Review

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PSMA Targeted Ligands in Imaging and Theranostics for Prostate Cancer

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Abstract

Prostate cancer (PCa) is the second most common type of cancer in men. Compared with conventional imaging methods, prostate-specific membrane antigen (PSMA)-targeted positron emission tomography has higher accuracy and specificity for the detection and treatment of PCa. Through targeted imaging, ligands are labelled with ^{18}F, ^{68}Ga, or ^{64}Cu, and the disease is staged and managed more accurately. It is also desirable to use PSMA-targeted theranostics that are labelled with either imaging radioisotopes or treatment isotopes such as ^{177}Lu, ^{225}Ac, ^{131}I. Here, we summarized some of the commonly used small molecule PSMA ligands for imaging and theranostic purposes.

Keywords: PET imaging, prostate cancer, theranostics

Introduction

Prostate cancer (PCa) is the second most prevalent type of cancer and the fifth cause of cancer-related mortality in men (1). Conventional imaging (CI) methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), have severe limitations, especially in detecting lymph nodes (LN), misleading the staging and management of the disease (2,3,4,5). Compared with CI, prostate-specific membrane antigen (PSMA)-positron emission tomography (PET) has a higher accuracy and plays an important role, especially for preliminary staging (6) and biochemical recurrence (BCR) of PCa (7,8).

PSMA is a type II transmembrane glutamate carboxypeptidase found in the prostate secretory-acinar epithelium (9,10,11,12). The amount of PSMA expression increases with increasing tumor dedifferentiation and in metastatic and hormone-refractory disease, and it is considerably overexpressed in PCa cells compared with its normal expression in prostate cells (13,14). This cell surface protein is highly expressed (nearly a thousand times more than in normal prostat tissues) in most PCa cells (15), and PSMA expression is a key predictor of disease prognosis (16). Because of these factors, PSMA targeting for imaging and therapy (I&T) of PCa has been considered a promising option in recent years.

PSMA inhibitors are divided into three groups: urea-based, phosphorus-based, and thiol-based. PSMA PET radiolabelled compound development focuses on small urea-based PSMA ligands that target the extracellular part of PSMA and recognize regions of high binding affinity to PCa cells, leading to rapid plasma clearance and high tumor background levels (17). In this review, we will discuss the well-known small-molecule PSMA-targeted ligands in two parts (Figure 1); diagnostics (tracers that can be labelled nuclides, such as ^{68}Ga or ^{18}F, Figure 2) and theranostics (tracers that can be labelled with both imaging and therapeutic nuclides, such as ^{177}Lu or ^{225}Ac; Figure 3). This review is not entirely comprehensive as not mentioning antibodies, conjugation therapies and immunotherapies.

PSMA Ligands for PET Imaging

Imaging has two main functions in the early determination of PCa. First, it identifies the disease in patients who are confirmed by biopsy and have a high possibility of metastasis. Second, it determines the primary tumor site in cases with a negative biopsy but a high probability of PCa. Proper staging has an important impact on guiding additional local or systemic treatment options, such as radical prostatectomy, radiation therapy, or palliative care, as well as dissection of pelvic LN during surgery or planning for radiotherapy. Before the start of

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the treatment plan, PSMA imaging is also used in patients with BCR or metastatic castration-resistant PCa for the determination of disease management.

^{68}Ga-PSMA-11

^{68}Ga-HBED-CC (PSMA-HBED or HBED) was first synthesized by Eder et al. (18) in 2012. HBED-CC was added as a radiometal chelator to the PSMA inhibitor motif Glu-urea-Lys to improve the interactions of the pharmacophore with the hydrophobic pocket of the PSMA S1 binding site (the structure is shown in Figure 2). HBED-CC is a highly efficient and stable radiometal chelator that enables quick radiolabelling at room temperature and exhibits exceptionally high complex stability, much like the DOTA chelator, which is commonly used in clinical settings. Different temperature during the radiolabelling reaction can be controlled to promote the formation of a diastereomer that is more thermodynamically stable. Nonetheless, because HBED-CC is highly selective for ^{68}Ga, the radiopharmaceutical cannot be used for labeling with therapeutic radionuclides such as ^{177}Lu or ^{90}Y. This drug is also quickly eliminated from non-target tissue. Physiological absorption is strong in the salivary and lacrimal glands. There is moderate uptake in the intestine, liver, spleen, and ganglia, e.g., cervical and celiac ganglia, and negligible uptake in normal prostate cells (19). When compared with traditional imaging, PSMA PET/CT has a much reduced radiation dose (8.4 mSv vs. 19.2 mSv, respectively) (20). For all these reasons, nearly 10 years after its discovery, in 2020 ^{68}Ga-PSMA-11

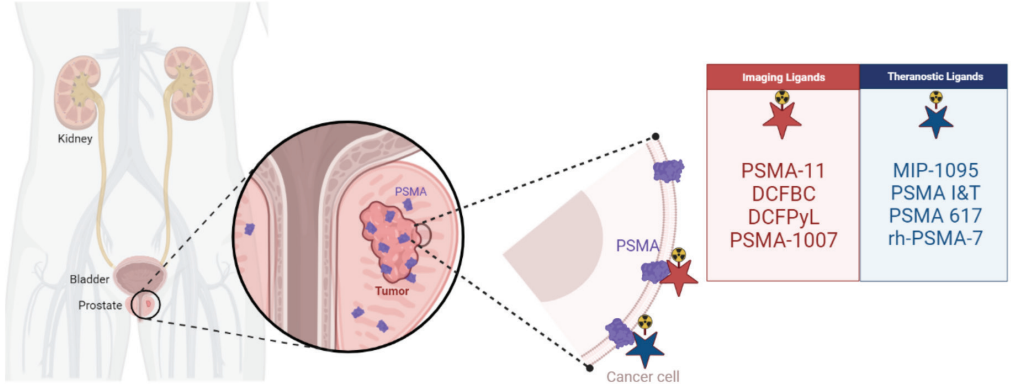

Figure 1. PSMA-targeted imaging and theranostic ligands
PSMA: Prostate-specific membrane antigen

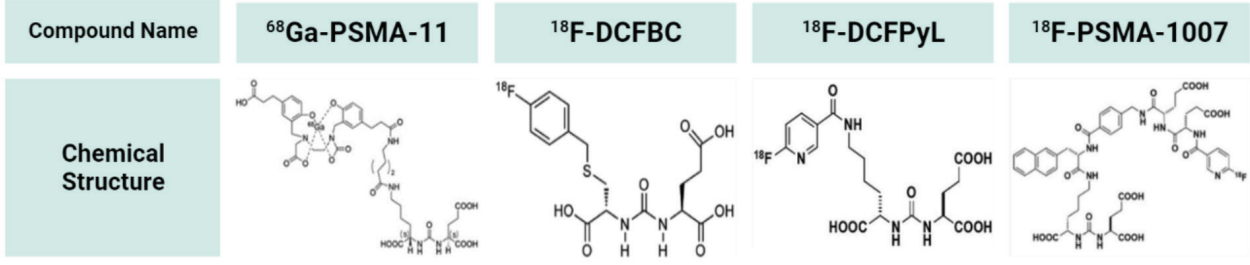

Figure 2. PSMA-targeted small-molecule PET agents and their structures
PSMA: Prostate-specific membrane antigen, PET: Positron emission tomography

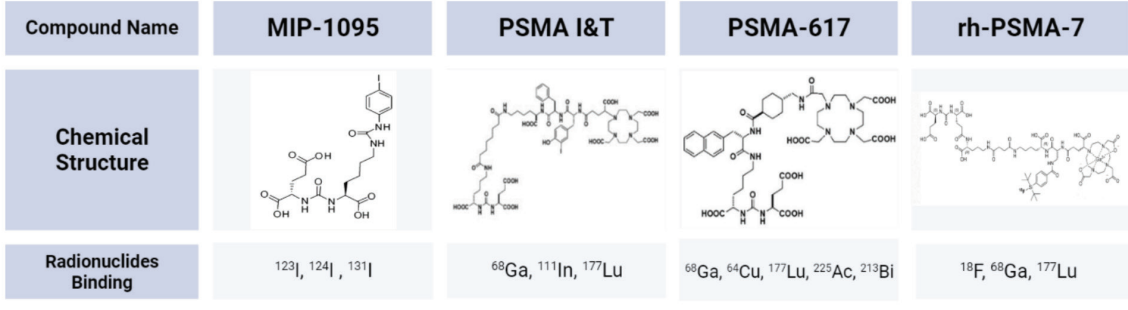

Figure 3. PSMA-targeted small molecule theranostics and their structures
PSMA: Prostate-specific membrane antigen

was approved as the first ^{68}Ga-labelled radiopharmaceutical for imaging of PCa.

In one of the earliest studies, Afshar-Oromieh et al. (20) examined ^{68}Ga-PSMA PET imaging for biodistribution and PCa lesion detection abilities in 37 patients. The highest radiotracer uptake was observed in the kidneys and salivary glands of healthy organs. As early as 1 h after injection, PCa-like lesions showed excellent contrast even at low PSA levels, with high detection rates (20). Similarly, recent studies have also shown a high detection rate, ranging from 33-56% at low PSA levels to 95-97% at PSA levels above 2.0 ng/mL (7,8,21).

According to Müller et al., (21) ^{68}Ga-PSMA-11 PET/CT has an important influence in modifying the therapeutic plans of patients with PSA rise (21), greater than 50% of patients experienced a treatment approach adjustment. It is very effective in the diagnosis of recurrent PCa (22). The ability of the ^{68}Ga-PSMA-11 probe to detect diffused PCa was also demonstrated. In two studies of PCa patients with BCR, 90% of those with elevated PSA levels had recurrent sites (23,24). Perera et al. (8) found that 76% of patients with BCR and 40% of patients with main staging were positive for ^{68}Ga-PSMA PET. The expected positive results were 48% for PSA levels of 0.2 ng/mL, 56% for PSA levels of 0.5 ng/mL, and 70% for PSA levels of 1.0 ng/mL. Shorter PSA doubling times also improved ^{68}Ga-PSMA PET positivity (8).

Because of a significant degree of binding and intracellular accumulation, ^{68}Ga-PSMA-11 can also identify highly small metastases. When compared with CT (specificity: 82% and sensitivity: 42%); and MRI (specificity: 82% and sensitivity: 39%), ^{68}Ga-PSMA-11 was reported to be able to detect metastasis in the nodal region with a specificity of 99% and sensitivity of 75% (8). According to the Pro-PSMA 2020 trial, ^{68}Ga PSMA PET/CT for nodal staging was 27% more precise than CI. They reported that CI had lower specificity (91% vs. 98%) and sensitivity (38% vs. 85%) than PSMA PET/CT (19). Over 5% of the options, treatment change was conducted in 27% of patients who had ^{68}Ga-PSMA-11 PET/CT. With combined specificity and sensitivity of 82% and 79%, respectively, bone scintigraphy (BS) is the most extensively used approach for evaluating bone metastases derived from PCa (25). Pyka et al. (24) showed that ^{68}Ga-PSMA PET was superior to BS for detecting afflicted bone areas and assessing overall bone metastases in PCa. The specificity and sensitivity for total bone activity were 99-100% and 88-100% for PET, respectively, and 87-89% and 61-96% for BS (24).

Because of its unpatented structure, ^{68}Ga-PSMA-11 has been used to gather a significant amount of PSMA PET data throughout the years. The broad accessibility of ^{68}Ga-DOTATATE shows the viability of developing a chain of ^{68}Ga generators for local distribution, even if ^{67}Ge/^{68}Ga generators are not currently the norm for every nuclear medicine clinic globally. It may be possible to provide ^{68}Ga generator more quickly with increased availability, an increase in clinically effective ^{68}Ga-using PET agents, and kit-based radioactive labeling methods that make radiotracer production easier at the spot and are currently being developed for PSMA (26,27). Since the very first human research completed in 2013 (22), ^{68}Ga-PSMA-11 has gained widespread acceptance as well as use at research centers all over the world, and data of over 15,000 patients have been published.

From an economical viewpoint, using data gathered from a clinical trial (19), de Feria Cardet et al. (28) assessed the costs and precision of diagnosis associated with applying ^{68}Ga-PSMA-11 PET/CT vs traditional imaging for staging high-risk PCa. PET/CT using ^{68}Ga-PSMA-11 cost estimate was shown to be AUD 1203, which was less expensive than the traditional imaging price of AUD 1,412. ^{68}Ga-PSMA-11 PET/CT is inexpensive and more accurate. There were also documented savings of AUD 959 for every extra accurate nodal localization and AUD 1,412 for every accurate distant metastases diagnosis.

^{18}F-DCFBC

^{68}Ga can provide less radiation exposure to patients with a quicker absorption time compared to ^{18}F, yet ^{18}F has a superior positron energy (633keV vs. 1,899keV for ^{68}Ga) and inferior positron yield (96.9% vs. 89,1% for ^{68}Ga), affecting both the qualitative and quantitative parameters of the image. Given its longer half-life (108 mins for ^{18}F vs. 68 mins for ^{68}Ga), ^{18}F can provide higher image quality because of the time prolongation between injection and imaging, resulting in an image with less interference and a preferable tumor-to-background ratio. ^{18}F also allows for centered manufacturing and delivery across longer distances. The discovery of ^{18}F-labelled PSMA drugs has resulted in an important change in the availability of PET imaging for metastatic, primary, and recurrent PCas (29,30,31). This is largely due to a larger supply of the radioisotope ^{18}F generated by cyclotrons than that of ^{68}Ga, which is eluted from generators.

The first-generation ^{18}F-PSMA agent, ^{18}F-DCFBC (N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-^{18}F-fluorobenzyl-l-cysteine), is a low-molecular-weight urea-based radiotracer that targets PSMA (Figure 2). First, it was synthesized by Mease et al. (29) in 2008 and was later developed from firstly introduced ([^{11}C]DCMC) by the same group. For ^{18}F-labelled PSMA radioinhibitors, a 2019 meta-analysis found a cumulative detection percentage of 49% on a PSA level that is 0.5 ng/mL or fewer along with 86% on a PSA value of equal or greater than 0.5 ng/mL (30). ^{18}F-DCFBC was investigated for its detection rates, and it was discovered that, although using a poor contrast resolution, they were equivalent to those of recent studies using ^{68}Ga-PSMA PET agents (7,8,21). A drawback of using this drug was its high background activity, which interfered with the identification of LN metastases (32). This led to the synthesis of second-generation ligands.

^{18}F-DCFPyL

^{18}F-DCFPyL exhibits less blood pool activity, stronger affinity, and quicker clearance, increasing the tumor-to-background ratio and potentially enabling the detection of lower-grade or smaller PCa compared with ^{18}F-DCFBC (31) The second generation ^{18}F-labelled PSMA ligand, ^{18}F-DCFPyL, was introduced in 2011 with promising findings due to improved image quality and the ability to show small prostatic lesions with high sensitivity (33). For PSMA-PET/CT imaging in recurrent PCa, ^{18}F-DCFPyL is a potential alternative to ^{68}Ga-PSMA-11 with similar biodistribution (34,35). This ligand is distinguished by its fast excretion through the urinary system (the structure is shown in Figure 2).

A phase II single-center prospective study evaluating PET/CT results using ^{18}F-DCFPyL in 25 patients demonstrated that the specificity and sensitivity for detecting nodal metastasis were 88.9% and 71.4%, respectively. Three mm nodes made up about 50% of the nodes, and 12% of the patients had unexpected distant metastases (36). Even among men with low PSA levels who had BCR in the CONDOR study, DCFPyL effectively determined disease regions. Most males with BCR presenting negative or inconclusive with CI (bone scan plus CT) were found to have localized disease by DCFPyL PET/CT, which changed the course of treatment for most patients. According to these results, ^{18}F-DCFPyL PET seems to be more advantageous than ^{68}Ga-PSMA-HBED-CC PET for the identification of recurrence in PCa patients. However, neither ^{18}F-DCFBC nor ^{18}F-DCFPyL includes radionuclide-binding chelators for targeted treatment.

^{18}F-PSMA-1007

Fluorinated tracers currently in use are frequently not suitable for theranostic applications. Although not applied for therapeutic purposes, only ^{18}F-PSMA-1007, another second-generation PSMA agent, was synthesized for developing a radiofluorine molecule similar to the structure of the PSMA-617 which is used for theranostic purposes (the structure is shown in Figure 2) (37). Because PSMA-1007 is derived from PSMA-617 ^{18}F-PSMA-1007 and ^{177}Lu-PSMA-617 can be used as theranostic pairs of the PSMA radioligand. Other tandem combinations are also possible because the diagnostic component does not have to be an accurate reproduction of the therapeutic component. ^{18}F-PSMA-1007 PET imaging at very low PSA levels provided critical information to correctly restage disease and to discuss appropriate treatment options in a case report by Giesel et al. (36).

^{18}F-PSMA-1007 shows high labelling yield, high tumor absorption and rapid non-urine background removal (38). PSMA-1007 is at least comparable to ^{68}Ga-PSMA-11, but the longer half-life, superior energy properties, and urinary excretion overcome some of the practical limitations of ^{68}Ga-PSMA target tracers. Because of the benefit of hepatobiliary excretion excretion, ^{18}F-PSMA-1007 is a very useful tool for providing more precise pelvic nodal evaluation (36). According to a meta-analysis, in patients with biochemical relapse the detection rate of ^{18}F-PSMA-1007 PET/CT is comparable to that of ^{68}Ga-PSMA-11 PET/CT (27), providing the information of its usefulness in BCR PCa patients. Despite these advantages, compared with ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007 revealed a higher absorption in benign tissue, resulting in more probable false positive conclusions (39).

Apart from these agents, some relatively new agents such as ^{18}F-CTT-1057 use a phosphoramidate backbone to enable irrepleviable binding to PSMA, a lower dose of radiation to the salivary glands and kidneys compared to urea-based agents, and an elevated tumor-to-background ratio in some patients (40).

Clinical Application of PSMA Imaging

The medical community appears to agree that PSMA PET should not be used in low-risk patients; however, further studies are needed to estimate its use in patients with intermediate risk. In high-risk patients, however, PSMA PET outperforms CT and BS combined. Patients with biochemical failure, regardless of castration status, should be referred for PSMA PET. Although PSMA PET shows a more extensive disease than predicted or exonerates similar lesions, this influences therapy optimization. However, if an extensive metastatic burden has already been proven, there is no need for PSMA PET because it will not modify the treatment plan (apart from identifying the PSMA target in the case of radioligand therapy). Furthermore, there is no convincing evidence that PSMA PET may be used to stage PC with Gleason <7 (41). Long-term androgen deprivation treatment (ADT) lowers tracer uptake, possibly due to therapeutic response and associated limitation of the extent of lesions, as well as a larger chance for fractional volume effects. As a result, the European Association of Urology recommendations propose using PSMA PET/CT as a restaging method when a patient's PSA level rises beyond 0.2 ng/mL, ideally before ADT initiation. Considering the contribution of PSMA expression by short-term ADT, the sensitivity of PSMA PET/CT might be enhanced in patients with BCR with PSA levels less than 0.5 ng/mL.

PSMA Ligands for Theranostics

Despite numerous advancements in recent years, managing metastatic PCa remains a challenge. To detect PCa lesions through PET or SPECT imaging, low-molecular-weight ligands have been developed by studying PSMA inhibitors extensively. However, optimizing the endoradiotherapeutic use of these compounds requires optimum consideration of the chelating agent of the radionuclide and the linker moiety between the chelator and pharmacophore, as they affect the overall pharmacokinetic properties of the resulting radioligand. The radioactive isotopes ^{90}Y, ^{131}I, ^{177}Lu, and ^{225}Ac are suitable options for systemic radionuclide therapy. While ^{131}I and ^{177}Lu emit both β-particles and γ-radiation, ^{90}Y is solely a β-particle emitter and ^{225}Ac is an alpha emitter (42,43). Here, we summarize some theranostic agents developed for PCa.

MIP-1095

MIP-1095 [(*S*)-2-(3-((*S*)-1-carboxy-5-(3-(4 iodophenyl)ureido) pentyl)ureido)pentanedioicacid] was first synthesized by Maresca et al. (41) in 2009 (Figure 3). First-in-man evaluation in 2013 showed that ^{123}I-MIP-1095 detects soft tissue, bone, and prostate lesions in just 1-4 h and exhibits excellent pharmacokinetic and pharmacodynamic profiles (44). This makes it a promising diagnostic agent for the ability of labeling with therapeutic radionuclides. Accordingly, in 2014, Zechmann et al. (43) reported first therapy results with ^{124}I/^{131}I-labelled MIP-1095 in individuals suffering from PCa that is resistant to hormone therapy. The radioactive tracer displayed remarkable absorption in the lesions of all patients. Over 50% of treated males experienced a decline in PSA levels, whereas 84.6% of males with bone discomfort reported either complete or substantial relief from pain. However, because of the high level of gamma radiation emitted, patients were required to stay in the hospital for approximately one week, and mild hematological toxicities were observed (43).

PSMA-I&T

For the first time, in 2015, Weineisen et al. (45) synthesized PSMA-I&T ligand with DOTAGA [1,4,7,10-tetraazacyclododecane-1-(glutamic acid)-4,7,10-triacetic acid] conjugate with a peptidic linker to enable rapid and high yield labeling with ^{68}Ga and ^{177}Lu (the structure is shown in Figure 3). Compared with ^{131}I, ^{177}Lu emits a lower proportion of gamma radiation, which would reduce hospital stays and decrease the hemotoxicity observed in patients. Using ^{68}Ga-PSMA-I&T for the first time in human PET imaging provided high-contrast detection of bone lesions, LN and liver metastases. Internal radiotherapy with ^{177}Lu-PSMA-I&T was also proved to be effective and safe for both patients, with no obvious side effects, suggesting that its targeting and confinement properties are suitable for successful endoradiotherapy (46).

Due to the suitability of the chelator, the ligand is also radiolabelled with ^{111}In for SPECT imaging. Rauscher et al. (44) assessed the efficacy of ^{111}In-PSMA-I&T SPECT/CT for detecting early recurrent PCa in comparison with ^{68}Ga-PSMA-11 PET in a group of patients. Nonetheless, ^{111}In-PSMA-I&T SPECT/CT demonstrated a patient-based detection rate of 59%, indicating its potential as a useful imaging tool in situations where PET is unavailable. PSMA-I&T also appears to be diagnostically similar to PSMA-11 and PSMA-617 (47,48,49).

For theranostic purposes, ^{177}Lu-PSMA-I&T was used in a trial of 56 patients with mCRPC who received a mean dosage of 5.76 GBq in each cycle. PSA progression-free survival (PFS) was 14 months, and 59% of patients had PSA levels that were reduced by more than 50% (45). In another trial with 100 patients, within 12 weeks of therapy, PSA levels were reduced by almost 50%. PFS (4.1 months) and OS (12.9 months) in 38 patients were both longer than average (47). ECLIPSE is another clinical study in males with mCRPC to evaluate the effectiveness of ^{177}Lu-PSMA-I&T in males with metastatic castration-resistant PCa. In total, 400 males with mCRPC will be administered ^{177}Lu-PSMA-I&T, enzalutamide, or abiraterone at random (48). The completion of the study is scheduled for 2029, with rPFS as the main research outcome.

^{68}Ga-THP-PSM, a kit-based formulation with a different chelator than PSMA-I&T, offers the advantage of one-step manufacturing but poorer tumor absorption (50).

PSMA-617

Although the clinical outcomes are very promising with the abovementioned radiopharmaceuticals, further studies are needed to optimize the effectiveness of the treatment and to decrease the side effects that have been reported. To achieve both detection and optimal treatment of PCa, a tailor-made PSMA inhibitor containing naphthyl and DOTA has been developed. PSMA-617, consisting of the pharmacophore glutamate-urea-lysine, was developed and advanced through systematic chemical modification of the linker region, leading to improved tumor-targeting and pharmacokinetic properties (Figure 3) (49). It can advance the treatment of patients with recurring PCa through the use of a single radiolabelling precursor that can be radiolabelled with either ^{68}Ga or ^{64}Cu for diagnosis or ^{177}Lu, ^{225}Ac, or ^{213}Bi for therapy. The PSMA-617 compound demonstrated high PSMA-specific tumor uptake, rapid background clearance, and fast kidney excretion. This provides clear clinical advantages for high-quality imaging of recurrent PCa. In terms of therapeutic use, the extended tumor uptake and high tumor-to-background rate provide advantages for PSMA-617 over previously published DOTA-based PSMA inhibitors (51,52). Compared with PSMA-11 (53), PSMA-617 appears to be more suitable for endoradiotherapy because of its higher tumor uptake at later time points, lower spleen accumulation, and highly efficient kidney clearance.

PET/CT imaging has already been applied with successful results using ^{68}Ga-PSMA-617. However, the superior internalization rate of ^{68}Ga-PSMA-617 in the diagnosis of PCa is counterbalanced by slightly slower tracer kinetics than that of PSMA-11, which may be caused by PSMA-617's larger size (53). As a result, images taken only 3 h after injection could benefit from the improved internalization rate. Another approach for imaging, PSMA agents based on copper 64 (^{64}Cu), have been developed because the prolonged ^{64}Cu half-life (12.7 hours) allows for delayed imaging of ambiguous lesions as well as enhanced long-distance delivery logistics (54). In a 2018 study, ^{64}Cu-PSMA-617 PET/CT was reported to be superior to ^{18}F-choline PET/CT in BCR PCa (55). Although the results of the diagnostic performance of ^{64}Cu-PSMA agentare promising, it may expose patients to more radiation compared with ^{18}F inhibitors.

^{177}Lu-PSMA-617 radioligand treatment is widely used in clinical practice and has been the topic of several recent clinical investigations (50,56,57). A retrospective analysis found that 59% and 75% of patients had a PSA decrease after 1 and 2 treatments, respectively, while after 1 injection, 32% of patients and two injections after 50% of patients had a PSA decline of 50% or more. In the past, the optimal supportive therapy group had a median survival of 19.7 weeks; the predicted median lifetime was 29.4 weeks in this study; this difference was statistically significant (58). With the use of ^{177}Lu-PSMA-617, receptor binding causes endocytosis, aggregation within the cell, and intracellular free radical production, which causes cell damage and death. The use of ^{177}Lu-PSMA therapy for treating metastatic CRPC has also been shown to be a promising approach (47,56). Thirty patients were treated during the LuPSMA trial, and 57% of the patients showed PSA responses (59). With the TheraP trial, ^{177}Lu-PSMA-617 was compared to cabazitaxel, which is commonly used for mCRPC treatment. PSA responses were more prevalent among male individuals in the ^{177}Lu-PSMA-617 group than in the cabazitaxel group (60). The VISION trial enrolled 831 patients with mCRPC and revealed important progress in overall survival with a median survival of 4 months along with PFS-based imaging showing significantly greater survival spans. The FDA approved ^{177}Lu-PSMA-617 on March 23, 2022, and it is now marketed as Pluvicto (61). This is because the study's positive treatment outcome and relatively low rate of adverse events support the use of ^{177}Lu-PSMA-617 as a standard procedure in advanced PSMA-positive metastatic castration-resistant PCa. Patients with mCRPC who have earlier received treatment with taxane-based chemotherapy and androgen receptor pathway inhibitor (ARPI) and who

have PSMA imaging results that show PSMA expression in metastatic lesions are suitable for this treatment.

^{177}Lu-PSMA-617 has been shown in several trials to have a strong objective response and tolerable dosimetry, including an advancement in radiological findings and PSA levels, in the treatment of mCRPC. However, ^{177}Lu-labelled PSMA ligands were ineffective in approximately 30% of patients. ^{177}Lu-PSMA-617 therapy-resistant individuals have been observed to respond well to targeted alpha radiotherapy, which may be a better option for treating mCRPC. High ^{177}Lu radioactivity buildups in bone metastases that are in or near the red marrow, despite being well tolerated, indicate that the real dosage taken in to some parts of the active marrow could be somewhat more than anticipated due to disintegration, resulting in a related developing associated risk for hematologic toxic effects. Recent research has demonstrated that patients with mCRPC in this situation greatly benefit from targeted alpha radiation treatment (62).

Having a 20-fold greater linear energy transfer than beta emitters, alpha emitters are the focus of numerous radioligand treatments in preclinical and clinical research (63). ^{225}Ac-PSMA-617 has been shown to be a potential PSMA treatment drug in early studies (64). In a 2019 pilot study, Sathekge et al. (65) evaluated 17 patients with advanced PCa for the treatment efficacy of ^{225}Ac-PSMA-617. The findings revealed that 94.1% of patients experienced a good antitumor response, as shown by PSA levels and ^{68}Ga-PSMA-PET/CT. After therapy, 82.4% of cases experienced at least 90% PSA decrease. All patients had grade 1/2 xerostomia; however, none of them had any serious symptoms (65). Another study found a more than 50% decrease in PSA levels in 33% of such individuals, suggesting that ^{225}AcPSMA-617 may be beneficial in patients who have failed ^{177}Lu-PSMA-617 (63). The half-life of the alpha emitter ^{225}Ac is 9.9 days, which is relatively long. Targeted therapy with ^{225}Ac-PSMA-617 is currently regarded as experimental, but it appears that individuals with advanced stage PCa might benefit greatly from it.

Bismuth-213, a combination of alpha and beta emitting agents with a relatively short half-life of 45.6 min, is also labelled with PSMA-617 for use in treatment (39). Sathekge et al. (66) reported a first-treatment patient with ^{213}Bi-PSMA-617 (two cycles, 592 MBq) who showed PSMA imaging response and biochemical response with a reduced PSA from 237 g/L to 43 g/L in mCRPC patients who had advanced on standard treatment. Kratochwil et al.'s (67) earlier work revealed that the dosimetry of ^{213}Bi-PSMA-617 is suitable for clinical application. This drug is an alternate preferred radiolabel choice for the targeted alpha treatment of PCa because PSMA-617's biological half life in dose-limiting organs is longer than ^{213}Bi's physical half life. However, when compared with ^{225}Ac-PSMA-617, it suffers from higher perfusion-dependent non-target radiation. The AcTION trial is a phase I investigation of ^{225}Ac-PSMA-617 that is being studied in patients with metastatic castration-resistant PCa who have had or have not received ^{177}Lu-PSMA-I&T or ^{177}Lu-PSMA-617. The trial is only taking place in Australia and South Africa, with a projected enrollment of 60 participants (68).

Trials in Progress

PSMAfore is a phase III, randomized, open-label clinical study that evaluates the efficacy of ^{177}Lu-PSMA-617 in mCRPC cases (69). Approximately 450 people will be randomly assigned to either ^{177}Lu-PSMA-617 or an ARPI. All patients must have advanced on just one ARPI (darolutamide, abiraterone, apalutamide or enzalutamide). rPFS is the trial's principal study endpoint. PSMA addition is a phase III, randomized, open-label clinical research that will compare the effectiveness of ^{177}Lu-PSMA-617 when combined with a standard of therapy against a standard of therapy alone in patients with mCSPC. One thousand one hundred twenty-six people will be divided into two groups at random: those who receive ^{177}Lu-PSMA-617 plus ARPI plus ADT and those who receive ARPI alone. rPFS (70) is the main study endpoint. In the phase II clinical study BULLSEYE, individuals with PCa and oligometastatic hormone-sensitive illness received ^{177}Lu-PSMA-I&T as a metastasis-focused treatment. Patients in the randomized controlled study will either receive the standard of care or the interventional arm, which consists of two cycles of ^{177}Lu-PSMA-I&T. However, the manufacturing of ^{177}Lu-PSMA-I&T was stopped because of issues with coronavirus disease-2019, and a protocol adjustment was made to switch out ^{177}Lu-PSMA-I&T with ^{177}Lu-PSMA-617. Disease progression, which is characterized as a 100% increase in PSA or clinical progression, is the main outcome of the trial (71).

^{68}Ga-PSMA-617 PET imaging economic benefits were also evaluated in individuals with possible recurrent PCa, ^{68}Ga-PSMA PET/MRI was compared with standard treatment (72). It was anticipated that ^{68}Ga-PSMA would cost AUD 56,961 and result in 7.48 life years, as opposed to AUD 64,499 and 7.41 years of life with standard care. ^{68}Ga-PSMA had a potential cost savings of AUD 7592 and had an indistinct higher effectiveness of 0.07 life years. According to this preliminary economic analysis, using ^{68}Ga-PSMA PET/MRI to identify recurrent PCa is more affordable than receiving standard medical attention.

^{18}F-rhPSMA-7

Radiohybrids are radiopharmaceuticals that have two labeling positions: one stable radionuclide along with a radioactive radionuclide, depending on the type of imaging or therapy purpose (Figure 3) (73). ^{18}F-rhPSMA-7 is a radiohybrid with advantageous properties with fast labeling, minimal bladder retention, and a reported identification rate of 71% in BCR PCa at low PSA (74). The phase III studies LIGHTHOUSE and SPOTLIGHT are actively investigating this drug for preprostatectomy and BCR, respectively (75,76).

Apart from the abovementioned theranostic ligand targeting PSMA, there are also some new agents being investigated. ^{177}-Lu-DOTA-N3-CTT1403 is being examined in a phase I clinical study for males with PSMA-positive mCRPC who have had a minimum of one ARPI (77). A total of 40 patients are expected to participate. In contrast, the SECuRE trial is a phase the I/II study evaluating both the safety and efficacy of ^{67}Cu-SARbisPSMA in individuals with mCRPC (78). For this study, patients must exhibit positive PSMA expression, as shown via a positive PET/CT scan using ^{64}Cu-SAR-bisPSMA. The study will

involve 44 people, and its main findings will focus on tolerability, safety, and effectiveness.

Conclusion

The imaging and treatment of PCa has become an important issue because PCa is a prevalent disease in male individuals with a high fatal rate. PSMA has recently become an attractive target to support the idea of "precision medicine" in PCa. Compared with CI, PSMA-targeted imaging can be used for the early diagnosis of PCa even at low levels of PSA, BCR, or mCRPC to define the treatment plan. Theranostics is an important concept of "treat what you see" and this approach has gained a lot of attention in the treatment and diagnosis of PCa with PSMA-targeting. It has been shown to be promising for the treatment of PCa, and it is expected that PSMA-based theranostics will soon become the norm for treating patients with PCa.

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Short Quiz

1- What is PSMA and why is it important in prostate cancer?

2- What is the most commonly used PSMA-targeted radioligand for imaging?

3- What is the most commonly used PSMA-targeted radioligand for therapy?