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# Radiopharmaceuticals in Modern Cancer Therapy

*Aisyah Elliyanti*

## Abstract

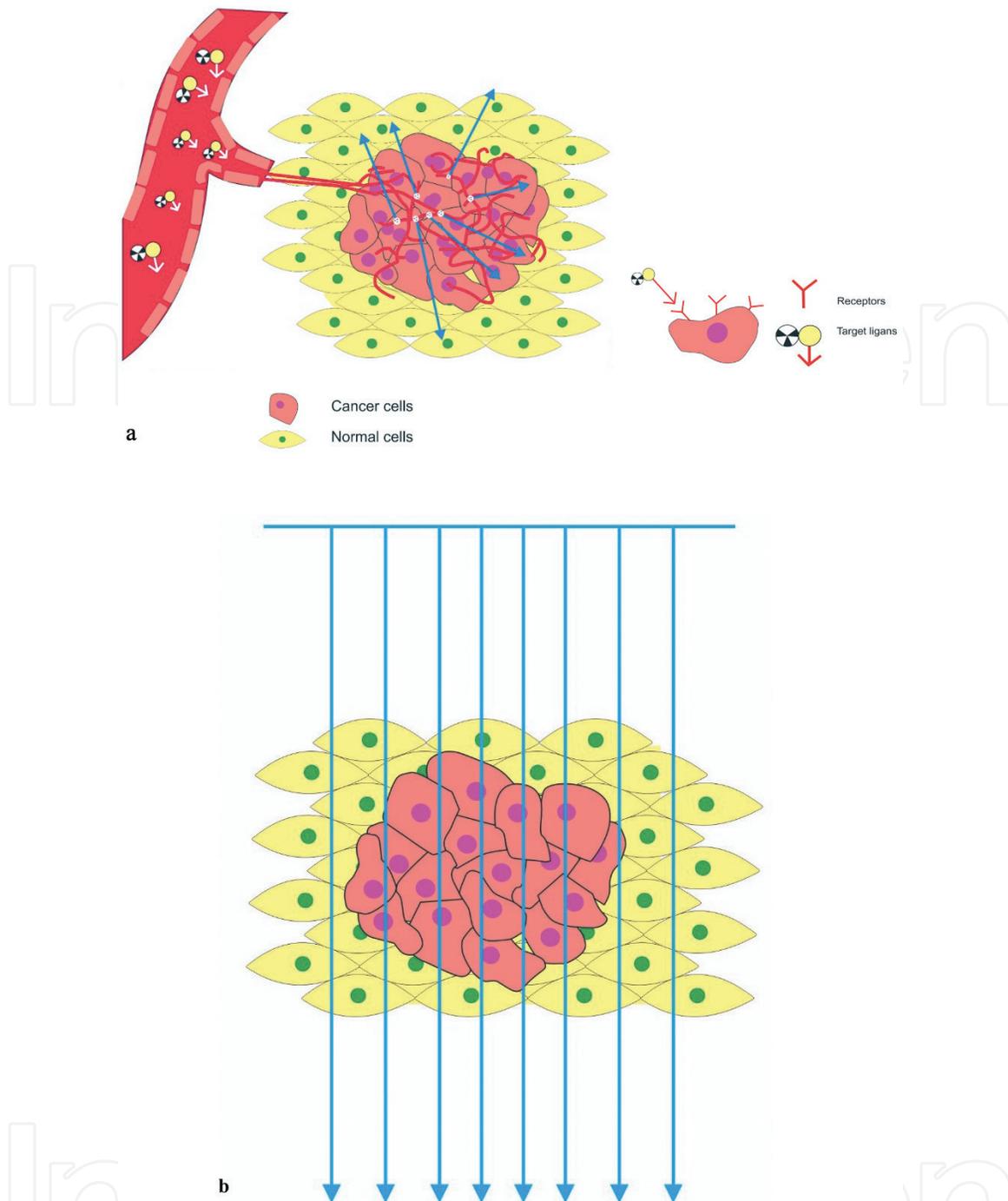
Nuclear medicine plays a role in oncology. It uses tracers (radiopharmaceuticals) to study physiological processes and treat diseases. The radiopharmaceuticals can be formed as radionuclides alone or radionuclides labeled with other molecules as a drug, a protein, or a peptide. The radiopharmaceutical is introduced into the body and accumulates in the target tissue of interest for therapy or imaging purposes. It offers to study cancer biology in vivo to optimize cancer therapy. Another advantage of radiopharmaceutical therapy is a tumor-targeting agent that deposits lethal radiation at tumor sites. This review outlines radiopharmaceuticals agents in current cancer therapy.

**Keywords:** radionuclides, beta particles, alpha particles, auger electron, radioimmunotherapy, peptide receptor radionuclide therapy

## 1. Introduction

Usage of radiopharmaceuticals has increased in recent decades, mainly for the treatment of cancer diseases [1]. However, the oncology community is still unfamiliar with radiopharmaceutical therapy (RPT). Compared with all other systemic cancer treatment options, radiopharmaceuticals have an efficacy result with minimal toxicity [2]. The radiopharmaceutical therapy application introduces new tumor-targeting agent therapy, different from external radiotherapy (**Figure 1**). It quantifies radioactivity distribution in tumor sites and in vivo detection [2]. The advantages of RPT are: firstly, it is targeted into tumor, included metastasis sites. Secondly, the high linear energy transfer (LET) radionuclides are effectively killed the radioresistant hypoxic cells. Thirdly, relatively lower whole-body absorbed dose [3–5]. The therapy might be used as adjuvant therapy with or after other treatment options such as chemotherapy and surgery [6, 7]. In controlling the symptoms, shrink and stabilize the tumors for systemic metastatic cancer, where conventional radiotherapy or chemotherapy is impossible, RPT can be a choice, especially for patients who no longer respond to other treatments [2, 6].

The radiopharmaceuticals can be in the form of radionuclides alone or radionuclides labeled (radiolabeled) for imaging or therapy. They can be labeled with molecules such as a drug, a protein, or a peptide for the therapy. Physical and biochemical characteristics of radiopharmaceuticals/radionuclides should be considered for treatment purposes. The physical characters are included physical half-life, energy radiation(s), type of emissions, daughter product(s), production method, and radionuclide purity [6, 8]. The biochemical characteristic includes tissue targeting, radioactivity retention in the tumor, in vivo stability, toxicity and the



**Figure 1.** Radiopharmaceutical therapy versus external radiotherapy. In RPT, radionuclide has administrated intravenous delivery to the targeted tumor. The tumor cells will receive an absorbed dose which is exponentially decreasing over the period. The dose is delivered per cell by emissions originating from cells is influenced by the range of the emissions. When the range of the emitted particle is much longer than the dimension of the cell, periphery tumor cells of tumor mass will receive absorbed dose and crossfire dose from other target cells, and it caused a crossfire dose to normal tissue. However, the response of the normal cell will differ from the tumor cell (a). In external radiotherapy, radiation delivers the same absorbed dose per cell regardless the number of cells (b).

effective half-life within the patient's body [2]. A convenience range of the physical half-life of radionuclide is between 6 hours and seven days [9]. A very short physical half-life has a limitation due to the delivery time, and a long half-life of radiopharmaceuticals will expose the surrounding environment to more time radiation. The physical half-life should not too long, but it should have sufficient retention time. So, the radiation can be delivered to the tumor efficiently [1]. On the other hand, when the biological half-life is too short, the radionuclide will be discharged with significantly high activity. Therefore, for efficient radiation delivery for therapy

purposes, a balanced optimal biological and physical half-life should be considered, besides the type of tumor, method of administration, and uptake mechanism [1, 6]. Radionuclides radiations as alpha ( $\alpha$ )-particle (50–230 keV/ $\mu$ m) and beta ( $\beta$ )-particle (0.2 keV/ $\mu$ m), and Auger electrons (4–26 keV/ $\mu$ m) are used for therapy purposes [1, 3, 6, 10, 11]. These particles allow ionization per travel length, and they are fully deposited within a small range of tissue. The distance traveled, and the energy deposited in cells is vital that lead the most efficient route for cell destruction is the direct interaction of ionization events with DNA.

Some  $\beta$ -emitter radionuclides also decay  $\gamma$ -particle, which is used for imaging. Radionuclides that emit  $\alpha$  or  $\beta$ -particles are preferred for the treatment of bulky solid tumors, and radionuclides that emit Auger electrons are considered for the treatment of tiny clusters of cancer cells or small tumor deposits because of their high-level cytotoxicity and short-range biological effectiveness [3]. The other factor that needs to be considered is the daughter product of the radionuclides. If the daughter product is unstable, it should be short-life and may decay within hours into a stable product, and un-stable daughter nuclide will contribute to the amount of absorbed dose. Radiopharmaceuticals' biochemical characteristics are selective tumor target concentrations and have optimal retention time in the tumor and avoid uptake in the normal cells [6, 9]. Depending on the tumor uptake mechanism, either by bone deposition, protein binding, or metabolic uptake, the ratio concentration of radionuclides on the tumor to normal tissues should be as optimal as possible [6]. The other factors that have to be considered are the radionuclides particles' size, low toxicity, specific gravity for optimal flow and distribution, and clearance rate [6, 12–16].

Iodine-131 ( $^{131}\text{I}$ ) was one of the first radionuclides used for therapy in clinical oncology, especially for thyroid cancer patients. Phosphorous-32 ( $^{32}\text{P}$ ), strontium-89 ( $^{89}\text{Sr}$ ), and yttrium-90 ( $^{90}\text{Y}$ ) also have been used for the treatment of benign and malignant diseases [6, 17, 18]. Various alpha- and beta-radiation-emitting isotopes are used lately. Most of them are labeled with peptides and antibodies for specific tumor targeting, where radiopharmaceuticals are used as vehicles to deliver ionizing radiation to the tumor tissue. This review discusses radiopharmaceuticals are used for therapy and their application in the modern era of cancer therapy.

## 2. Radionuclides

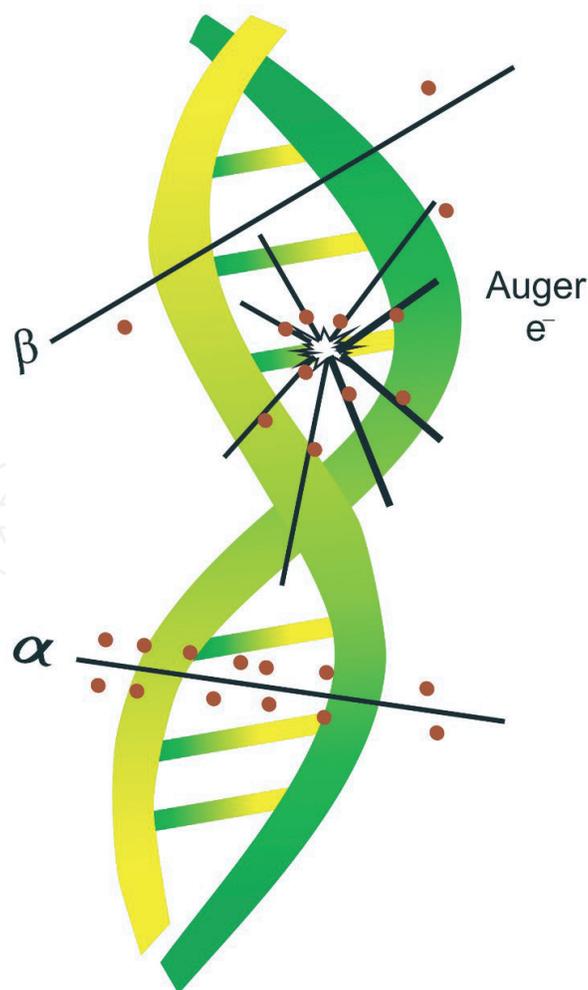
The growth in nuclear medicine has been stimulated by introducing several new radionuclides and radiopharmaceuticals. They have been used to treat benign and malignant tumors. Types of radiation that are relevant to RPT are electrons and  $\alpha$ -particles. Electron emissions are classified by energy and by the type of decay; Auger electrons, beta ( $\beta$ )-particles are related to RPT [2]. Currently,  $\beta$  particle emitters radionuclides are mostly used for therapy purposes. However, they have a limitation of radiobiological properties. An alpha particle emitting as a new generation radionuclides is being developed, with advantages in high energy and a short path length, which show higher efficacy [19]. Below we discuss the physical differences between a beta particle, Auger electrons, and an alpha particle.

### 2.1 Beta particles

Beta particles are produced in the beta decay process, wherein an unstable nucleus, a neutron, is converted to a proton, creating an energetic electron (beta particle) [2, 19]. They are the most frequently used for RPT agents and widely available. Many of them also emit photon energy that is easily imaged. Beta particles are negatively charged and have a relatively long path length from 0.0 to 12 mm.

They have low linear energy transfer (LET) of approximately  $0.2 \text{ keV}/\mu\text{m}$ , and more particles are required for a similar absorbed dose as alpha particles (**Figure 2**). For high energy beta, like  $^{90}\text{Y}$  and  $^{188}\text{Re}$ , which they energy  $2.28 \text{ MeV}$  and  $2.21 \text{ MeV}$  respectively (**Table 1**), they can cause crossfire doses to neighbor cells. So, they are preferable for higher volume solid tumors, poorly perfuse tumors, and less suited for targeting micro-metastases [3, 8, 23]. For the small tumor, low-energy  $\beta$ -rays such as lutetium-177 ( $^{177}\text{Lu}$ ) would be more  $\beta$ -emitting efficient [8].

The most familiar and frequent beta particle used is iodine-131 ( $^{131}\text{I}$ ) for hyperthyroidism and thyroid cancers therapy [20, 24, 25]. Subsequently, samarium-153, lutetium-177, yttrium-90 and have been introduced over the last 40 years (**Table 1**) [2]. Several other  $\beta$ -emitting radionuclides have been investigated or considered. However, those agents have not widely adopted, related to several reasons: limited availability, complex radiochemistry process, or the absence of a commercial products [26]. A variety of reasons for the shift to different radionuclides of the different  $\beta$ -particle emitters used over time. For example, an early evaluation of changing to different radionuclides was based on the tumor to non-tumor-absorbed dose ratio [2].  $^{90}\text{Y}$  has a high-energy  $\beta$ -particle, and it is widely available like  $^{131}\text{I}$  iodine. It was used in colloidal form, mainly for rheumatoid treatment [27, 28].  $^{90}\text{Y}$  labeled antibodies initially focused on ovarian cancer, followed by hematological cancers and radiolabeled peptide therapy [2, 29, 30].  $^{90}\text{Y}$  is a popular radionuclide for RPT because of the clinical impact of  $^{90}\text{Y}$ -impregnated microspheres used for hepatic metastases therapy [31–33]. Lutetium-177 becomes



**Figure 2.**

*Linear energy transfer alpha and beta particles and auger electron on DNA. Alpha particles have high LET ( $\sim 80 \text{ keV}/\mu\text{m}$ ) compared with the low LET ( $\sim 0.2 \text{ keV}/\mu\text{m}$ ) of beta particles, and auger electron intermediate LET  $4\text{--}26 \text{ keV}/\mu\text{m}$ . Thus, alpha particles result in more double-strand breaks in DNA.*

Radionuclides	Mode of decay	Physical half-life	Energy (KeV)	Indication
<sup>223</sup> Ra	α	11.44 d	5979.2	Bone pain palliation
<sup>211</sup> At	α (41.8.9) EC(58.2)	7.21 h	5870–7450	Clinical trials in glioblastoma, ovarian cancer, blood-borne cancers
<sup>212</sup> Bi	α (35.9) β <sup>-</sup> (97.8)	60.55 mins	6051–8785	Clinical trials in prostate cancer, ovarian cancer, pancreatic cancer, neuroendocrine tumor.
<sup>213</sup> Bi	α (2.2) β <sup>-</sup> (64.1)	46.61 mins	5875–8376	Clinical trials in acute myeloid leukemia (AML), prostate cancer, lymphoma, melanoma, glioblastoma, neuroendocrine tumor and bladder cancer.
<sup>225</sup> Ac	α	10 d	5732–5830	Clinical trial in AML, breast cancer, ovarian cancer, prostate cancer, glioblastoma, neuroblastoma.
<sup>227</sup> Th	α	18.68 d	5709–6038	Clinical trial in AML, NHL, breast cancer, ovarian cancer.
<sup>131</sup> I	β <sup>-</sup>	8.02 d	606	Hyperthyroidism, thyroid cancer, Radioimmunotherapy (RIT) for non-Hodgkin's lymphoma (NHL) and neuroblastoma, pheochromocytoma, carcinoid, medullary thyroid cancer
<sup>32</sup> P	β <sup>-</sup>	14.26 d	1710	Polycythemia vera, keloid, cystic craniopharyngioma.
<sup>89</sup> Sr	β <sup>-</sup>	50.53 d	1496	Bone pain palliation
<sup>90</sup> Y	β <sup>-</sup>	64.10 d	2280	Liver metastasis, hepatocellular carcinoma, RIT for NHL, neuroendocrine tumor
<sup>153</sup> Sm	β <sup>-</sup>	46.50 h	808.2	Bone pain palliation, synovitis
<sup>169</sup> Er	β <sup>-</sup>	9.4 0d	350	Synovitis
<sup>177</sup> Lu	β <sup>-</sup>	6.73 d	497.8	Synovitis and RIT for various cancer
<sup>186</sup> Re	EC,β <sup>-</sup>	3.72 d	1069.5	Bone pain palliation, arthritis Bone pain
<sup>188</sup> Re	β <sup>-</sup>	17.00 h	2120.4	Bone pain palliation, RIT for various cancer, rheumatoid arthritis

**Table 1.** Characteristics of alpha and beta emitters radionuclides for therapy [6, 8, 20–22].

popular because it emits photons in the 100–200-keV optimal imaging range and has a β-particle energy between <sup>131</sup>I and <sup>90</sup>Y, which is appropriate for therapy, particularly for small tumors [2, 8]. All these factors, along with a half-life that is compatible with the pharmacokinetics of both antibodies and peptides. It is a reactor production and widely available, with relatively straightforward conjugation chemistry [2]. Samarium-153 (<sup>153</sup>Sm) is a β-emitting radionuclide that is used for palliative treatment in breast and prostate cancer with bone metastases, and other primary cancers [34, 35]. Radiopharmaceuticals therapy agent that uses the ethylenediamine-tetra-methylene-phosphonic acid (EDTMP) chelator, binding samarium-153 through six ligands (four phosphate groups and two amines) is FDA approved. <sup>153</sup>Sm alternative formulation as <sup>153</sup>Sm-DOTMP (1,4,7, 10-tetraazacyclododecanetetramethylenephosphonic acid), which is thought to have a more favorable chelant-to-metal ratio [2].

## 2.2 Auger electrons

Auger electrons are generated from suborbital transitions. They are typically very short-range emissions, of the order of 1–1000 nm, depending on their emission energy. Auger electron is intermediate (4–26 keV/μM) of LET [3, 22, 23]. These emissions could be highly cytotoxic if the RPT drug localizes within the cell nucleus [36, 37]. Bromine-77, indium-111, iodine-123, and iodine-125 are the most commonly used Auger electron emitters. In vitro studies had shown highly effective and specific tumor cell killing when they labeled with targeting vehicles that can localize these subcellular-range radiations close to cellular DNA [38, 39]. Human studies using locoregional administration showed promise regarding tumor cell incorporation of the Auger emitters [2]. However, Auger electron-emitter RPT has not been widely adopted yet. Besides, auger electron agents must be incorporated into the DNA, and their unfavorable pharmacokinetics might be the reasons for the lack of efficacy. Technological developments that could overcome those factors will interest RPT development [2].

## 2.3 Alpha particle

Alpha particles have a similar structure to a  $^4\text{He}$  nucleus without surrounding electrons (sometimes denoted as  $\text{He}^{2+}$ ) [19]. They are produced in alpha decay and emitted from the nucleus of a radioactive atom [2, 40]. Alpha particles have higher energy (4–9 MeV) and travel in tissue over a few cell diameters. Thus, the particle range is equivalent to the thickness of 1–3 cell widths (40–100 μm) [1, 2, 40]. They have high LET (~100 keV/μm) throughout their range and three times greater at the end of the path range (the Bragg peak) [19, 40]. Intracellular accumulation of the alpha particle effectively creates double-strand breaks (DSBs) in DNA [2, 40]. The cytotoxicity of α-particles is thus considered much higher than that of β-particles (**Figure 2**). Another advantage of α-particles compared with β-particles is the short distance traveled by the ionization products, reducing the damage to healthy surrounding cells. Moreover, the effect is not dependent on dose and oxygen concentration during any cell cycle (**Table 2**) [1].

Targeted alpha therapy (TAT) is an attractive therapeutic option for multiple micro-metastases. It has many advantages, such as easy administration, the ability

	Alpha particle	Beta particle
Type of particle	$^4\text{He}$ nucleus	Energetic electron
Particle energy	4–9 MeV	50–2,300 keV
Particle path length	40–100 μm	0.05–12 mm
Linear energy transfer	~80 keV/μm	~0.2 keV/μm
Hypoxic tumors	Effective	Less effective
Toxicity	effective in creating double strand breaks (DSBs) in DNA	high dose rates (tumor survival rates close to linear exponential) low dose rates (single-strand breaks (repairable) with shouldering of the dose–response curve
Bystander effect	Yes	Yes
Tumor cross-fire	Low	Yes
Tumor size	Micro/small	Solid high tumor volume

**Table 2.**

*Physics and biology characteristic of alpha and beta particles [2, 19, 40, 41].*

to treat multiple lesions simultaneously, and the possibility of combining with other therapeutic approaches, and primarily for cancer treatment. By attaching an  $\alpha$ -particles to a biological molecule with targeting capabilities, such as a monoclonal antibody (mAb), with the help of a bi-specific chelating agent or bonding it to a disease-targeting vector, and the vector used as a targeting agent. In this way, RPT selectively delivers a high radiation dose directly to the target, with generally limited toxicity to the surrounding normal tissues. Advances in understanding tumor biology, together with progress in mAb technology, chemical labeling techniques, and other related disciplines, provide significant advances in developing of new clinical applications of  $\alpha$ -particles radionuclides in novel therapeutic agents [1, 2, 42].

The  $\alpha$ -particles are used for RPT over 40 years included as bismuth-212 ( $^{212}\text{Bi}$ ), bismuth-213 ( $^{213}\text{Bi}$ ) and astatine-211 ( $^{211}\text{At}$ ), actinium-225 ( $^{225}\text{Ac}$ ), radium-223 ( $^{223}\text{Ra}$ ) and thorium-227 ( $^{227}\text{Th}$ ) as shown in **Table 1** [2].  $^{223}\text{RaCl}_2$  is the first alpha-emitting radiopharmaceutical for prostate and breast cancer patients' bone pain palliation [2, 3, 8, 19, 40]. The energetic  $\alpha$ -particles emitted by  $^{223}\text{Ra}$  can generate irreparable DNA DSBs in the adjacent osteoblasts and osteoclasts, leading to their death. The results in detrimental effects on the neighboring cells, inhibit abnormal bone formation, both at a cellular level and a signaling level, ultimately negatively affect tumor growth [2].  $^{223}\text{Ra}$  is being studied in combination with other cytotoxic agents such as docetaxel (DORA trial), poly(ADP-ribose) polymerase inhibitors (olaparib), and new androgen axis inhibitors as enzalutamide and abiraterone citrate. It is also being explored in combination with immuno-oncology agents such as pembrolizumab and in combination with external-beam radiotherapy [2].

Bismuth-213 ( $^{213}\text{Bi}$ ) and astatine-211 ( $^{211}\text{At}$ ) labeled monoclonal antibodies in patients with leukemia and brain tumors, respectively [3, 22]. Moreover,  $^{225}\text{Ac}$  and  $^{213}\text{Bi}$  labeled somatostatin receptor (SSR) are preclinical and clinical trials [1, 19, 40].  $^{213}\text{Bi}$  has a short half-life and can be produced from the generator, and because of that, it is required on-site labeling to produce TAT compound. The short half-life of  $^{213}\text{Bi}$  has some advantages as higher dose rates given over a short period are more effective than low dose rates given over a longer period [19, 40]. Studies reported that  $^{213}\text{Bi}$  had been labeled with DOTA peptides in preclinical and clinical trials with >99% purity [1, 19].

Furthermore, also there is a growing interest in using  $^{225}\text{Ac}$  as a therapeutic alpha particle source. It is produced via the neutron transmutation of  $^{226}\text{Ra}$  or decay of  $^{233}\text{U}$  [19]. The type of production caused  $^{225}\text{Ac}$  has a lack the capacity of clinical use of labeled peptide. So, production via a high-energy proton accelerator at multiple sites will overcome  $^{225}\text{Ac}$  labeled to treat neuroendocrine tumors. It has been labeled with PSMA with a radiochemical purity of >98% to treat prostate cancer [19].  $^{225}\text{Ac}$  labeled antibodies are being tested in advanced myeloid malignancy [8].  $^{225}\text{Ac}$  shows a potential appealing radionuclide for TAT, and post-therapy imaging of  $^{225}\text{Ac}$  is possible, although images are also suboptimal [19, 40, 41].

The results of clinical trials using TAT indicate that this treatment strategy presents a promising alternative for targeted therapy of cancer [22]. Lately, it has been gaining popularity that TAT to be a successful treatment in prostate cancer in patients refractory to  $^{177}\text{Lu}$  prostate-specific membrane antigen (PSMA) [19]. Therefore, alpha-emitters and Auger electron emitters ( $^{77}\text{Br}$ ,  $^{111}\text{In}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ) are getting more attention for targeted therapy lately. Auger electron and alpha-emitter are intermediate (4–26 keV/ $\mu\text{M}$ ) and high (50–230 keV/ $\mu\text{M}$ ) of LET radiation respectively. They deliver the radiation dose within the short range of the tissue (~ tens microns) have an actual tumor cell killing if they can be conjugated with suitable ligands that effectively targeted micro-metastasis therapy [3, 22, 23].

### 3. The concept of therapy

Various alpha- and beta-radiation-emitting isotopes for therapy are mostly labeled with peptides or antibodies for specific tumor targeting, which are used only as vehicles to deliver ionizing radiation to the tumor tissue. The vehicle concentrates radioactivity at the tumor tissue expressing specific tissue elements and avoiding concentrating at normal cells [2, 7, 10]. Different radioligands are being developed and investigated for uniquely targeting molecular receptors or intracellular components that currently lead to planning personal patient-tailored therapy [43]. Radionuclides are coupled to ligands that recognize and bind the tumor-associated molecules, ensuring the precise targeting of cancerous cells that can be used for therapeutic approaches and live-monitoring of treatment efficacy [43].

### 4. Radioimmunotherapy (RIT)

Radioimmunotherapy (RIT) is targeting therapy using radionuclide labeled with specific mAbs directed against tumor antigens [6, 8]. The antibody is primarily a delivery vehicle of radiation to tumors sites. Besides therapy, radionuclide combines with mAbs has been used for imaging. The imaging provides specific non-invasive information regarding the expression, location, and modulation of targets. The therapeutic effect of RIT is achieved by tissue absorption of the energies from continuous radiation emitted from the radionuclides tagged to mAbs. More specific bound between antibody and tumor antigen increase the dose delivered to tumor cells and, at the same time, reduce the dose to normal cells [6]. RIT has been evaluated in clinical trials across the full spectrum of malignancies [8].

The type of radioactive combines with mAb depends on emission characteristics, the radiolabeling chemistry, and the malignancy of cells targeted [8]. Beta and alpha emitter particles are labeled with mAbs. However, alpha emitters have limitations in practice due to mostly very short half-life (**Table 1**) [41]. For optimal therapy, the residence time of RIT ranges from a few days to weeks, which reach optimal tumor-to-background ratios 2–4 days post-injection. Radionuclides labeled mAbs bind several antigens and receptors expressed on the surface of tumor cells. They include CD20, prostate-specific membrane antigen (PSMA), human epidermal growth factor receptor 2+ (HER2+), mucin 1 (MUC1), epidermal growth factor receptor (EGFR), tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), and et cetera [8].

Radioimmunoconjugates targeting CD20 have been approved to treat non-Hodkin's lymphoma ( $^{90}\text{Y}$ -ibritumomab tiuxetan and  $^{131}\text{I}$ -tositumomab) [6, 8]. Both radiolabeled mAbs are more efficacious at inducing remissions than the respective unlabeled molecules and are also more effective than earlier courses of chemotherapy in these patients [8]. Other potentials of RIT include lung, pancreatic, stomach, ovarian, breast, colorectal cancers, leukemia, high-grade brain glioma [6]. On the other hand, the application of RIT for solid tumors has been less successful than in patients with malignant lymphoma. Several problems have to be addressed to its efficacy:

1. Higher solid tumor volume indicates lower radiosensitivity compare to small volume tumors usually.
2. The delivery of therapeutic radionuclide to solid tumors might be less effective. It can be by poor perfusion, elevated intra-tumoral hydrostatic pressure, and heterogeneous radionuclide uptake by tumor cells.

3. Furthermore,  $^{223}\text{Ra}$ -chloride showed that these limitations could be successfully circumvented in patients with castration-resistant prostate cancer and bone metastases. RIT therapy may become an effective treatment modality for disseminated solid tumors in the future [8].

## 5. Peptide receptor radionuclide therapy (PRRT)

Several radionuclides have been used for peptide therapy in neuroendocrine tumor (NET) patients. The expression of peptide receptors on various tumor cells, including NETs, was significantly higher than normal tissues or cells [25]. Over the last decade, such receptors have become recognized targets for molecular imaging and therapy because they are expressed on the cell surface. Upon binding a ligand, the receptor-ligand complex is internalized. Radiolabeled peptide ligands are known to be used for imaging and somatostatin receptor therapy (SSTR) [25].

Peptide receptor radionuclide therapy (PRRT) has been known to be an effective systemic treatment of patients with advanced, metastatic, or inoperable, slowly progressing NETs with high somatostatin receptor expression. The principles behind PRRT efficacy are the somatostatin receptor ligand that binds the specific receptor (SSTR1–5). Particularly, SSTR2 overexpressed on the surface of neuroendocrine tumor cells. The high energy of  $\beta$ -particle ( $^{90}\text{Y}$  or  $^{177}\text{Lu}$ ) labeled to a somatostatin receptor (SSTR) ligand caused cell death through direct or indirect DNA damage of target cells (self-dose) or neighboring cells (crossfire effect) [42]. The binding of the radiopharmaceutical to the targeted cells will be indispensable when using Auger emitters. Beta-particles become more effective in damaging and killing target cells that radiopharmaceutical is bound to and several cells around the target. It is the so-called “crossfire” effect. Lower tissue penetration of  $^{177}\text{Lu}$  favors the use in small-sized tumors, whereas, in larger tumors,  $^{90}\text{Y}$  might be a better choice [25].  $^{117}\text{Lu}$  or  $^{90}\text{Y}$  labeled DOTATATE (DOTA, Tyr(3)-octreotate) was the most widely used peptide. It is a higher SSTR2 affinity compared to DOTATOC (DOTA, D-Phe1, Tyr (3)-octreotide) and DOTANOC (DOTA, 1-Nal(3)-octreotide) [43].

Furthermore, targeted peptide receptor alpha therapy with  $^{213}\text{Bi}/^{225}\text{Ac}$  has been clinically tested to treat brain tumors, neuroendocrine tumors, and prostate cancer.  $^{213}\text{Bi}$  and  $^{225}\text{Ac}$ -DOTA chelated peptides developed for peptide receptor radiotherapies, such as DOTA-Substance P targeting the neurokinin-1 receptor and the widely used somatostatin-analogs (e.g., DO-TATOC, DOTATATE). The complexation efficiency, in vitro and in vivo stability of the radiopeptides is high [1, 44]. However, these promising results still need to be confirmed in further studies with therapeutic activities  $^{213}\text{Bi}$  and  $^{225}\text{Ac}$ .

## 6. Prostate-specific membrane antigen (PSMA)-targeting ligands

After promising results with  $^{131}\text{I}$ -labeled prostate-specific membrane antigen (PSMA) ligands for prostate cancer therapy, it was introduced  $^{177}\text{Lu}$ -PSMA by the German Cancer Research Center in 2015 [45]. PSMA is known as folate hydrolase 1 (FOLH1) or glutamate carboxypeptidase II (GCP II) and is overexpressed on the membrane of prostate cancer cells [45–47]. It remains high even after multiple lines of therapy [45, 46]. Metastatic castration-resistant prostate cancer (mCRPC) patients who shown ineffective by chemotherapy, radioligand therapy targeting the PSMA is a promising therapy approach [41, 45, 46]. First data showed that  $^{177}\text{Lu}$ -PSMA is safe and effective in reducing tumor burden. It has been widely adopted in German and international sites, with likely more than a thousand therapy cycles performed [45].

PSMA targeting ligand using the beta emitter lutetium-177 [<sup>177</sup>Lu]Lu-PSMA-617 or [<sup>177</sup>Lu]Lu-PSMA-I&T) are currently being tested in phase III trials. It revealed encouraging data in several studies in mCRPC patients [46, 48, 49]. PSMA-targeting ligand using alpha emitters as actinium-225 may be advantageous compared to PSMA-targeting ligand with beta emitters. Clinical studies using <sup>225</sup>Ac-labeled PSMA-ligands ([<sup>225</sup>Ac]Ac-PSMA-617 or [<sup>225</sup>Ac]Ac-PSMA-I&T) have reported remarkable therapeutic results lately. However, it shows more substantial radiobiological effect of alpha particles on the organs at risk [46]. Combining alpha emitters in adjusted doses with beta emitters called ‘tandem therapy’ may reduce these significant adverse effects compared to using alpha emitters alone [46]. Furthermore, a novel alpha therapy approach with a thorium-227-labeled PSMA antibody shows strongly in vitro potency in several PSMA-positive cell lines and in vivo efficacy in xenograft models of prostate cancer [47]. These treatment approaches need more studies for effectiveness and limited toxicity.

## **7. Future prospective, challenges in radiopharmaceutical therapy**

Radiopharmaceutical targeted therapy is a promising tumor treatment, particularly  $\alpha$ -emitter, for effective and rapid cancer therapy due to the localized cell killing originated from high LET and short ranges of particles [8, 41]. Strategies to combine  $\alpha$ -emitter with immunomodulators demonstrated higher tumor growth inhibition than  $\alpha$  therapy alone [44].

Furthermore, intelligent drug delivery agents apart from peptides, small molecules, mAb, and mAb fragments can also achieve target-specific cancer therapy [41]. They are among the most searched cancer treatment issues due to their desired properties, including tumor-targeting uptake, bio-compatibility, reducing side-effects, and nonspecific uptake and distribution. So, the main problem of targeted radionuclide therapy, such as the radiation exposure effect in healthy tissues upon the emission of the particles, can be removed significantly. The number and variety of studies about the delivery of radionuclides particles by drug delivery agents are still limited. The studies will probably increase considerably in the future due to the need for effective, rapid, and personalized cancer therapy approaches.

Regarding supply issues of radionuclides also need to be address. Some main reactors in the world now are aging, which affect to constant and reliable supply globally [6]. In particular, for  $\alpha$ -particle-emitting radionuclide (such as actinium-225), the supply is considered a potential obstacle for the growth of RPT. Some opinions suggest that the supply problems are transient technical issues that will be resolved with a more significant investment if RPT is adopted as a mainstream cancer therapy [2]. RPT is an effective cancer treatment, particularly when other standard therapeutic approaches have failed. However, even more than 40 years of clinical investigation, RPT has not become a part of cancer treatment in the same way as other therapy approaches. Even though ‘targeted’ cancer therapies are associated with clinical trial failure rates of 97%, but experience with RPT was ignored mainly or presented as a burdensome multidisciplinary endeavor [2, 50]. Additionally, public perception and fear of radioactivity and the perceived complexity of the treatment are challenges in developing and applying RPT.

## **8. Conclusions**

Radiopharmaceutical therapy is a safe and effective targeted approach to treating many types of cancer. Compared to other systemic cancer treatment options, RPT has shown efficacy with minimal toxicity. Different types of radionuclides

relevant to the purpose are  $\beta$ -emitters, Auger electrons, and  $\alpha$ -emitters. However, the targeted  $\alpha$ -emitter has potential advantages over  $\beta$ -emitter therapy due to the high energy and short path length of  $\alpha$  emissions causing double-stranded breaks in DNA and the relative tolerance to cell cycle effects and hypoxic conditions. Radionuclides are coupled to ligands that recognize and bind the tumor-associated molecules, ensuring the precise targeting of cancerous cells that can be used for therapeutic approaches and live-monitoring of treatment efficacy. Different radioligands are developed for uniquely targeting molecular receptors or intracellular components that currently lead to planning personal patient-tailored therapy in modern cancer therapy management.

### Author details

Aisyah Elliyanti<sup>1,2</sup>

1 Department of Medical Physics, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

2 Department of Radiology, Division of Nuclear Medicine, Dr. M. Djamil Hospital, Padang, Indonesia

\*Address all correspondence to: [aelliyanti@med.unand.ac.id](mailto:aelliyanti@med.unand.ac.id)

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