

# Radiolabeled Peptide as Diagnostic, Therapeutic, and Theranostic agents for Prostate Cancer: Systematic Literature Review

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**ABSTRACT:** Prostate cancer (PCa) is the most common sex-related malignancy and the second most common cause of mortality after lung cancer for men. Around 61.8% of Indonesian people undergo cancer treatment with surgery. This study aimed to figure out the use of radiolabeled peptides for diagnosis, therapy, and theranostics of prostate cancer. This study performed a literature review by searching the web databases such as PubMed, MDPI, Elsevier (Science Direct), and ACS Publications. The result showed that peptide compounds such RM2, VCN (Vicrostatin), DB15, and BBN7-14 were utilized as radionuclide-carriers for diagnostic imaging, meanwhile, peptides such as NeoBOMB1, PSMA-617, and [RGD-Glu-[DO3A]-6-Ahx-RM2] containing alpha or beta-emitted radionuclide were used as therapeutic and theranostic agents. They were tagged using  $^{68}\text{Ga}$ ,  $^{161}\text{Tb}$ ,  $^{177}\text{Lu}$ ,  $^{64}\text{Cu}$ ,  $^{124}\text{I}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{90}\text{Y}$ , and  $^{86}\text{Y}$  radionuclides. Great efforts have been conducted in developing peptide-based radiopharmaceuticals for diagnosis and therapy of prostate cancer. Research groups focusing in nuclear medicine will continue to develop radiopharmaceuticals in the future, especially radiopeptide compounds for the diagnosis and therapy of prostate cancer.

**KEYWORDS:** Radiolabelled-peptide; therapy; diagnosis; prostate cancer.

## 1. INTRODUCTION

As time goes by, the pattern of human life is getting worse. This is evidenced by the increasing number of new diseases, such as cancer. Cancer is a disease characterized by the presence of abnormal cells that can grow uncontrollably and have the ability to invade and move between cells and body tissues (Pangribowo, 2019). Data from the *Global Burden of Cancer* (GLOBOCAN) released by the World Health Organization (WHO) states that in the worldwide an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths. Among them around 7.3% of patients were diagnosed prostate cancer (Sung, 2021). Deaths from cancer are expected to continue to increase to more than 13.1 million by 2030 (Pangribowo, 2019).

Prostate cancer (PCa) is the most common sex-related malignancy and the second most common cause of death after lung cancer that is around 10% of all tumors in men (Siegel, 2019; Li, 2020). The type of cancer treatment undertaken by cancer patients depends on the type and stage at the time of diagnosis. In some cases, patients undergo more than one treatment method. The results of Riskesdas 2018 showed that around 61.8% of Indonesian-cancer patients used surgery for therapy. Patients also chose other treatment methods, namely chemotherapy (24.9%) and radiation (17.3%) (Pangribowo, 2019).

Nuclear Medicine is a medical specialty that diagnoses and treatments diseases using radiolabeled compounds. Doctors use radiopharmaceuticals to diagnose, evaluate, and treat various diseases such as cancer, neurologic disorder, and heart disease (Rosilawati, 2018; Touijer, 2019). The carrier of radionuclides for diagnosis and therapy including small molecules, peptides, affibody molecules, and antibodies should have a high affinity to the molecular target. Some of them approved by Food and Drug Administration (FDA) not only for prostate-cancer diagnosis but also for therapy. Based on the description above, this study was conducted to determine the use of peptide-based radiotracers for the diagnosis and therapy of prostate cancer by conducting a literature search from several databases.

### 1.1 Aim of the review

This study aimed to identify peptides as the radionuclide carriers targeting prostate cancer as diagnostic, therapeutic, as well as theranostic agents.

## 2. METHODOLOGY

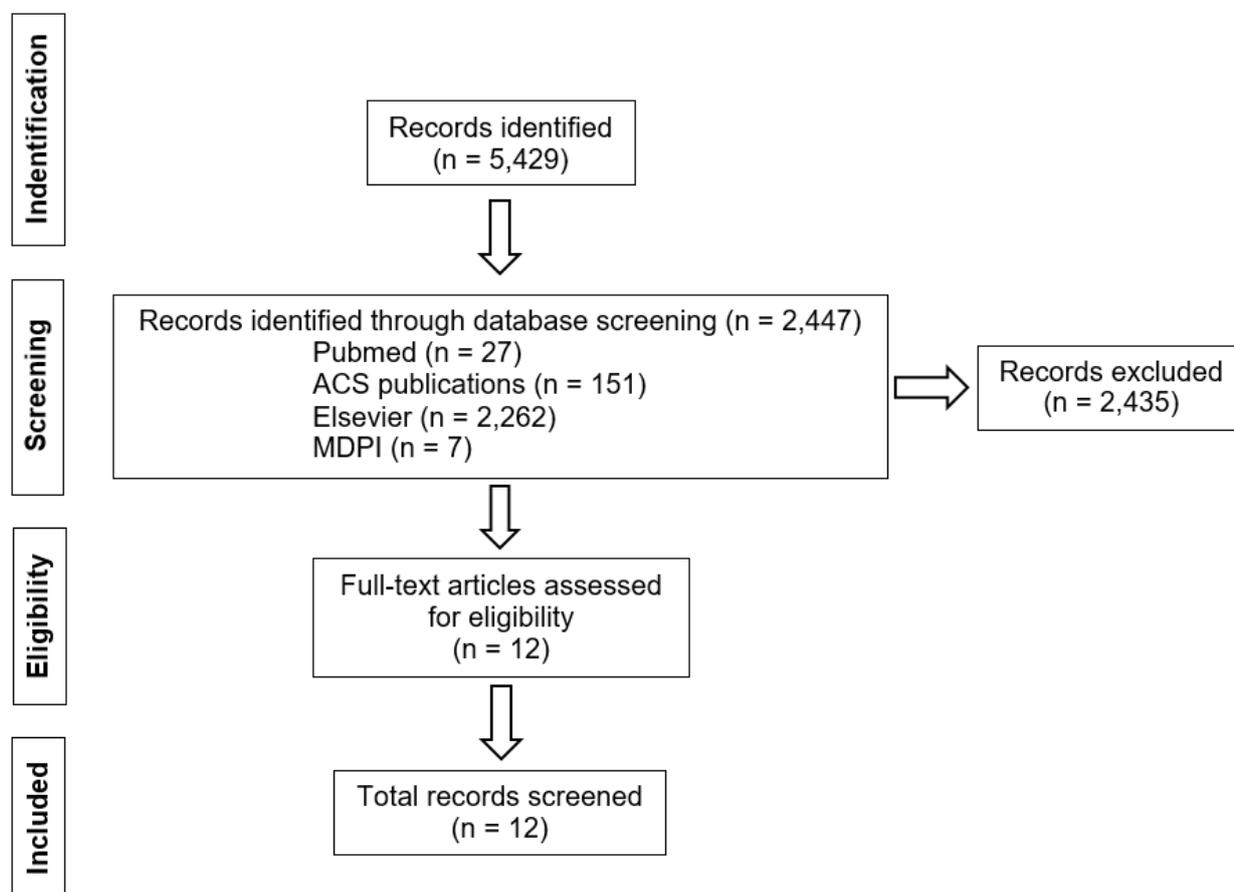
In this study, a review of the literature related to the use of radioactively marked peptide compounds was carried out for the diagnosis and therapy of prostate cancer. The literature search was conducted using databases such as PubMed, Elsevier, MDPI, and ACS Publications to find data that had been published as scientific articles that were published in the last 5 years (2016 to 2021). The keywords used in the literature search were prostate cancer diagnosis, prostate cancer therapy, and radiolabeled peptide compounds. The entire literature was then reselected using the inclusion criteria.

The search was focused on locating studies eligible for inclusion or exclusion based on the criteria below. The following are the inclusion criteria:

1. Only primary studies (qualitative, quantitative, and/or mixed studies)
2. Reported between 2016-2021
3. Peptide-based radiotracers targeting prostate cancer

The exclusion criteria as the following:

1. Studies written in a language other than English
2. Studies reported by literature review
3. Studies published by closed-access journals
4. Studies presented as editorials, protocols, and commentaries



**Figure 1.** The PRISMA flow chart shows the study selection processes.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart (Figure 1) shows the identification, screening, and selection of papers for this review. There were no included studies for which to assess the risk of bias or to apply for evidence synthesis. On the examination of the full text, 12 studies identified as relevant category in this review (Table 1, which includes a tabulated list of the 12 studies along with aim of study, kind of peptide as radionuclide carrier, and the purpose of author's studies).

**Table 1.** List of detailed studies of 12 reported article targeting prostate cancer.

No	Authors	Title of article	Radiotracer's name	Peptide	Receptor target	Aim of the study
1	Toujier (2019)	Prospective Study of the Radiolabeled GRPR Antagonist BAY86-7548 for Positron Emission Tomography/Computed Tomography Imaging of Newly Diagnosed Prostate Cancer	<sup>68</sup> Ga-RM2	RM2	GRPR	Diagnosis
2	Müller (2019)	Terbium-161 for PSMA-targeted radionuclide therapy of prostate cancer	<sup>161</sup> Tb-PSMA-617	PSMA-617	PSMA	Therapy
3	Leibowitz (2020)	A Retrospective Analysis of the Safety and Activity of Lutetium-177-Prostate-Specific Membrane Antigen Radionuclide Treatment in Older Patients with Metastatic Castration-Resistant Prostate Cancer	<sup>177</sup> Lu-PSMA-617	PSMA-617	PSMA	Therapy
4	Jadvar (2019)	Preclinical evaluation of a <sup>64</sup> Cu-labeled disintegrin for PET imaging of prostate cancer	<sup>64</sup> Cu-Sar-PEG-VCN	Vincrostatin (VCN)	Integrin	Diagnosis
5	Nock (2017)	Theranostic Perspectives in Prostate Cancer with the Gastrin-Releasing Peptide Receptor Antagonist NeoBOMB1: Preclinical and First Clinical Results	<sup>67/68</sup> Ga/ <sup>111</sup> In/ <sup>177</sup> Lu-NeoBOMB1	NeoBOMB1	GRPR	Theranostics
6	Dalm (2017)	<sup>68</sup> Ga/ <sup>177</sup> Lu-NeoBOMB1, a Novel Radiolabeled GRPR Antagonist for Theranostic Use in Oncology	<sup>68</sup> Ga/ <sup>177</sup> Lu-NeoBOMB1	NeoBOMB1	GRPR	Theranostic
7	Xia (2021)	Application Analysis of <sup>124</sup> I-PPMN for Enhanced Retention in Tumors of Prostate Cancer Xenograft Mice	<sup>124</sup> I-PPMN (PSMA-PEG-MNPs)	PSMA	PSMA	Diagnosis
8	Rahbar (2016)	Response and Tolerability of a Single Dose of <sup>177</sup> Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis	<sup>177</sup> Lu-PSMA-617	PSMA	PSMA	Therapy
9	Nock (2021)	[ <sup>99m</sup> Tc]Tc-DB15 in GRPR-Targeted Tumor Imaging with SPECT: From Preclinical Evaluation to the First Clinical Outcomes	[ <sup>99m</sup> Tc]Tc-DB15	DB15	GRPR	Diagnosis
10	Abouzayed (2021)	Preclinical Evaluation of <sup>99m</sup> Tc-Labeled GRPR Antagonists maSSS/SES-PEG <sub>2</sub> -RM26 for Imaging of Prostate Cancer	[ <sup>99m</sup> Tc]Tc-maSSS-PEG <sub>2</sub> -RM26	RM26	GRPR	Diagnosis
11	Bandara (2018)	Matched-pair, <sup>86</sup> Y/ <sup>90</sup> Y-labeled, bivalent RGD/bombesin antagonist, [RGD-Glu-[DO3A]-6-Ahx-RM2], as a potential theranostic agent for prostate cancer	[ <sup>86</sup> Y/ <sup>90</sup> Y]-DO3A-RGD-Glu-6-Ahx-RM2	RGD and RM2	Integrin and GRPR	Theranostic
12	Cheng (2018)	Positron Emission Tomography Imaging of Prostate Cancer with Ga-68-Labeled Gastrin-Releasing Peptide Receptor Agonist BBN <sub>7-14</sub> and Antagonist RM26	<sup>68</sup> Ga-NOTA-PEG3-RM26 & <sup>68</sup> Ga-NOTA-Aca-BBN <sub>7-14</sub>	RM26 & BBN <sub>7-14</sub>	GRPR	Diagnosis

### 3. RESULTS

#### 3.1 Literature Section

The search engines such as ACS Publications, PubMed, MDPI, and Elsevier (Science Direct) were used in this study. Obtained 2447 articles from the entire database then filtered using inclusion criteria to obtain 12 relevant articles for review.

#### 3.2 Peptide

Peptides which are mainly synthesized in the brain, especially in neurons, are called neuropeptides. However, since most of these peptides are also found in the intestine, lymphatic tissue, endocrine system, etc the term regulatory peptide is often used. Some of the most important regulatory peptides and their receptors that are overexpressed in tumors such as RGD, GRPR, PSMA (Fani, 2012). These receptors represent useful molecular targets for cancer diagnosis and therapy because they are located on the plasma membrane and binding targets for the radioligands. The internalization of the receptor-ligand complexes allows the prolonged retention of radioactivity in tumor cells (Fani, 2012).

#### 3.3 Radionuclides

The radiopharmaceutical is a combination of pharmaceutical agents and radionuclides. Pharmaceutical agents act as carriers and radionuclides act as tracers that can be detected by radiation-detected cameras. Radionuclides can be

gamma, positron, beta, and alpha emitters. Gamma and photon-emitting radionuclides are used for diagnosis purposes, while beta and alpha-emitting radionuclides are used for therapy. Radionuclides can be produced by reactors, cyclotrons, or generators. Radiopharmaceutical doses are not based on weight or volume but are based on the radiation emitted. The tool to determine the amount of radiation dose is the dose calibrator and the unit used is mCi (milliCuries) or MBq (Megabecquerels) (Pangribo, 2019). There are 2 characteristics of radioisotopes that can be utilized. Firstly, radioisotopes can be detected easily throughout the body in very small amounts through the radiation that they emitted. Secondly, radioisotopes emitting charged particles have a high destructive power on cells because of the large Linear Energy Transfer (LET) released by their radiation (Awaludin, 2006). The emission released by the radionuclide will be captured by an imaging camera. The most commonly used are PET (Positron Emission Tomography) and SPECT (Single Photon Emission Tomography), which can also be combined with other tools such as MRI (Magnetic Resonance Imaging) and CT (Computed Tomography).

Photon-emitting radionuclides are used for SPECT radio-imaging such as  $^{111}\text{In}$ ,  $^{67}\text{Ga}$ ,  $^{99\text{m}}\text{Tc}$ , while positron-emitting radionuclides for PET-radio-imaging such as  $^{64}\text{Cu}$ ,  $^{68}\text{Ga}$ , and  $^{18}\text{F}$ . Peptide-based radiopharmaceuticals for therapy were labeled with radionuclides such as  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{90}\text{Y}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{177}\text{Lu}$ ,  $^{211}\text{At}$ ,  $^{225}\text{Ac}$ ,  $^{212}\text{Bi}$ ,  $^{213}\text{Bi}$ , and  $^{131}\text{I}$ . Alpha radiation is known as the most damaging particulate radiation because of its high local energy deposition and high Linear Energy Transfer (LET), so it can be applied in small concentrations (Awaludin, 2006).

## 4. DISCUSSION

### 4.1 Radiopeptides as diagnostic imaging agents

The use of radiopeptides for diagnostic imaging is currently growing rapidly. Diagnostic imaging using SPECT, PET, MRI, and CT cameras gives the expected results. In addition, to provide an overview of the location and severity of a tumor, molecular level imaging can also provide functional information on the organ target. GRPR (Gastrin Releasing Peptide Receptor) is a receptor that is secreted in excess in tumors in prostate cancer.

PET radionuclide that was frequently used with the carrier RM2 peptide, the bombesin-like peptide was  $^{68}\text{Ga}$ . PET-MRI imaging using  $^{68}\text{Ga}$ -RM2 simultaneously detected tumors in 64.8% of cancer areas (83 of 128) and accurately estimated their absence in 60.9% of the area without cancer (39 of 64) (Toujier, 2019). Another radiotracers with modification linker showed that [ $^{99\text{m}}\text{Tc}$ ]Tc-maSSS-PEG2-RM26 has absorption route in the gastrointestinal tract, clearly visualized and low liver uptake compared to [ $^{99\text{m}}\text{Tc}$ ]Tc-maSES-PEG2-RM26. It means [ $^{99\text{m}}\text{Tc}$ ]Tc-maSSSPEG2-RM26 is promising for GRPR overexpressing PCa (Abouzayed, A, 2021).

Radiolabeled BBN (Bombesin) analogs, namely tetradecapeptide BBN and the C-terminal fragment of BBN(6-14) are potential to detect the GRPR overexpressing cancers, especially prostate cancer and breast cancer. In addition, it can also detect several metastatic sites to mediastinal, esophageal, abdominal, and pelvic lymph nodes (Nock, 2017). Another modification of radiopharmaceuticals was linker modification and this has been known can affect the pharmacokinetic properties of radiotracers. Our literature study showed that  $^{68}\text{Ga}$ -NOTA-PEG3RM26 is a promising candidate for PET imaging of prostate cancer compared to  $^{68}\text{Ga}$ -NOTA-Aca-BBN7-14 (Cheng, 2018). Radiotracer targeting GRPR receptor namely [ $^{99\text{m}}\text{Tc}$ ]Tc-DB15 (N4-AMA-DGA-DPhe6,Sar11,Leu-NHET13)BBN(6-13) showed high uptake and prolonged retention in PC-3 xenografts and two breast cancer patients without adverse effect (Nock, 2021).

A chimeric disintegrin (69 amino acid monomer), Vicrostatin (VCN), showed high binding affinity to multi-integrins (e.g.,  $\nu\beta 3/\alpha 5\beta 1/\alpha \nu\beta 5$ ) and showed superior properties compared to other integrin-based antagonists.  $^{64}\text{Cu}$ -labeled Vicrostatin showed clearly visible and good contrast of PCa-bearing models at 2 and 24 hours after injection (Jadvar, 2019). PSMA targeting radiotracer,  $^{124}\text{I}$ -PPMN (PSMA-PEG-MNP) has high stability, high sensitivity, reliable targeting of prostate cancer cells as well as high specificity and long retention effect at the tumor site (Xia, 2021).

### 4.2 Radiopeptides as therapeutic agents

[ $^{161}\text{Tb}$ ]-labeled PSMA-617 was evaluated for PCa therapy targeting PSMA-receptor. The PC-3 PIP tumor cell viabilities of [ $^{161}\text{Tb}$ ]-PSMA-617 was more reduced compared to [ $^{177}\text{Lu}$ ]-PSMA-617. [ $^{161}\text{Tb}$ ]-PSMA-617 was further investigated in a therapeutic study using PC-3 PIP tumor-carrying mice. The results showed that [ $^{161}\text{Tb}$ ]-PSMA-617 and [ $^{177}\text{Lu}$ ]-PSMA-617 have similar in vitro properties and tissue distribution profiles in the tumor-bearing mice. Radiotracer [ $^{161}\text{Tb}$ ]-PSMA-617 showed a better therapeutic effect compared to [ $^{177}\text{Lu}$ ]-PSMA-617 (Müller, 2019).

### 4.3 Radiopeptides as theranostic agents

Peptide-based radiotracers as therapeutic agents have been investigated. Evaluation of the biodistribution of both [ $^{68}\text{Ga}$ ]-NeoBOMB1 and [ $^{177}\text{Lu}$ ]-NeoBOMB1 for imaging and therapeutic purposes, respectively in a tumor model mice to provide information for the theranostic use of radiotracers have been reported. The result showed that the highest tumor uptake was  $12.4 \pm 2.3\%$  ID/g tissue at 120 min after injection. PET/CT scanning at tumor-bearing mice injected with 11.5 MBq/230 pmol exhibited good visualization of tumor area. Accumulation of radiotracer at abdominal and pancreas was observed. SPECT-MRI images 240 min after injection of 20 MBq/200 pmol [ $^{177}\text{Lu}$ ]-NeoBOMB1 showed good tumor visualization (Dalm, 2017).

Another radiopeptide that explored its properties as a radiotheranostic agent was [RGD-Glu- $^{86/90}\text{Y}$ ]-DO3A]-6-Ahx-RM2]. The result showed that microPET/CT images of tumor-bearing mice have high-quality, high-contrast full-

body images with minimal tracers present in non-tumor tissue at all time points. In addition, in vivo study of biodistribution of [RGD-Glu-[[<sup>90/90</sup>Y]Y-DO3A]-6-Ahx-RM2] in tumor-bearing SCID mice showed that these two novel compounds exhibit excellent specificity and affinity for GRPR in PC-3 tumors. MicroPET imaging investigations of [RGD-Glu-[[<sup>90</sup>Y]Y-DO3A]-6-Ahx-RM2] at tumor-bearing mice after 24 h showed still high tumor retention. On the other hand, the accumulation of tracer in non-target tissues almost disappeared (Bandara, 2018).

## 5. CONCLUSION

In prostate cancer, the peptide has been used as a carrier for diagnoses such as RM2, VCN (Vicrostatin), DB15, and BBN7-14 and therapy such as PSMA-617. Other research groups developed peptides as theranostic agents, using the same peptide to deliver different types of radionuclides for diagnosis and therapy purposes. The peptides that have been utilized for this purpose are NeoBOMB1, PSMA, and [RGD-Glu-[DO3A]-6-Ahx-RM2]. The radionuclides such as <sup>68</sup>Ga, <sup>161</sup>Tb, <sup>177</sup>Lu, <sup>64</sup>Cu, <sup>124</sup>I, <sup>99m</sup>Tc, <sup>90</sup>Y, and <sup>86</sup>Y have been labeled to peptides for diagnosis and therapy of prostate cancer. Great efforts have been made in the development of peptide-based radiopharmaceuticals for the diagnosis of prostate cancer with good visual imaging results. In addition, the radiation effect of radiotherapeutic and radiotheranostic agents can be tolerated and well received by the body with mild side effects. The use of radiopeptides for the diagnosis and therapy of prostate cancer is very promising in the future, so it needs to be developed further.

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