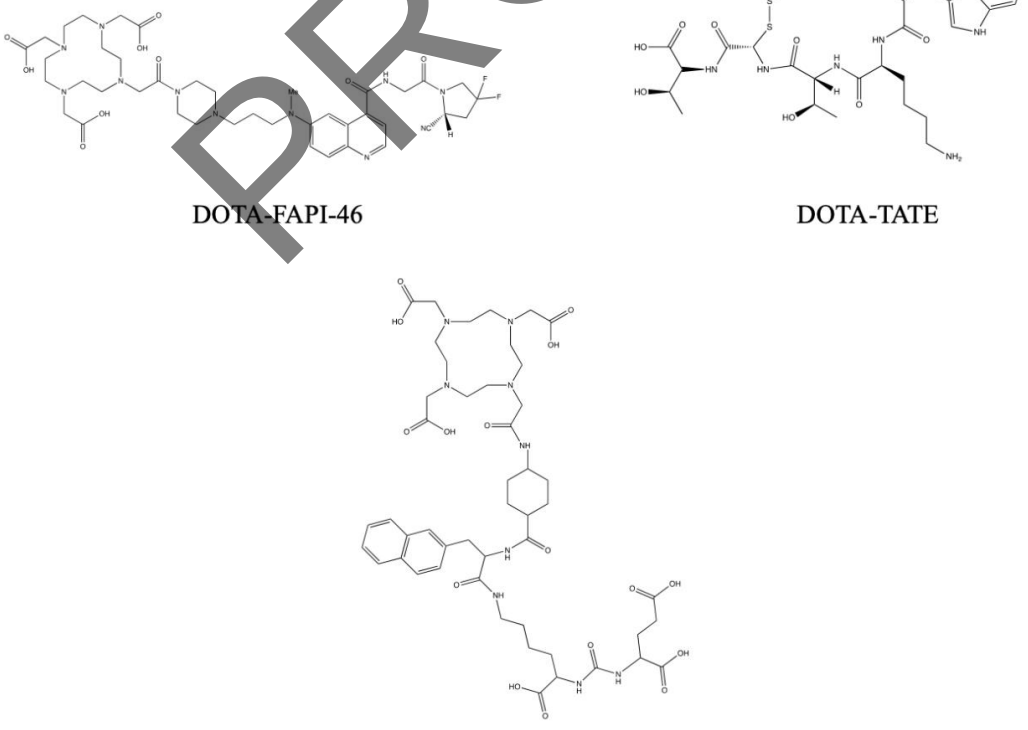

Figure 2. The chemical structure of DOTA-TATE, PSMA-617, and FAPI-46

Table 3. Physical characteristics of theranostic radionuclides

Radionuclide	Half-Life	Production Form	Imaging Modality	Emission
		Therapeutic Radioisotopes		
^{131}I	8.05 days	^{130}Te(n,γ)^{131}Te→^{131}I	SPECT	γ, β^-
^{90}Y	2.67 days	^{90}Sr/^{90}Y generator	PET/SPECT	β^-/ bremsstrahlung
^{153}Sm	46.3 hours	^{152}Sm (n,γ) →^{153}Sm	SPECT	γ, β^-
^{177}Lu	6.65 days	^{176}Yb(n,γ)^{177}Yb → ^{177}Lu	SPECT	γ, β^-
^{223}Ra	11.4 days	^{227}Ac(n,γ)^{227}Th → ^{223}Ra	SPECT	α, γ, β^-
		Diagnostic Radioisotopes		
^{68}Ga	68 minutes	^{68}Ge/^{68}Ga generator	PET	β^+
^{99m}Tc	6 hours	^{99}Mo/^{99m}Tc generator	SPECT	γ
^{111}In	67.9 hours	^{112}Cd (p,2n) ^{111}In	SPECT	γ
^{123}I	13.27 hours	^{124}Xe (p,2n) ^{123}Cs → ^{123}I	SPECT	γ

Table 4. Localization mechanism of theranostic radiopharmaceuticals

Radiopharmaceuticals	Mechanism of Localization & Action	References
[^{131}I]- Sodium iodide	Thyroid function	[40]
[^{131}I]-MIBG	Taken up by the postganglionic, presynaptic nerve endings	[23]
[^{177}Lu]Lu-PSMA 617/ 11/ I&T	Targeting Prostate-specific membrane antigen (PSMA) which is commonly upregulated in prostate carcinoma (PCa)	[28]
[^{177}Lu]Lu-DOTA-TATE/ TOC	Somatostatin receptor subtype 2-mediation	[20]
[^{153}Sm]Sm-EDTMP	Binding to hydroxyapatite	[40, 57]
[^{177}Lu]Lu-FAPI	Inhibition of FAP which is overexpressed by cancer-associated fibroblasts of several tumor entities	[25]

(SSTRs 1-5) can be mentioned as remarkable targets for diagnostic or therapeutic purposes to related dysfunctions [60-64]. A variety of PSMA derivatives have been radiolabeled with ^{68}Ga, including the widely used [^{68}Ga]Ga-PSMA-11 as a PET diagnostic tracer. It is well known today that PSMA-based radiopharmaceuticals act superior to conventional diagnostic agents for PC, such as choline-based radiopharmaceuticals [65, 66].

Recently developed ^{68}Ga radiolabeled FAPI derivatives are limelight for the detection of various types of cancers. They have been approved for use in 28 kinds of cancers due to their rapid and high tumor uptake [25].

Based on easy accessibility, convenient production, and favorable physical characteristics that were mentioned in Table 3, ^{68}Ga has been one of the most used radionuclides recently [67, 68]. We summarized some of the ^{68}Ga-based radiopharmaceuticals in Table 6.

From a therapeutic perspective, ^{177}Lu holds significant therapeutic potential in recent clinical studies [69, 70]. FDA-approved Lutathera® ([^{177}Lu]Lu-DOTA-TATE) has been used successfully as theranostic pair of available [^{68}Ga]Ga-DOTA-TATE/ DOTA-TOC/ DOTA-NOC in clinical trials [49, 71]. Generally, due to the concern about the therapeutic aims, β emitting radionuclides (^{177}Lu, ^{90}Y), as well as α emitting radionuclides (^{223}Ra, ^{225}Ac), are emerging as potent and promising documentaries (Table 7) [72, 73].

It should be pointed out that the implementation of α Targeted Therapy (TAT) as theranostic pairs is a consequential issue that is rapidly moving forward. Individual and exclusive properties of α- emitting radionuclides make them more considerable choices for therapy objectives [34]. Shorter penetration rate compared to β-emitting radionuclides, the capability of producing double-strand DNA breaking, severe chromosomal damage such as shattered chromosomes at mitosis and complex chromosomal rearrangements,

Table 5. General perspective of common diagnostic radiopharmaceuticals in nuclear medicine [82-84]

Organ/ Radiopharmaceutical characterizations	Diagnostic	Indication	Recommended Doses (mCi)	Administration Method	Imaging Protocol
Central Nervous System	[^{99m}Tc]Tc-HMPAO	Brain perfusion imaging	10-20	IV injection	20-120min PI
	[^{99m}Tc]Tc-ECD	Brain perfusion imaging	10-20	IV injection	20-40min PI
	[^{99m}Tc]Tc-Trodat	Neurodegenerative disease detection	20	IV injection	4hPI
	[^{11}C]C-Flumazenil	Neurodegenerative disease detection	20	IV injection	30-60min PI
	[^{18}F]F-DOPA	Neurodegenerative disease detection	5-10	IV injection	Began at the start of the tracer infusion over 94min
	[^{123}I]I-Ioflupane	Neurodegenerative disease detection	3-5	IV injection	3-6h PI
	[^{18}F]-FDG	Brain metabolic imaging	10-15	IV injection	45-60min
	[^{18}F]F-Florbetapir	Cognitive impairment detection	10	IV injection	10-50 PI
	[^{18}F]F-Flutemetamol	Cognitive impairment detection	5	IV injection	90 min PI
	[^{18}F]F-Florbetaben	Cognitive impairment detection	8.1	IV injection	45-130min PI
	[^{111}In]In-DTPA	Cisternography	0.5	Lumbar puncture injection (sarachnoid space)	4, 24-48 h PI
		Obstructive hydrocephalus	0.5	Lumbar puncture injection	0.5-1 h PI
		Detection of the actual site of CSF leakage	2-3	Injected via the reservoir for VP shunt and via lumbar puncture needle in subarachnoid space for LP shunt	4, 24-48 h PI
Lacrimal Glands	[^{99m}TC]TcO_4^-	Dacryoscintigraphy	0.05-0.2	A drop should be placed near the center of the cornea	1-5min PI
Salivary Glands	[^{99m}TC]TcO_4^-	Salivary gland function scintigraphy	5-10	IV injection	5min intervals for 30min
Thyroid	[$^{123/131}$I]-NaI	Thyroid function imaging	0.1 (^{131}I), 0.3 (^{123}I)	Oral	24h PI
	[^{99m}TC]TcO_4^-	Thyroid function imaging	10	IV injection	10-30min PI

Lungs	[^{99m}Tc]Tc-MAA ^{133}Xe Gas [^{99m}Tc]Tc-DTPA [^{99m}Tc]Tc-Technegas [^{67}Ga]Ga-Citrate	Lung perfusion imaging Lung ventilation imaging Lung ventilation imaging Lung ventilation imaging Lung nonembolic disease	2-4 10-15 30 0.5-1 5-10	IV injection Inhalation Inhalation Inhalation IV injection	Immediately PI Immediately PI Immediately PI Immediately PI 48-72h
Heart	[^{201}Tl]Tl-Thallous Chloride	MPI	Stress: 2-3	IV injection	5-10 min PI
	[^{99m}Tc]Tc-Sestamibi	MPI	2-day protocol: Stress:20-25 Rest:20-25	IV injection	15min PI 46-60 min PI
	[^{99m}Tc]Tc-Tetrafosmin	MPI	Stress:15-30 Rest:8-10	IV injection	30-60 min PI 46-60 min PI
	[^{82}Rb]-RbCl	MPI	Stress:60 Rest:60	IV injection	Immediately PI Immediately PI
	[^{18}F]-Flurpiridaz	MPI	Rest+stress≤14	IV injection	Immediately PI
	[^{18}F]-FDG	Myocardial metabolic imaging	10-15	IV injection	1h PI
	[^{99m}Tc]Tc-Pyrophosphate	Myocardial infarct imaging	10-15	IV injection	1-2 h PI
	[^{123}I]-MIBG	Cardiac innervation imaging	5-10	IV injection	3, 24, 48h PI
Liver	[^{99m}Tc]Tc-IDA Derivatives [^{99m}Tc]Tc-Sulfur Colloid [^{99m}Tc]Tc-RBC	Hepatobiliary function imaging liver imaging (Kupffer cells function) Focal lesion detection in the liver liver imaging (Kupffer cells function) Liver hemangioma imaging	3-5 2-4 10-15 25	IV injection IV injection Bolus injection IV injection	3-4h PI 5-10 min PI Rapid Sequential Imaging PI Immediately PI
Spleen	[^{99m}Tc]Tc-denatured RBC [^{99m}Tc]Tc-Sulfur Colloid	Spleen structure/ any abnormality Spleen function imaging	2-3 2-3	IV injection IV injection	30-60 min PI 15-30 min PI
Kidneys	[^{99m}Tc]Tc-MAG3	Renal function assessment	5-10	IV injection	Immediately PI (Dynamic)
	[^{99m}Tc]Tc-DMSA	Renal imaging	2-5	IV injection	2-4h PI (Static)
	[^{99m}Tc]Tc-DTPA	GFR measurement	10-15	IV injection	By tracer administration (Dynamic)
	[^{99m}Tc]TC-EC	Renal function assessment	5-8	IV injection	Immediately PI (Dynamic)
Skeleton	[^{99m}Tc]Tc-Phosphonate Compounds	Bone imaging	10-20	IV injection	2-3 h PI
	[^{18}F]-NaF	Bone imaging	4	IV injection	15-30 min PI

IV: Intravenous, PI: Post-Injection, MPI: Myocardial Perfusion Imaging, CSF: CerebroSpinal Fluid, GFR: Glomerular

Table 6. Introduction of ^{68}Ga-labeled radiopharmaceuticals [49, 85-94]
https://clinicaltrials.gov/ct2/results?recrs=&cond=68Ga&term=&cntry=&state=&city=&dist=#wrapper

Radiopharmaceutical	Indication	Mechanism of Action	Doses (mCi)	Imaging Protocol
DOTANOC	NET	GPCR Targeting: sst_2 receptor agonist	3-5	60min PI
DOTATOC	NET	GPCR Targeting: sst_2 receptor agonist	3-5	60min PI
DOTATATE	NET	GPCR Targeting: sst_2 receptor agonist	5	60min PI
OPS202	NET	GPCR Targeting: sst_2 receptor antagonist	4	60min PI
FAPI-46/ 04/ CHX	Tumor imaging	FAP Inhibition	3-8	15-30min PI
PSMA-11/ R2	PC	PSMA Targeting	3-7	50-100min PI
Pentixafor	CNS Lymphoma	Chemokine receptors Targeting	2.2-4.2	60min PI
RGD	Coronary Artery Disease	Interaction with integrin αVβ3	5	70min PI
Bisphosphonates: **DOTAM^{PAM}** **DOTAM^{ZOL}** **BPAMD** **NO2AP^{BP}**	Bone metastases	Binding to HA	3-5 4-5 12-13 3-5	60min PI 45min PI 50min PI 30min PI
NeoBOMB1	Breast Cancer Prostate Cancer Colorectal Cancer Non-Small Cell Lung Cancer Small Cell Lung Cancer	Binding to GRPR	3.5-6.5	120min PI
FAPI-2286	Tumor imaging	FAP Inhibition	6	60min PI
ICAM-1pep	Cancer	NA	6	60min PI
N188	Neoplasms	Nectin-4 Targeting	4-6	60min PI
NODAGA-E[c(RGDyK)]2	Neuroendocrine Carcinoma Breast Cancer Ovarian Cancer	Interaction with integrin αVβ3	5	60min PI
PSMA-617	PC	PSMA Targeting	3-7	50-100min PI
Grazytracer	NSCLC Melanoma	Identification of tumor responses to immune checkpoint inhibitory cancer therapy	5	60min PI
BNOTA-PRGD2	Rheumatoid Arthritis	Interaction with integrin αVβ3	5	60min PI
RM2/ 26	Stage II Prostate Adenocarcinoma Stage III Prostate Adenocarcinoma Stage IV Prostate Adenocarcinoma	Targeting GRPR that are overexpressed in several human tumors	3-4	40-90min PI
ABY-025	Esophageal Neoplasms Gastric Neoplasms Malignant Breast Cancer HER2-positive Gastric Cancer	HER2 Targeting	2.5	2-3h PI
NY104/105/108	Renal Cell Carcinoma	NA	2-5	45 -75PI

P16-093	PC	PSMA Targeting	4-5	60min PI
HX01	Malignant Neoplasm	Interaction with aminopeptidase N (APN/CD13) and/or integrin αvβ3	NA	30min PI
BNU-PSMA	Primary and metastatic lesions			
Citrate	Fever of Unknown Origin	Fe(III) biomimetic that binds to apo-transferrin	11.5	45-60min PI
FAP-RGD	Imaging agent for various cancers	FAP Inhibition	4-7	50-100min PI
FF58				
NOTA-SNA002	Solid Tumor		1-5	
NODAGA-exendin 4	Insulinoma	targeting the glucagon-like peptide-1 receptor (GLP-1R)	3.5	60min PI
HTK03149	Prostate Cancer Prostatic Neoplasm Prostatic Disease Urogenital Neoplasms Disease Attributes Neoplasms	PSMA Targeting	6.5	60min PI
DOTA-JR11	Neuroendocrine Tumors	Somatostatin Antagonist	4.5-6.5	60min PI
P16-093	PC	PSMA Targeting	4-6	60min PI
BMV101	Idiopathic Pulmonary Fibrosis	Macrophage response to inflammation	3.5	60min PI
NOTA-NFB	Glioma Breast Cancer	CXCR4 Targeting	5	NA
DOTA-NT-20.3	Pancreatic Ductal Adenocarcinoma	NTR-1 Targeting	4.5-9	60min PI
CBP8	Lung Cancer Radiation Fibrosis Radiation-Induced Lung Injury Pancreas Cancer	Targeting collagen type I (detection of detecting collagen deposition)		
NEB	Lymphatic Disorders	Forms a complex with serum albumin in the interstitial fluid after it is locally injected	2-3	20-40min PI
Sgc8	Colorectal Cancer	Targeting CCK4	0.3-0.6 after ^{18}FDG routine injection	30-60min PI
DOTA-5G	Metastatic Pancreatic Cancer Locally Advanced Pancreatic Adenocarcinoma	NA	NA	NA
NOTA-AE105	Lung CancerRadiation FibrosisRadiation Induced Lung InjuryPancreas Cancer	uPARs Targeting	5-6	20min PI
P16-093/ 15-041	PC	PSMA Targeting	4-5	60min PI
OPS202	NET		4-5	30min PI
DOTA-Siglec-9	Synovitis detection	Targeting Vascular Adhesion Protein 1(inflammation imaging)	5	60min PI

DPI-4452	Clear Cell Renal Cell Cancer (ccRCC) Pancreatic Ductal Adenocarcinoma (PDAC) Colorectal Cancer (CRC)	NA	NA	NA
IMP-288	HER2 Negative Breast Carcinoma Expressing CEA	TF2 antibody	4-5	60-120min PI
NODAGA-LM3	NET	sst_2 receptor agonist	4.5-6.5	60min PI
Tilmanocept	SLN mapping	binding to a cell surface receptor unique to macrophages and dendritic cells	0.3	30-90min PI
MSA	Lymph node imaging	NA	NA	NA
PLN-74809	Idiopathic Pulmonary Fibrosis	NA	NA	NA
VMT02	Melanoma diagnosis	NA	NA	NA
MLN6907	Imaging of Solid Gastrointestinal Tumors	NA	NA	NA
BAY86-7548	PC	Targeting bombesin receptor subtype II (PC)	4-5	60min PI
PNT6555	Pancreatic Ductal Adenocarcinoma Colorectal Cancer Esophageal Cancer Melanoma (Skin) Soft Tissue Sarcoma	FAP inhibition	NA	60min PI

NET: Neuroendocrine Tumor, GRPR: Gastrin-releasing peptide receptor, HER2: Human epidermal growth factor receptor type 2, MSA: Mannosylated human serum albumin, PC: Prostate cancer, PSMA: Prostate specific membrane antigen, uPARs: urokinase-type plasminogen activator receptors, HA: Hydroxyapatite, NTR-1: Neurotensin receptor 1, CCK4: Colon carcinoma kinase-4, NA: Not Available

destruction of tumoral cells independently of oxygenation, and the potential to overcome resistance against β-emitters can be mentioned as some of the brilliant properties of α emitters [74, 75]. [^{213}Bi]Bi-DOTA-TOC has demonstrated optimistic results in resistant NET cases to [^{177}Lu]Lu-DOTA-TATE therapeutic procedure [76] Multi-center studies on [^{225}Ac]Ac-PSMA-617 as a TAT agent have been started to confirm efficacy, safety profile, probable side effects, and toxicities in clinical applications [77, 78]. Recently, [^{225}Ac]Ac-PSMA-617 has been considered a well-tolerated radiopharmaceutical with acceptable side effects [79, 80].

Currently, different kinds of FAPIs' derivatives have been developed and radiolabeled with imaging and therapeutic radionuclides which were used in different clinical indications [81].

2. Conclusion

The application of radiopharmaceuticals is an appropriate consequential method not only for the management of disease or dysfunctions but also for the evaluation of disorders creations, which could be applicable for the developments of therapeutic procedures. In recent years so much precious progress in diagnostic and therapeutic processes in nuclear medicine has been accomplished. Nuclear medicine protocols were based on ^{131}I, ^{99m}Tc, ^{201}Tl, and ^{32}P for a long time. The introduction of 153Sm and after that ^{177}Lu as theranostic agents was a significant milestone in nuclear medicine. The concept of theranostics led to opening new horizons to simultaneously diagnose and treatment of NET and PC with significant optimistic results. An important paradigm took place in nuclear medicine parallel to the application of new PET radiotracers that paved the way for diagnosis with

Table 7. General perspective of common therapeutic radiopharmaceuticals in nuclear medicine

Radiopharmaceutical	Indication	Recommended Doses (mCi)	Administration Method	Reference
[^{223}Ra]Ra-Chloride	Skeletal metastases	0.1	IV Injection	[95-97]
[^{90}Y]Y-Glass Microspheres	Hepatic carcinoma	60-70	Delivery into the hepatic artery by slow injection	[98-100]
[^{90}Y]Y-Resin Microspheres	Hepatic carcinoma	30-80	Delivery into the hepatic artery by slow injection	[98, 100, 101]
[^{131}I]-NaI	Differentiated thyroid cancer Graves' disease Hyperfunctioning nodules	4-200*a	Oral	[102-104]
[^{153}Sm]Sm-EDTMP	Skeletal metastases	30-70	IV Injection	[105, 106]
[^{177}Lu]Lu-EDTMP	Skeletal metastases	30-70	IV Injection	[105]
[^{186}Re]Re-HEDP	Skeletal metastases	70-140	IV Injection	[107, 108]
[^{131}I]-MIBG	phaeochromocytomas neuroblastomas ganglioneuroblastomas ganglioneuromas paragangliomas carcinoid tumors medullary thyroid carcinomas Merkel cell tumors MEN2 syndromes	100-300	IV Injection	[109, 110]
[^{177}Lu]Lu-PSMA-617	PCa	200/cycle	IV Injection	[47, 111]
[^{177}Lu]Lu-PSMA-I&T	PCa	200/cycle	IV Injection	[112, 113]
[^{177}Lu]Lu-DOTATATE	NET	150-200	IV Injection	[114]
[^{177}Lu]Lu-DOTATOC	NET	150-200	IV Injection	[114]
[^{225}Ac]Ac-PSMA-617	PCa	0.2/cycle	IV Injection	[77, 115]
[^{225}Ac]Ac-PSMA-I&T	PCa	0.2/cycle	IV Injection	[116, 117]
[^{225}Ac]Ac-DOTATATE	NET	0.2/cycle	IV Injection	[118, 119]
[^{225}Ac]Ac-DOTATOC	NET	0.2/cycle	IV Injection	[120, 121]
[^{90}Y]Y-DOTATATE	NET	68-120*b	IV Injection	[114]
[^{90}Y]Y-DOTATOC	NET	68-120*b	IV Injection	[114]

**a It depends on the indication, *b It depends on the number of therapeutic cycles, NET: Neuroendocrine Tumor, IV: Intravenous, PCa: Prostate Cancer*

higher accuracy and resolution in cancer care protocols. Recently developed ^{18}F- and ^{68}Ga-based radiopharmaceuticals offer improved resolution and higher quantities. Additionally, they allow for the utilization of biological molecules as marker ligands, including analogs of glucose, antibodies, and amino acids. Furthermore, zirconium-89 (^{89}Zr) is well suited for immuno-targeted PET imaging with slow kinetics. It also provides opportunities for pre-targeting with mAb followed by ^{89}Zr-chelator binding and PET imaging.

The theranostic approach is gaining increasing interest, using the same vector primarily with β+/ γ emitter radionuclides for diagnostic purposes, and β/ α emitters for targeted radionuclide therapy purposes. Long-lived β+ emitter radionuclides have attracted significant attention for clinical applications in recent years. ^{89}Zr, ^{45}Ti, ^{64}Cu, and ^{44}Sc with half-lives of 78.41 hours, 184.8 minutes,

12.7 hours, and 4.042 hours respectively are more applicable compared to PET radionuclides with short half-lives. It is estimated that a widespread list of long-life PET radionuclides will be added to the diagnostic process in nuclear medicine. Preclinical trials are currently underway to investigate their effectiveness.

Recently, α-emitter therapeutic radionuclides including ^{211}At for glioblastoma, ^{225}Ac for leukemia and prostate cancer, ^{212}Pb for breast cancer, and ^{223}Ra for prostate cancer have been extensively studied. Some of them have also been used in clinical trials, as mentioned previously. It is anticipated that the use of α-emitting radiopharmaceuticals for treating difficult-to-treat cancers will continue to grow, based on the substantial clinical results of α-emitters in nuclear medicine.

References

1- Buck A Rhodes and Barbara Y Croft, Basics of radiopharmacy. *Mosby*, (1978).

2- Farid A Badria, "Radiopharmaceuticals: On-Going Research for Better Diagnosis, Therapy, Environmental, and Pharmaceutical Applications." *Radiopharmaceuticals: Current Research for Better Diagnosis and Therapy*, p. 3, (2022).

3- George Sgouros, Lisa Bodei, Michael R McDevitt, and Jessie R Nedrow, "Radiopharmaceutical therapy in cancer: clinical advances and challenges." *Nature Reviews Drug Discovery*, Vol. 19 (No. 9), pp. 589-608, (2020).

4- Filipe Boccato Payolla, Antonio Carlos Massabni, and Chris Orvig, "Radiopharmaceuticals for diagnosis in nuclear medicine: A short review." *Eclética Química*, Vol. 44 (No. 3), pp. 11-19, (2019).

5- Craig W Lindsley, Christa E Müller, and Salvatore Bongarzone, "Diagnostic and therapeutic radiopharmaceuticals." Vol. 5, ed: ACS Publications, (2022), pp. 835-37.

6- Teresa A O'Sullivan and Curtis G Jefferson, "A review of strategies for enhancing clarity and reader accessibility of qualitative research results." *American Journal of Pharmaceutical Education*, Vol. 84 (No. 1), p. 7124, (2020).

7- Vladimir Drozdovitch *et al.*, "Use of radiopharmaceuticals in diagnostic nuclear medicine in the United States: 1960–2010." *Health physics*, Vol. 108 (No. 5), pp. 520-37, (2015).

8- Buck A Rhodes and Barbara Y Croft, "Basics of radiopharmacy." *(No Title)*, (1978).

9- Michael F L'Annunziata, Radioactivity: introduction and history, from the quantum to quarks. *Elsevier*, (2016).

10- Seyed K Imam, "Molecular nuclear imaging: the radiopharmaceuticals." *Cancer biotherapy & radiopharmaceuticals*, Vol. 20 (No. 2), pp. 163-72, (2005).

11- George Crișan, Nastasia Sanda Moldovean-Cioroianu, Diana-Gabriela Timaru, Gabriel Andrieș, Călin Căinap, and Vasile Chiș, "Radiopharmaceuticals for PET and SPECT imaging: A literature review over the last decade." *International journal of molecular sciences*, Vol. 23 (No. 9), p. 5023, (2022).

12- Ora Israel *et al.*, "Two decades of SPECT/CT–the coming of age of a technology: an updated review of literature evidence." *European journal of nuclear medicine and molecular imaging*, Vol. 46pp. 1990-2012, (2019).

13- Adriano Duatti, "Review on 99mTc radiopharmaceuticals with emphasis on new advancements." *Nuclear medicine and biology*, Vol. 92pp. 202-16, (2021).

14- Joseph Lau, Etienne Rousseau, Daniel Kwon, Kuo-Shyan Lin, François Bénard, and Xiaoyuan Chen, "Insight into the Development of PET Radiopharmaceuticals for Oncology." *Cancers*, Vol. 12 (No. 5), p. 1312, (2020).

15- Terence J O'Brien *et al.*, "Comparative study of 99mTc-ECD and99mTc-HMPAO for peri-ictal SPECT: qualitative and quantitative analysis." *Journal of Neurology, Neurosurgery & Psychiatry*, Vol. 66 (No. 3), pp. 331-39, (1999).

16- Erhard Suess, Sigismund Huck, Hans Reither, Heide Hörtnagl, and Peter Angelberger, "Uptake mechanism of technetium-99m-d, 1-HMPAO in cell cultures of the dissociated postnatal rat cerebellum." *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, Vol. 33 (No. 1), pp. 108-14, (1992).

17- Seok Rye Choi *et al.*, "Correlation of amyloid PET ligand florbetapir F 18 (18F-AV-45) binding with β-amyloid aggregation and neuritic plaque deposition in postmortem brain tissue." *Alzheimer Disease and Associated Disorders*, Vol. 26 (No. 1), p. 8, (2012).

18- Jaya Shukla and Bhagwant Rai Mittal, "Dimercaptosuccinic acid: A multifunctional cost effective agent for imaging and therapy." *Indian Journal of Nuclear Medicine: IJNM: The Official Journal of the Society of Nuclear Medicine, India*, Vol. 30 (No. 4), p. 295, (2015).

19- Cheng-Han Wu, Bang-Hung Yang, Yuan-Hwa Chou, Shyh-Jen Wang, and Jyh-Cheng Chen, "Effects of 99mTc-TRODAT-1 drug template on image quantitative analysis." *PLoS One*, Vol. 13 (No. 3), p. e0194503, (2018).

20- Vera Artiko *et al.*, "Evaluation of neuroendocrine tumors with 99mTc-EDDA/HYNIC TOC." *Nuclear Medicine Review*, Vol. 19 (No. 2), pp. 99-103, (2016).

21- Steven M Larson, "Mechanisms of localization of gallium-67 in tumors." in *Seminars in nuclear medicine*, (1978), Vol. 8: *Elsevier*, pp. 193-203.

22- Heinz O Hirzel *et al.*, "Thallium-201 scintigraphy in complete left bundle branch block." *The American journal of cardiology*, Vol. 53 (No. 6), pp. 764-69, (1984).

23- Archi Agrawal, Venkatesh Rangarajan, Sneha Shah, Ameya Puranik, and Nilendu Purandare, "MIBG (metaiodobenzylguanidine) theranostics in pediatric and adult malignancies." *The British journal of radiology*, Vol. 91 (No. 1091), p. 20180103, (2018).

24- Werner Langsteger, Martin Heinisch, and Ignac Fogelman, "The role of fluorodeoxyglucose, 18F-dihydroxyphenylalanine, 18F-choline, and 18F-fluoride in bone imaging with emphasis on prostate and breast." in *Seminars in nuclear medicine*, (2006), Vol. 36: *Elsevier*, pp. 73-92.

25- Clemens Kratochwil *et al.*, "68Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer." *Journal of Nuclear Medicine*, Vol. 60 (No. 6), pp. 801-05, (2019).

26- Padmaja Yalamanchili *et al.*, "Mechanism of uptake and retention of F-18 BMS-747 158-02 in cardiomyocytes: a novel PET myocardial imaging agent." *Journal of Nuclear Cardiology*, Vol. 14pp. 782-88, (2007).

27- John O Prior *et al.*, "Quantification of myocardial blood flow with 82 Rb positron emission tomography: clinical validation with 15 O-water." *European journal of nuclear medicine and molecular imaging*, Vol. 39pp. 1037-47, (2012).

28- Jan H Rüschoff *et al.*, "What's behind 68 Ga-PSMA-11 uptake in primary prostate cancer PET? Investigation of histopathological parameters and immunohistochemical PSMA expression patterns." *European journal of nuclear medicine and molecular imaging*, Vol. 48pp. 4042-53, (2021).

29- Xiang Li *et al.*, "[68 Ga] Pentixafor PET/MR imaging of chemokine receptor 4 expression in the human carotid artery." *European journal of nuclear medicine and molecular imaging*, Vol. 46pp. 1616-25, (2019).

30- George Sgouros, "Radiopharmaceutical therapy." *Health physics*, Vol. 116 (No. 2), p. 175, (2019).

31- Attila Keresztes, Attila Borics, and Csaba Tömböly, "Therapeutic and diagnostic radiopharmaceuticals." (2015).

32- Nasir Abbas, Helen Heyerdahl, Øyvind S Bruland, Jørgen Borrebæk, Jahn Nesland, and Jostein Dahle, "Experimental α-particle radioimmunotherapy of breast cancer using 227Th-labeled p-benzyl-DOTA-trastuzumab." *EJNMMI research*, Vol. 1 (No. 1), pp. 1-12, (2011).

33- Narges K Tafreshi *et al.*, "Development of targeted alpha particle therapy for solid tumors." *Molecules*, Vol. 24 (No. 23), p. 4314, (2019).

34- Albert Jang, Ayse T Kendi, Geoffrey B Johnson, Thorvardur R Halfdanarson, and Oliver Sartor, "Targeted Alpha-Particle Therapy: A Review of Current Trials." *International journal of molecular sciences*, Vol. 24 (No. 14), p. 11626, (2023).

35- Kwamena E Baidoo, Kwon Yong, and Martin W Brechbiel, "Molecular pathways: targeted α-particle radiation therapy." *Clinical Cancer Research*, Vol. 19 (No. 3), pp. 530-37, (2013).

36- Matt Shirley and Paul L McCormack, "Radium-223 dichloride: a review of its use in patients with castration-resistant prostate cancer with symptomatic bone metastases." *Drugs*, Vol. 74pp. 579-86, (2014).

37- Fable Zustovich and Francesca Fabiani, "Therapeutic opportunities for castration-resistant prostate cancer patients with bone metastases." *Critical reviews in oncology/hematology*, Vol. 91 (No. 2), pp. 197-209, (2014).

38- Jon L Aro, Stephen I Dinning, Eugene Y Leung, and Lionel S Zuckier, "Safe Use of Radium-223 Dichloride (223RaCl2) Across a Wide Range of Clinical Scenarios, Incorporating a 10-year Single-Institution Radiation Safety Experience." *Journal of Medical Imaging and Radiation Sciences*, Vol. 50 (No. 4), pp. S36-S40, (2019).

39- Malick Bio Idrissou, Alexandre Pichard, Bryan Tee, Tibor Kibedi, Sophie Poty, and Jean-Pierre Pouget, "Targeted radionuclide therapy using auger electron emitters: the quest for the right vector and the right radionuclide." *Pharmaceutics*, Vol. 13 (No. 7), p. 980, (2021).

40- Abdelhamid H Elgazzar, The pathophysiologic basis of nuclear medicine. *Springer Science & Business Media*, (2006).

41- Diane S Abou *et al.*, "Improved 223Ra Therapy with Combination Epithelial Sodium Channel Blockade." *Journal of Nuclear Medicine*, Vol. 62 (No. 12), pp. 1751-58, (2021).

42- Philippa J Cheetham and Daniel P Petrylak, "Alpha particles as radiopharmaceuticals in the treatment of bone metastases: mechanism of action of radium-223 chloride (Alpharadin) and radiation protection." *Oncology*, Vol. 26 (No. 4), p. 330, (2012).

43- Nasim Vahidfar, Elisabeth Eppard, Saeed Farzanehfar, Anna Yordanova, Maryam Fallahpoor, and Hojjat Ahmadzadehfar, "An impressive approach in nuclear medicine: Theranostics." *PET clinics*, Vol. 16 (No. 3), pp. 327-40, (2021).

44- Nasim Vahidfar, Ayuob Aghanejad, Hojjat Ahmadzadehfar, Saeed Farzanehfar, and Elisabeth Eppard, "Theranostic advances in breast cancer in nuclear

medicine." *International journal of molecular sciences*, Vol. 22 (No. 9), p. 4597, (2021).

45- Cristina Barca *et al.*, "Expanding theranostic radiopharmaceuticals for tumor diagnosis and therapy." *Pharmaceuticals*, Vol. 15 (No. 1), p. 13, (2021).

46- Jonathan Strosberg *et al.*, "Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors." *New England Journal of Medicine*, Vol. 376 (No. 2), pp. 125-35, (2017).

47- Ute Hennrich and Matthias Eder, "[177Lu] Lu-PSMA-617 (PluvictoTM): the first FDA-approved radiotherapeutical for treatment of prostate cancer." *Pharmaceuticals*, Vol. 15 (No. 10), p. 1292, (2022).

48- Irene Virgolini *et al.*, "Procedure guidelines for pet/ct tumour imaging with 68 Ga-dota-conjugated peptides: 68 Ga-dota-toc, 68 Ga-dota-noc, 68 Ga-dota-tate." *European journal of nuclear medicine and molecular imaging*, Vol. 37pp. 2004-10, (2010).

49- Ute Hennrich and Martina Benešová, "[68Ga] Ga-DOTA-TOC: the first FDA-approved 68Ga-radiopharmaceutical for PET imaging." *Pharmaceuticals*, Vol. 13 (No. 3), p. 38, (2020).

50- Wallace Jones, Kelly Griffiths, Pedro C Barata, and Channing J Paller, "PSMA theranostics: Review of the current status of PSMA-targeted imaging and radioligand therapy." *Cancers*, Vol. 12 (No. 6), p. 1367, (2020).

51- Nikhil Mayor *et al.*, "Prostate-specific membrane antigen theranostics in advanced prostate cancer: an evolving option." *BJU international*, Vol. 126 (No. 5), pp. 525-35, (2020).

52- Nasim Vahidfar, Maryam Fallahpoor, Saeed Farzanehfar, Ghasemali Divband, and Hojjat Ahmadzadehfar, "Historical review of pharmacological development and dosimetry of PSMA-based theranostics for prostate cancer." *Journal of Radioanalytical and Nuclear Chemistry*, Vol. 322pp. 237-48, (2019).

53- Thomas Lindner, Frederik L Giesel, Clemens Kratochwil, and Sebastian E Serfling, "Radioligands targeting fibroblast activation protein (FAP)." *Cancers*, Vol. 13 (No. 22), p. 5744, (2021).

54- Marko Magdi Abdou Sidrak *et al.*, "Fibroblast Activation Protein Inhibitor (FAPI)-Based Theranostics—Where We Are at and Where We Are Heading: A Systematic Review." *International journal of molecular sciences*, Vol. 24 (No. 4), p. 3863, (2023).

55- Liang Zhao *et al.*, "Fibroblast activation protein-based theranostics in cancer research: A state-of-the-art review." *Theranostics*, Vol. 12 (No. 4), p. 1557, (2022).

56- Muhsin H Younis, Xiaoli Lan, and Weibo Cai, "PET with a 68Ga-Labeled FAPI Dimer: Moving Toward Theranostics." *Journal of Nuclear Medicine*, Vol. 63 (No. 6), p. 860, (2022).

57- Emran Askari, Sara Harsini, Nasim Vahidfar, Ghasemali Divband, and Ramin Sadeghi, "177Lu-EDTMP for metastatic bone pain palliation: A systematic review and meta-analysis." *Cancer biotherapy & radiopharmaceuticals*, Vol. 36 (No. 5), pp. 383-90, (2021).

58- José Carlos Dos Santos *et al.*, "Development of novel PSMA ligands for imaging and therapy with copper isotopes." *Journal of Nuclear Medicine*, Vol. 61 (No. 1), pp. 70-79, (2020).

59- Maija Radzina *et al.*, "Novel radionuclides for use in Nuclear Medicine in Europe: where do we stand and where do we go?" *EJNMMI radiopharmacy and chemistry*, Vol. 8 (No. 1), p. 27, (2023).

60- Yuriko Mori, Katharina Dendl, Jens Cardinale, Clemens Kratochwil, Frederik L Giesel, and Uwe Haberkorn, "FAPI PET: fibroblast activation protein inhibitor use in oncologic and nononcologic disease." *Radiology*, Vol. 306 (No. 2), p. e220749, (2023).

61- Yizhen Pang *et al.*, "PET imaging of fibroblast activation protein in various types of cancer using 68Ga-FAP-2286: comparison with 18F-FDG and 68Ga-FAPI-46 in a single-center, prospective study." *Journal of Nuclear Medicine*, Vol. 64 (No. 3), pp. 386-94, (2023).

62- Manish Ora *et al.*, "Fibroblast Activation Protein Inhibitor–Based Radionuclide Therapies: Current Status and Future Directions." *Journal of Nuclear Medicine*, (2023).

63- Rahul V Parghane and Sandip Basu, "PSMA-targeted radioligand therapy in prostate cancer: current status and future prospects." *Expert Review of Anticancer Therapy*, Vol. 23 (No. 9), pp. 959-75, (2023).

64- Vishnu Murthy *et al.*, "Prognostic value of end-of-treatment PSMA PET/CT in patients treated with 177Lu-PSMA radioligand therapy: a retrospective, single-center analysis." *Journal of Nuclear Medicine*, Vol. 64 (No. 11), pp. 1737-43, (2023).

65- Maija Radzina *et al.*, "Accuracy of 68Ga-PSMA-11 PET/CT and multiparametric MRI for the detection of local tumor and lymph node metastases in early biochemical recurrence of prostate cancer." *American Journal of Nuclear Medicine and Molecular Imaging*, Vol. 10 (No. 2), p. 106, (2020).

66- Ali Afshar-Oromieh *et al.*, "Comparison of PET imaging with a 68 Ga-labelled PSMA ligand and 18 F-choline-based PET/CT for the diagnosis of recurrent prostate cancer." *European Journal of Nuclear Medicine and Molecular Imaging*, Vol. 41pp. 11-20, (2014).

67- Lena Koller *et al.*, "Preclinical Comparison of the 64Cu- and 68Ga-Labeled GRPR-Targeted Compounds RM2 and AMTG, as Well as First-in-Humans [68Ga] Ga-AMTG PET/CT." *Journal of Nuclear Medicine*, Vol. 64 (No. 10), pp. 1654-59, (2023).

68- Yanqing Zheng *et al.*, "The value of targeting cxcr4 with 68ga-pentixafor pet/ct for subtyping primary aldosteronism." *The Journal of Clinical Endocrinology & Metabolism*, Vol. 109 (No. 1), pp. 171-82, (2024).

69- Kambiz Rahbar *et al.*, "Safety and Survival Outcomes of 177Lu-Prostate-Specific Membrane Antigen Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer with Prior 223Ra treatment: The RALU Study." *Journal of Nuclear Medicine*, Vol. 64 (No. 4), pp. 574-78, (2023).

70- Siju C George and E James Jebaseelan Samuel, "Developments in 177Lu-based radiopharmaceutical therapy and dosimetry." *Frontiers in Chemistry*, Vol. 11(2023).

71- Rosalba Mansi, Guillaume Pierre Nicolas, Luigi Del Pozzo, Karim Alexandre Abid, Eric Grouzmann, and Melpomeni Fani, "Evaluation of a new 177Lu-labeled somatostatin analog for the treatment of tumors expressing somatostatin receptor subtypes 2 and 5." *Molecules*, Vol. 25 (No. 18), p. 4155, (2020).

72- Wael Jalloul *et al.*, "Targeted alpha therapy: all we need to know about 225Ac's physical characteristics and production as a potential theranostic radionuclide." *Pharmaceuticals*, Vol. 16 (No. 12), p. 1679, (2023).

73- R Eychenne, M Chérel, F Haddad, F Guérard, and JF Gestin, "Overview of the most promising radionuclides for targeted alpha therapy: The "hopeful eight", Pharmaceutics, 2021, 13, 906." *This article is licensed under a Creative Commons Attribution-NonCommercial*, Vol. 3(2021).

74- Franziska Graf *et al.*, "DNA double strand breaks as predictor of efficacy of the alpha-particle emitter Ac-225 and the electron emitter Lu-177 for somatostatin receptor targeted radiotherapy." *PloS one*, Vol. 9 (No. 2), p. e88239, (2014).

75- Saman Khaled and Kathryn D Held, "Radiation biology: a handbook for teachers and students." ed: Taylor & Francis, (2012).

76- Clemens Kratochwil *et al.*, "213 Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience." *European journal of nuclear medicine and molecular imaging*, Vol. 41pp. 2106-19, (2014).

77- Madhav Prasad Yadav, Sanjana Ballal, Ranjit Kumar Sahoo, Madhavi Tripathi, Amlesh Seth, and Chandrasekhar Bal, "Efficacy and safety of 225Ac-PSMA-617 targeted alpha therapy in metastatic castration-resistant prostate cancer patients." *Theranostics*, Vol. 10 (No. 20), p. 9364, (2020).

78- Maarten J van der Doelen *et al.*, "Clinical outcomes and molecular profiling of advanced metastatic castration-resistant prostate cancer patients treated with 225Ac-PSMA-617 targeted alpha-radiation therapy." in *Urologic Oncology: Seminars and Original Investigations*, (2021), Vol. 39 (No. 10): *Elsevier*, pp. 729. e7-29. e16.

79- Mike Sathekge *et al.*, "225Ac-PSMA-617 radioligand therapy of de novo metastatic hormone-sensitive prostate carcinoma (mHSPC): preliminary clinical findings." *European journal of nuclear medicine and molecular imaging*, Vol. 50 (No. 7), pp. 2210-18, (2023).

80- Mike Sathekge *et al.*, "225 Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study." *European Journal of Nuclear Medicine and Molecular Imaging*, Vol. 46pp. 129-38, (2019).

81- Mahshid Kiani *et al.*, "Recent Clinical Implications of FAPI: Imaging and Therapy." *Clinical nuclear medicine*, p. 10.1097, (2022).

82- Gopal B Saha, Fundamentals of nuclear pharmacy. *Springer*, (2004).

83- Aki Akai, Yukie Yamamura, Manabu Nonaka, and Toshio Yoshihara, "99mTcO4− accumulation in scintigraphy and expression of Na+/I− symporter in salivary gland tumors." *Auris Nasus Larynx*, Vol. 41 (No. 6), pp. 532-38, (2014).

84- M Nakayama, K Nakajima, and K Takahashi, "Approach to diagnosis of salivary gland disease from nuclear medicine images, in salivary glands-new approaches in diagnostics and treatment. 2017." ed: IntechOpen.

85- Samira M Sadowski *et al.*, "Prospective study of 68Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites." *Journal of Clinical Oncology*, Vol. 34 (No. 6), p. 588, (2016).

86- Valentina Ambrosini *et al.*, "68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors." *Journal of Nuclear Medicine*, Vol. 51 (No. 5), pp. 669-73, (2010).

87- Constantin Lapa *et al.*, "68Ga-pentixafor-PET/CT for imaging of chemokine receptor 4 expression in glioblastoma." *Theranostics*, Vol. 6 (No. 3), p. 428, (2016).

88- Marco Fellner *et al.*, "PET/CT imaging of osteoblastic bone metastases with 68 Ga-bisphosphonates: first human study." *European journal of nuclear medicine and molecular imaging*, Vol. 37pp. 834-34, (2010).

89- Nina Pfannkuchen *et al.*, "Novel radiolabeled bisphosphonates for PET diagnosis and endoradiotherapy of bone metastases." *Pharmaceuticals*, Vol. 10 (No. 2), p. 45, (2017).

90- Averilicia Passah *et al.*, "Evaluation of bone-seeking novel radiotracer 68 Ga-NO2AP-Bisphosphonate for the detection of skeletal metastases in carcinoma breast." *European journal of nuclear medicine and molecular imaging*, Vol. 44pp. 41-49, (2017).

91- Ambreen Khawar *et al.*, "Preliminary results of biodistribution and dosimetric analysis of [68 Ga] Ga-DOTA ZOL: a new zoledronate-based bisphosphonate for PET/CT diagnosis of bone diseases." *Annals of nuclear medicine,* Vol. 33pp. 404-13, (2019).

92- Guillaume P Nicolas *et al.*, "Comparison of 68Ga-OPS202 (68Ga-NODAGA-JR11) and 68Ga-DOTATOC (68Ga-Edotreotide) PET/CT in patients with gastroenteropancreatic neuroendocrine tumors: evaluation of sensitivity in a prospective phase II imaging study." *Journal of Nuclear Medicine,* (2017).

93- Jae Seon Eo and Jae Min Jeong, "Angiogenesis imaging using 68Ga-RGD PET/CT: therapeutic implications." in *Seminars in Nuclear Medicine,* (2016), Vol. 46: *Elsevier*, pp. 419-27.

94- Steve Durante *et al.*, "Head and neck tumors angiogenesis imaging with 68 Ga-NODAGA-RGD in comparison to 18 F-FDG PET/CT: a pilot study." *EJNMMI research,* Vol. 10pp. 1-11, (2020).

95- Patrick M Colletti, "New Treatment Option: 223: Ra Chloride, the First Approved Unsealed α-Emitting Radiopharmaceutical." *Clinical nuclear medicine,* Vol. 38 (No. 9), pp. 724-25, (2013).

96- Giuseppe Boni *et al.*, "223Ra-chloride therapy in men with hormone-refractory prostate cancer and skeletal metastases: real-world experience." *Tumori Journal,* Vol. 104 (No. 2), pp. 128-36, (2018).

97- Emmanuel Deshayes *et al.*, "Radium 223 dichloride for prostate cancer treatment." *Drug design, development and therapy,* pp. 2643-51, (2017).

98- Thomas P Thamboo, Kong-Bing Tan, Shih-Chang Wang, and Manuel Salto-Tellez, "Extra-hepatic embolisation of Y-90 microspheres from selective internal radiation therapy (SIRT) of the liver." *Pathology,* Vol. 35 (No. 4), pp. 351-53, (2003).

99- Julien Edeline *et al.*, "Glass microspheres 90Y selective internal radiation therapy and chemotherapy as first-line treatment of intrahepatic cholangiocarcinoma." *Clinical nuclear medicine,* Vol. 40 (No. 11), pp. 851-55, (2015).

100- S Peter Kim, Claire Cohalan, Neil Kopek, and Shirin A Enger, "A guide to 90Y radioembolization and its dosimetry." *Physica Medica,* Vol. 68pp. 132-45, (2019).

101- I Kurilova *et al.*, "90 Y Resin Microspheres Radioembolization for Colon Cancer Liver Metastases Using Full-Strength Contrast Material." *Cardiovascular and interventional radiology,* Vol. 41pp. 1419-27, (2018).

102- The American Thyroid Association Taskforce on Radioiodine Safety Sisson *et al.*, "Radiation safety in the treatment of patients with thyroid diseases by radioiodine 131I: practice recommendations of the American Thyroid Association." *Thyroid,* Vol. 21 (No. 4), pp. 335-46, (2011).

103- Jacqueline Jonklaas *et al.*, "Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement." *Thyroid,* Vol. 24 (No. 12), pp. 1670-751, (2014).

104- Bryan R Haugen *et al.*, "2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer." *Thyroid,* Vol. 26 (No. 1), pp. 1-133, (2016).

105- Sarika Sharma, Baljinder Singh, Ashwani Koul, and Bhagwant Rai Mittal, "Comparative therapeutic efficacy of 153Sm-EDTMP and 177Lu-EDTMP for bone pain palliation in patients with skeletal metastases: patients' pain score analysis and personalized dosimetry." *Frontiers in medicine,* Vol. 4p. 46, (2017).

106- Narjess Ayati *et al.*, "Treatment efficacy of 153Sm-EDTMP for painful bone metastasis." *Asia Oceania Journal of Nuclear Medicine and Biology,* Vol. 1 (No. 1), p. 27, (2013).

107- ALBERTO ERNESTO HARDY PEREZ, EUGENIO TORRES GARCIA, CONSUELO ARTEAGA PEREZ, MARTHA PEDRAZA LOPEZ, ELENI MITSOURA, and KEILA ISAAC OLIVE, "Preliminary clinical experience of the systemic use of 153Sm-EDTMP as a pain palliation agent in arthrosis and as an option for bone scanning in patients with bone metastases."

108- Ana M Denis-Bacelar *et al.*, "Phase I/II trials of 186 Re-HEDP in metastatic castration-resistant prostate cancer: post-hoc analysis of the impact of administered activity and dosimetry on survival." *European journal of nuclear medicine and molecular imaging,* Vol. 44pp. 620-29, (2017).

109- Daiki Kayano and Seigo Kinuya, "Current consensus on I-131 MIBG therapy." *Nuclear medicine and molecular imaging,* Vol. 52pp. 254-65, (2018).

110- Francesco Giammarile, Arturo Chiti, Michael Lassmann, Boudewijn Brans, and Glenn Flux, "EANM procedure guidelines for 131 I-meta-iodobenzylguanidine (131 I-mIBG) therapy." *European journal of nuclear medicine and molecular imaging,* Vol. 35pp. 1039-47, (2008).

111- Oliver Sartor and Ken Herrmann, "Prostate Cancer Treatment: 177Lu-PSMA-617 Considerations, Concepts, and Limitations." *Journal of Nuclear Medicine,* Vol. 63 (No. 6), pp. 823-29, (2022).

112- Ting Bu *et al.*, "177Lu-PSMA-I&T Radioligand Therapy for Treating Metastatic Castration-Resistant Prostate Cancer: A Single-Centre Study in East Asians." *Frontiers in oncology,* Vol. 12(2022).

113- Amir Karimzadeh *et al.*, "177Lu-PSMA-I&T for treatment of metastatic castration resistant prostate cancer: prognostic value of scintigraphic and clinical biomarkers." *Journal of Nuclear Medicine,* (2022).

114- John J Zaknun *et al.*, "The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours." *European journal of nuclear medicine and molecular imaging*, Vol. 40pp. 800-16, (2013).

115- Clemens Kratochwil *et al.*, "225Ac-PSMA-617 for PSMA-targeted α-radiation therapy of metastatic castration-resistant prostate cancer." *Journal of Nuclear Medicine*, Vol. 57 (No. 12), pp. 1941-44, (2016).

116- Mathias Johannes Zacherl *et al.*, "First clinical results for PSMA-targeted α-therapy using 225Ac-PSMA-I&T in advanced-mCRPC patients." *Journal of Nuclear Medicine*, Vol. 62 (No. 5), pp. 669-74, (2021).

117- Eline L Hooijman *et al.*, "Development of [225Ac] Ac-PSMA-I&T for targeted alpha therapy according to GMP guidelines for treatment of mCRPC." *Pharmaceutics*, Vol. 13 (No. 5), p. 715, (2021).

118- Madhav Prasad Yadav, Sanjana Ballal, Ranjit Kumar Sahoo, and Chandrasekhar Bal, "Efficacy and safety of 225 Ac-DOTATATE targeted alpha therapy in metastatic paragangliomas: a pilot study." *European journal of nuclear medicine and molecular imaging*, pp. 1-12, (2022).

119- Mengqi Shi *et al.*, "Alpha-peptide receptor radionuclide therapy using actinium-225 labeled somatostatin receptor agonists and antagonists." *Front. Med*, Vol. 9p. 1034315, (2022).

120- Jingjing Zhang, Harshad R Kulkarni, and Richard P Baum, "225Ac-DOTATOC–Targeted Somatostatin Receptor α-Therapy in a Patient With Metastatic Neuroendocrine Tumor of the Thymus, Refractory to β-Radiation." *Clinical nuclear medicine*, Vol. 46 (No. 12), pp. 1030-31, (2021).

121- Clemens Kratochwil *et al.*, "Dosing 225Ac-DOTATOC in patients with somatostatin-receptor-positive solid tumors: 5-year follow-up of hematological and renal toxicity." *European journal of nuclear medicine and molecular imaging*, Vol. 49 (No. 1), pp. 54-63, (2021).