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The Application of Radiolabeled Targeted Molecular Probes for the Diagnosis and Treatment of Prostate Cancer

Luyi Cheng[1], Tianshuo Yang[1], Jun Zhang[2], Feng Gao[3], Lingyun Yang[4], Weijing Tao[1]

[1]Department of Nuclear Medicine, The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, Huai'an, Jiangsu, China
[2]Department of Nuclear Medicine, The Affiliated Taizhou People's Hospital of Nanjing Medical University, Taizhou, Jiangsu, China
[3]Key Laboratory for Experimental Teratology of the Ministry of Education and Center for Experimental Nuclear Medicine, School of Basic Medical Sciences, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China
[4]JYAMS PET Research and Development Limited, Nanjing, Jiangsu, China

Radiopharmaceuticals targeting prostate-specific membrane antigens (PSMA) are essential for the diagnosis, evaluation, and treatment of prostate cancer (PCa), particularly metastatic castration-resistant PCa, for which conventional treatment is ineffective. These molecular probes include [^{68}Ga]PSMA, [^{18}F]PSMA, [Al^{18}F]PSMA, [^{99m}Tc]PSMA, and [^{89}Zr]PSMA, which are widely used for diagnosis, and [^{177}Lu]PSMA and [^{225}Ac]PSMA, which are used for treatment. There are also new types of radiopharmaceuticals. Due to the differentiation and heterogeneity of tumor cells, a subtype of PCa with an extremely poor prognosis, referred to as neuroendocrine prostate cancer (NEPC), has emerged, and its diagnosis and treatment present great challenges. To improve the detection rate of NEPC and prolong patient survival, many researchers have investigated the use of relevant radiopharmaceuticals as targeted molecular probes for the detection and treatment of NEPC lesions, including DOTA-TOC and DOTA-TATE for somatostatin receptors, 4A06 for CUB domain-containing protein 1, and FDG. This review focused on the specific molecular targets and various radionuclides that have been developed for PCa in recent years, including those mentioned above and several others, and aimed to provide valuable up-to-date information and research ideas for future studies.
Keywords: Prostate cancer; Prostate specific membrane antigen; Neuroendocrine prostate cancer; Radionuclide imaging; Radionuclide treatment

INTRODUCTION

Prostate cancer (PCa) arises from prostate epithelial cells and is the most common malignancy of the male genitourinary system (7.1% of all cancers) and the second leading cause of cancer-related deaths in men [1]. Current treatment options for early-stage PCa include prostatectomy or local radiotherapy, which are generally effective. Nevertheless, approximately 35% of PCa patients develop biochemical recurrence, for which the diagnostic criterion is elevated prostate-specific antigen (PSA) levels. Moreover, a significant proportion of these patients also exhibit distant metastases [2]. Prostate-specific membrane antigen (PSMA) shows significantly higher expression in primary and metastatic lesions than in normal tissues and has become an important molecular target in PCa.

Androgen receptor (AR)-targeted therapy is required when PCa progresses or recurs. However, although such treatment can temporarily control tumor progression (usually for 2–3 years), it inevitably promotes the adaptation of tumor cells to low-androgen conditions, resulting in highly aggressive (and lethal) metastatic castration-resistant prostate cancer (mCRPC) [3]. AR pathway inhibition, which is widely used clinically, leads to the neuroendocrine differentiation of PCa cells, promoting the more general castration-resistant prostate cancer (CRPC) subtype, namely, neuroendocrine prostate cancer (NEPC) [4]. NEPC is unresponsive to AR-targeted therapy and is characterized by decreased PSMA

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Corresponding author: Weijing Tao, MD, Department of Nuclear Medicine, The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, 1 Huanghe Road West, Huaiyin District, Huai'an 223300 Jiangsu, China.
• E-mail: weijingtao2021@vip.163.com

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expression [5].

Radionuclide-targeted molecular probes can facilitate the precise positioning and treatment of lesions and effectively prolong progression-free and overall survival [6-8]. Therefore, radiopharmaceuticals play an important role in the detection and treatment of primary and metastatic PCa lesions, particularly those in the mCRPC and NEPC stages. Currently, there are various radionuclide molecular probes targeting PCa. In this review, we divided these molecular probes into two main categories: PSMA and non-PSMA. Non-PSMA molecular probes are further classified into those targeting NEPC and others. It is hoped that this review involving dozens of radiopharmaceuticals (Tables 1, 2) will help to improve the overall understanding of available radionuclide molecular probes for PCa.

PSMA

PSMA is a 100kDa type II transmembrane protein [9-11], with glutamate carboxypeptidase and folate hydrolase activity [12,13]. PSMA expression is increased 100- to 1000-fold in PCa cells compared to that in normal cells and is correlated with PCa grade based on the Gleason score (GS), which is an independent predictor of PCa progression [14-16]. Monoclonal antibodies and small-molecule inhibitors have been found to effectively bind to the extracellular portion of PSMA, where most small-molecule compounds, such as PSMA-617, PSMA-I&T (I&T: imaging and treatment), MIP-1404, and MIP-1405, are rapidly excreted by cells, which reduces the radiation exposure. PSMA acts as an important site for the coupling of radionuclides, allowing for the detection and treatment of PCa lesions. The following is a summary of the radiopharmaceuticals that target PSMA in the diagnosis and treatment of PCa.

^{68}Ga-PSMA

Gallium-68 is a short half-life positron radionuclide (half-life:68 min) used for positron emission tomography (PET) imaging [17]. In general, ^{68}Ga-labeled PSMA PET performs significantly better than conventional imaging examinations because of its exceptionally high sensitivity and specificity for primary and metastatic PCa lesions [18]. [^{68}Ga]PSMA PET has been reported to detect 35.4% more PCa lesions than MRI [19,20]. Additionally, compared to ^{18}F-choline and ^{11}C-choline, [^{68}Ga]PSMA PET increases the detection of local recurrence and metastases to the lymph nodes and bone by 14% [21,22]. Furthermore, when PSA levels are very low, [^{68}Ga]PSMA PET can accurately detect PCa recurrent lesions biochemically [9,23]. [^{68}Ga]PSMA PET can also be used for accurate TNM staging, which helps guide appropriate treatment strategies for patients [24-26].

Common PSMA ligands coupled to gallium-68 include PSMA-11, PSMA-617, and PSMA-I&T. These are all small-molecule inhibitors. For small molecule inhibitors, the strong zinc-binding motif of the enzyme's active site and the glutaric acid portion of the P1' position bound to the S1' pocket are critical [27,28]. In PSMA-11, the lipophilicity between the radionuclide and the PSMA-active group (glutamate-urea-lysine) is enhanced via the conjugated HBED-CC group. This has now become the preferred chelate for gallium-68 PSMA tracers [27,29,30]. [^{68}Ga]Ga-PSMA-11 significantly accumulates in the spleen and salivary glands and is equally eliminated via the renal and hepatobiliary routes. When [^{68}Ga]Ga-PSMA-11 PET is used for the detection of PCa lesions, the positive predictive value was consistently greater than 0.8 and 0.75 for pelvic nodal metastasis [31,32]. [^{68}Ga]Ga-PSMA-11 positron emission tomography-computed tomography (PET-CT) detected PCa recurrence in 86% of patients who did not meet the definition of biochemical recurrence [33,34].

PSMA-617 is another PSMA ligand that connects radionuclides via conjugated DOTA chelates. DOTA-conjugated PSMA-617 was labeled with ^{68}Ga for PET imaging and ^{177}Lu/^{225}Ac for nuclide therapy. However, because [^{68}Ga]Ga-PSMA-617 is rapidly excreted (mainly through the kidneys), it can interfere with the diagnosis of primary and periurethral PCa lesions. Therefore, this tracer is primarily used to evaluate metastatic PCa. PSMA-I&T is similar to PSMA-617, and can be coupled to multiple radionuclides. However, it uses the chelating compound DATAGA, as opposed to DOTA, for PSMA-617. [^{68}Ga]Ga-PSMA-I&T has a low background uptake in the liver and spleen. Therefore, [^{68}Ga]Ga-PSMA-I&T shows greater sensitivity for the detection of primary and metastatic periurethral PCa lesions compared with [^{68}Ga]Ga-PSMA-617, especially for high-grade PCa (GS 8 or above, PSA > 10 ng/mL). However, the kidneys have a much higher uptake of PSMA-I&T than PSMA-617, which is unfavorable for treatment [35-37].

PSMA-TO-1 (tumor-optimized-1) and iPSMA-BN (iPSMA-Lys3-bombesin) are relatively rare gallium-labeled PSMA ligands. PSMA-TO-1 was developed to have a prolonged circulation time using an extended linker with additional naphthyl groups to increase protein binding in the blood and promote lipophilicity. Therefore, it has a higher uptake

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Table 1. The Structural Formula, Indication, Advantages, and Disadvantages of Various Radiopharmaceuticals in PCa

Radiopharmaceuticals	Formula of Ligand	Indication	Advantage	Limitation
Imaging				
^{68}Ga-PSMA-11	N,N′-bis(2-hydroxy-5- (carboxyethyl)Benzyl] ethylenediamineN,N′-diacetic acid	Primary and recurrent adenocarcinoma of prostate and its metastatic lesions	1. Clear blood and organs quickly 2. Low liver accumulation	1. Half-life short 2. Slightly low spatial resolution
^{68}Ga-PSMA-617	2-[3-(1-Carboxy-5-{3-naphthalen-2-yl-2-[(4-{[2-(4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetylamino]-methyl}-cyclohexanecarbonyl)-amino]-propionylamino}-pentyl)-ureido]-pentanedioic acid	Primary and recurrent adenocarcinoma of prostate and its metastatic lesions	1. The kidneys excrete quickly 2. High ratio of tumor to background tissue 3. Ligands can be attached to therapeutic nuclides	High intake of salivary glands and intestines
^{68}Ga-PSMA-I&T	(2S)-2-[[(1S)-1-carboxy-5-[[8-[[(5R)-5-carboxy-5-[[(2R)-2-[[(2R)-2-[[4-carboxy-4-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetrazacyclododec-1-yl]butanoyl]amino]-3-(4-hydroxy-3-iodophenyl)propanoyl]amino]-3-phenylpropanoyl]amino]pentyl] amino]-8-oxooctanoyl] amino]pentyl]carbamoylamino]pentanedioic acid	Primary and recurrent adenocarcinoma of prostate and its metastatic lesions	1. Low background uptake in liver and spleen 2. Ligands can be attached to therapeutic nuclides	High renal intake
^{68}Ga-iPSMA-BN	HO-Glu-CO-Lys{Nal-Cys[Pyr-Gln-Lys(maleimidobutyl)-Leu-Gly-AsnGln-Trp-Ala-Val-Gly-His-Leu-Met-NH2]-DOTA}-OH	Primary and recurrent adenocarcinoma of prostate and its metastatic lesions	Detect liver metastases because of low liver background	Low hepatobiliary clearance
^{68}Ga-PSMA-TO-1	(3S,7S,12S,19R,26R,29R,32R,35S)-19-(3,5-dicarboxybenzamido)-32-(4-hydroxybenzyl)-29,35-bis(naphthalen-2-ylmethyl)-5,10,17,20,28,31,34,37-octaoxo-40-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)-4,6,11,16,21,27,30,33,36-nonaazatetracontane-1,3,7,12,26,40-hexacarboxylic acid	All lesions from adenocarcinoma of prostate and NEPC	1. Higher lesions' uptake value than ^{68}Ga-PSMA-I&T 2. Liver metastases because of low background in liver 3. Detect various differentiated prostate cancer 4. Ligands can be attached to therapeutic nuclides	High renal uptake
^{68}Ga-NeoBOMB1	2-[4-[2-[[4-[[2-[2-[[(2R)-1-[[(2S)-5-amino-1-[[(2S)-1-[[(2S)-1-[[(2S)-1-[[2-[[(2S)-1-(2,6-dimethylheptan-4-ylamino)-3-(1H-imidazol-5-yl)-1-oxopropan-2-yl] amino]-2-oxoethyl]amino]-3-methyl-1-oxobutan-2-yl] amino]-1-oxopropan-2-yl]amino]-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino]-1,5-dioxopentan-2-yl]amino]-1-oxo-3-phenylpropan-2-yl]amino]-2-oxoethoxy] acetyl]amino]phenyl] methylamino]-2-oxoethyl]-7,10-bis(carboxylatomethyl)-1,4,7,10-tetrazacyclododec-1,4,7-triyl]triacetic acid	All lesions from adenocarcinoma of prostate and NEPC	1. Retain longer in tumor 2. High metabolic stability 3. Rapid renal excretion 4. Detect various differentiated prostate cancer	-
^{68}Ga-DOTA-NT-20.3	Ac-Lys(DOTA)-Pro-Me-Arg-Arg-Pro-Tyr-Tle-Leu-OH	NEPC	Exhibit high stability and retention within tumors	Low sensitivity for adenocarcinoma of prostate

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Table 1. The Structural Formula, Indication, Advantages, and Disadvantages of Various Radiopharmaceuticals in PCa (continued)

Radiopharmaceuticals	Formula of Ligand	Indication	Advantage	Limitation
^{68}Ga-RM26	D-Phe–Gln–Trp–Ala–Val–Gly–His–Sta–Leu–NH2	NEPC	High tumor-to-background ratio	Low sensitivity for adenocarcinoma of prostate
^{18}F-PSMA-1007	2-(3-(1-carboxyl-5-(6-[^{18}F]pyridine-3-carbonyl) -amino)-Amyl)-urea)-glutaric acid	Adenocarcinoma of prostate	1. More sensitive to bone marrow metastasis 2. Lesions near the bladder and ureter	Difficult to observe liver lesions
^{18}18F-DCFPyL	2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)- pentanedioic acid	Adenocarcinoma of prostate	1. Low background of blood pool 2. Detect prostate lesions with low grade and small volume	High intake of salivary glands, liver, small intestine
^{18}F-JK-PSMA-7	2-MeO-2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)- pentanedioic acid	Adenocarcinoma of prostate	Compared with ^{18}F-DCFPyL: 1. High image quality 2. High small PSMA-expressing foci sensitivity	Low detection rate when PSA < 0.3 ng
Al^{18}F-PSMA-BCH	(((S)-5-((S)-2-((1r,4S)-4-((2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl)acetamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)-1-carboxypentyl)carbamoyl)-L-glutamic acid	Adenocarcinoma of prostate	Easy to prepare	Compared to ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007: Low detection rate of lesions
Al^{18}F-PSMA-11	N,N′-bis(2-hydroxy-5- (carboxyethyl)Benzyl] ethylenediamineN,N′-diacetic acid	Adenocarcinoma of prostate	Easy to prepare	Poor stability at room temperature
^{99m}Tc-MIP-1404	((7S,12S,16S)-1-(1-(2-(bis(carboxymethyl)amino)-2-oxoethyl)-1H-imidazol-2-yl)-2-((1-(2-(bis(carboxymethyl) amino)-2-oxoethyl)-1H-imidazol-2-yl)methyl)-9,14-dioxo-2,8,13,15-tetraazaoctadecane-7,12,16,18-tetracarboxylic acid	Adenocarcinoma of prostate	1. Can delay imaging 2. Detect the gland and pelvis lesions in early stage because of minimal urinary excretion	Low detection rate of liver lesions
^{99m}Tc-MIP-1405	(7S,14S,18S)-7-amino-1-(1-(carboxymethyl)-1H-imidazol-2-yl)-2-((1(carboxymethyl)-1H-imidazol-2-yl)methyl)-8,16-dioxo-2,9,15,17tetraazaicosane-14,18,20-tricarboxylic acid	Adenocarcinoma of prostate	Compared with ^{99m}Tc-MIP-1404: The whole-body clearance was significantly greater	Less sensitive to liver lesions than ^{99m}Tc-MIP-1404
^{89}Zr-PSMA-Df*	-	Adenocarcinoma of prostate	Compared with ^{68}Ga-PSMA-11 and ^{18}F-JK-PSMA-7: 1. Long half-life 2. High tumor-to-background ratio 3. High sensitivity of metastatic lymph nodes near the ureter	Difficult to prepare
^{89}Zr-df-IAB2M*	-	Adenocarcinoma of prostate	1. Rapid bio-distribution with efficient target penetration 2. Facilitate earlier lesion detection	Difficult to prepare
^{89}Zr-4A06*	-	All lesions from adenocarcinoma of prostate and NEPC	1. High sensitivity 2. Detect various differentiated prostate cancer	Difficult to prepare
^{18}F-FDG	2-Fluoro-2-deoxy-D-glucose	NEPC	1. Easy to prepare 2. NEPC can be detected	Not specific

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Table 1. The Structural Formula, Indication, Advantages, and Disadvantages of Various Radiopharmaceuticals in PCa (continued)

Radiopharmaceuticals	Formula of Ligand	Indication	Advantage	Limitation
^{18}F-FSPG	(S)-4-(3-[^{18}F]fluoropropyl)-L-glutamate	Adenocarcinoma of prostate	1. Excrete rapidly through the kidney 2. Low background activity 3. Reflect tumor redox status and antioxidant capacity to predict tumor chemotherapy resistance	Difficult to observe lesions near the bladder and ureter
Treatment				
^{177}Lu-PSMA-617	Like ^{68}Ga-PSMA-617	mCRPC	Integration of diagnosis and treatment	Excessive lacrimal gland intake
^{177}Lu-EB-PSMA-617	(((1S)-5-((2S)-2-(4-((2-((1-(2-(((R)-6-((4'-((Z)-(8-amino-1-hydroxy-5,7-disulfonaphthalen-2-yl)diazenyl)-3,3'-dimethyl-[1,1'-biphenyl]-4-yl)amino)-6-oxo-5-(2-(4,7,10-tris (carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl) acetamido)hexyl)amino)-2-oxoethyl)-2,5-dioxopyrrolidin-3-yl)thio)acetamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)-1-carboxypentyl) carbamoyl)-L-glutamic acid	mCRPC	Compared with ^{177}Lu-PSMA-617: 1. Longer half-life 2. The maximum therapeutic effect with the lowest dose	Excessive lacrimal gland intake
^{177}Lu-PSMA-I&T	Like ^{68}Ga-PSMA-11	mCRPC	Integration of diagnosis and treatment	Nephrotoxicity
^{177}Lu-PSMA-TO-1	Like ^{68}Ga-PSMA-TO-1	mCRPC and NEPC	Compared with ^{177}Lu-PSMA-617: 1. Long circulation time and improve the therapeutic effect 2. Therapy various differentiated prostate cancer	1. Nephrotoxicity 2. Hematotoxicity 3. Bone marrow involvement
^{177}Lu-4A06*		mCRPC and NEPC	1. Can better inhibit and eliminate mCRPC lesions 2. Therapy various differentiated prostate cancer	-
^{225}Ac-PSMA-617	Like ^{68}Ga-PSMA-617	mCRPC	1. Long physical half-life and high linear energy of α nuclides 2. Better therapeutic effect than ^{177}Lu-PSMA-617	Xerostomia
^{225}Ac-PSMA-TO-1	Like ^{68}Ga-PSMA-TO-1	mCRPC and NEPC	1. Long physical half-life and high linear energy of α nuclides 2. Better therapeutic effect than ^{225}Ac-PSMA-617 3. Therapy various differentiated prostate cancer	Nephrotoxicity
^{90}Y-DOTA-TOC	1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetra-acetic acid-D-Phe1-Tyr3-Octreotide	NEPC	Improve the treatment effect of neuroendocrine tumors	Hematotoxicity

*There is no formula for antibodies. PCa = prostate cancer, NEPC = neuroendocrine prostate cancer, mCRPC = metastatic castration-resistant prostate cancer, PSMA = prostate-specific membrane antigens, PSA = prostate-specific antigen, I&T = imaging and treatment

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Table 2. Clinical Significance of Radionuclides in Patients with Prostate Cancer

Radiopharmaceuticals	Clinical Significance
[^{68}Ga]Ga-PSMA-11 [^{68}Ga]Ga-PSMA-617 [^{68}Ga]Ga-PSMA-I&T [^{68}Ga]Ga-iPSMA-BN	They can detect more than 80% of clinically unpredictable biochemical relapses, which could be benefit for early diagnosis, staging and curative effect of prostatic adenocarcinoma and guide clinicians to formulate personalized treatment plans. Among them, [^{68}Ga]Ga-PSMA-I&T can detect high-grade prostatic adenocarcinoma (GS 8 or above, PSA > 10 ng/mL) sensitively and [^{68}Ga]Ga-iPSMA-BN accumulates the least in the body.
[^{68}Ga]Ga-PSMA-TO-1	It can improve the accuracy of early diagnosis, staging and curative effect of prostatic adenocarcinoma under the delayed imaging.
[^{68}Ga]NeoBOMB1	It stays in the tumor longer than other organs, so it can detect the prostatic adenocarcinoma and NEPC more accurately.
[^{68}Ga]Ga-DOTA-NT-20.3 [^{68}Ga]RM26	They can make early diagnosis and curative effect of NEPC, including the PRRT treatment.
[^{18}F]F-PSMA-1007 [^{18}F]DCFPyL [^{18}F]F-JK-PSMA-7	They can sensitively detect small periurethral lesions of prostatic adenocarcinoma.
Al[^{18}F]F-PSMA-BCH Al[^{18}F]F-PSMA-11	In the absence of the Ge/Ga generator, they are easy to be prepared, which is beneficial to examination of more prostatic adenocarcinoma patient.
[^{99m}Tc]Tc-MIP-1404 [^{99m}Tc]Tc-MIP-1405	Radiation dose of patients with prostatic adenocarcinoma can be reduced in the examination with single-photon radionuclides.
[^{89}Zr]Zr-PSMA-Df	It can improve the detection rate of lymph node metastasis near ureter, which is conducive to the accurate staging of the prostatic adenocarcinoma.
[^{89}Zr]Zr-df-IAB2M	It can perform delayed imaging and can rapid from the body quickly.
[^{89}Zr]4A06 [^{18}F]FDG	They can detect neuroendocrine prostate cancer to distinguish between different types of prostate cancer.
[^{18}F]FSPG	It can reflect tumor redox status and antioxidant capacity, and predict tumor chemotherapy resistance of prostatic adenocarcinoma.
[^{177}Lu]Lu -PSMA-617 [^{177}Lu]Lu-EB-PSMA-617 [^{177}Lu]Lu -PSMA-I&T	These radionuclides are suitable for patients with prostatic adenocarcinoma who have already developed mCRPC.
[^{177}Lu]Lu-PSMA-TO-1 [^{177}Lu]4A06 [^{177}Lu]NeoBOMB1	They can therapy prostatic adenocarcinoma and NEPC at all stages.
[^{225}Ac]Ac-PSMA-617 [^{225}Ac]Ac-PSMA-TO-1	They can therapy lesions that are insensitive to ^{177}Lu-lableded pharmaceuticals.
[^{90}Y]Y-DOTA-TOC	It can therapy patients with NEPC at all stages.

There is almost no difference in the clinical significance of nuclides in the same cell. GS = Gleason score, PSA = prostate-specific antigen, NEPC = neuroendocrine prostate cancer, PRRT = peptide receptor radionuclide therapy, mCRPC = metastatic castration-resistant prostate cancer

in the primary and metastatic lesions than PSMA-617 and PSMA-I&T. Liver metastases show higher tracer uptake of [^{68}Ga]Ga-PSMA-TO-1 than of [^{68}Ga]Ga-PSMA-11 (mean standard uptake value [SUV_{mean}]: 6.0 vs. 4.0). After 120 min, the SUV_{mean} of [^{68}Ga]Ga-PSMA-TO-1 in metastases increased to 8.0 (up to 33%) [38]. Furthermore, there have been few comparative studies of PSMA-TO-1 and other gallium-labeled PSMA tracers. iPSMA-BN includes a heterodimer with the sequence HO-Glu-CO-Lys-OH and was recently designed to target PSMA and gastrin-releasing peptide receptor (GRPR), which are overexpressed in different stages of PCa. iPSMA-BN can be labeled with ^{68}Ga and ^{177}Lu, making it possible to integrate diagnosis and treatment. [^{68}Ga]Ga-iPSMA-BN showed faster blood clearance than [^{68}Ga]Ga-PSMA-11 (half-life in the blood = 2.64 min vs. 6.5 min). [^{68}Ga]Ga-iPSMA-BN clearly visualized the pancreas and is eliminated mainly via the kidneys, with low hepatobiliary clearance and low salivary gland uptake.

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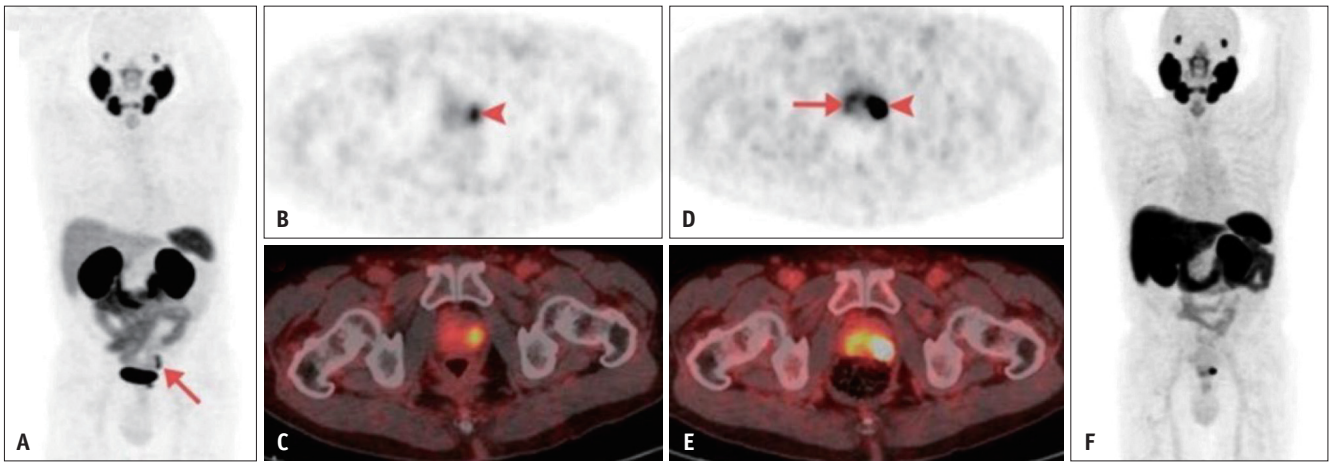

Fig. 1. Maximum intensity projections (MIPs), axial images of positron emission tomography (PET), and axial fusion images of PET-computed tomography (CT) using [^{68}Ga]Ga-PSMA-11 **(A, B, C)** and [^{18}F]F-PSMA-1007 **(D, E, F)** in a 67-year-old male with Gleason 8 and PSA 4.9 ng/mL. The MIP image of [^{68}Ga]Ga-PSMA-11 **(A)** (arrow) shows significant uptake in the bladder and left ureter, while urinary excretion of [^{18}F]F-PSMA-1007 **(F)** is virtually absent. Lesions in the left prostate lobe are visible on both scans (arrowheads in **B**, **D**). However, the second lesion in the right lobe is only visible under [^{18}F]F-PSMA-1007 (arrow in **D**), and has been pathologically confirmed to be a malignant lesion. Reprinted with permission from Kuten et al. [39] (*J Nucl Med* 2020;61:527-532; https://doi.org/10.2967/jnumed.119.234187). PSMA = prostate-specific membrane antigen

^{18}F-PSMA

^{18}F is produced by a cyclotron and has a higher yield and longer half-life than ^{68}Ga (110 min vs. 68 min) [39,40]. ^{18}F-labeled PSMA ligands have the potential for centralized production and distribution, thus enabling cost savings. PSMA-1007 is a novel PSMA ligand with Glu-urea-Lys targeting the PSMA enzyme pocket S1′ and a naphthalenyl linkage region thought to co-target the hydrophobic accessory pocket S1. The main difference is that the radiolabeled molecule in the carboxyl group of the DOTA chelating agent is replaced by two glutamic acids [27,41]. [^{18}F]F-PSMA-1007 is excreted mainly in hepatic bile and minimally in urine, facilitating a high detection rate of lesions that are near the bladder and ureter. Moreover, [^{18}F]F-PSMA-1007 offers advantages in terms of imaging quality and sensitivity, making it a promising candidate for clinical applications [42-44]. Another ^{18}F labeled PSMA-specific small molecule imaging agent, 2-(3-[45]-ureido)-pentanedioic acid ([^{18}F]DCFPyL), has also been developed based on the Glu-urea-Lys motif. This molecule is characterized by high affinity and favorable pharmacokinetics in vivo [23,45,46], thus allowing the earlier detection of local recurrence, even at lower PSA levels [47]. The novel probe, JK-PSMA-7, was identified by screening multiple DCFPyL analogs, with the main difference being the addition of a methoxy group to the pyridine ring. [^{18}F] F-JK-PSMA-7 is rapidly excreted via the kidneys [48,49] and yields high-quality images, allowing the detection of small PSMA-expressing foci with high sensitivity [50,51] (Fig. 1).

Al^{18}F-PSMA

Al^{18}F was developed as an ^{18}F-labeling technique that allows convenient ^{18}F-labeling and requires less time under mild conditions. Al[^{18}F]F-PSMA-BCH can be prepared at a reasonable yield within 30 min and is mostly a stable complex with the macrocyclic NODA chelate and Al^{18}F2þ. Al[^{18}F]F-PSMA-BCH shows promising imaging capabilities for PCa with appropriate radiation exposure. Al[^{18}F]F-PSMA-BCH is highly hydrophilic. The uptake of Al[^{18}F]F-PSMA-BCH is dependent on PSMA levels in cells and tumors. Al[^{18}F]F-PSMA-BCH accumulates in the kidneys and can be significantly blocked by ZJ-43(a PSMA inhibitor) because of the high hydrophilicity of Al[^{18}F]F-PSMA-BCH and high PSMA levels in the kidneys. The maximum standard uptake values (SUV_{max}) for patients with high-risk PCa (GS ≥ 8) are significantly higher than those for patients with intermediate-risk PCa. This is similar to the findings of a previous study on [^{68}Ga]Ga-PSMA-617 [52]. The SUV_{max} and SUV_{mean} of Al[^{18}F]F-PSMA-BCH in PCa lesions are significantly increased after 1 h and 2 h. Al[^{18}F]F-PSMA-BCH is almost non-toxic and more economical for patients [41,52]. Al[^{18}F]F-PSMA-11 is another PSMA radioligand, and its uptake in the kidneys is greatly reduced compared to [^{68}Ga]Ga-PSMA-11 both at

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1 h and 4 h. Meanwhile, Al[^{18}F]F-PSMA-11 develops well in tumors with high PSMA expression and is influenced by its own molar activity. The higher the molar activity, the better the developmental effect. However, studies have found that the uptake of Al[^{18}F]F-PSMA-11 is higher in bone and lower in PSMA-positive tumors than that of both [^{68}Ga]Ga-PSMA-11 and [^{18}F]F-PSMA-1007 [53,54].

^{99m}Tc-PSMA

Single-photon emission computed tomography CT (SPECT-CT) is a more cost-effective imaging method than PET-CT. Technetium-99m has better physical properties for gamma probe measurements, thus reducing the radiation exposure for both patients and medical personnel [55]. ^{99m}Tc-labeled PSMA ligands, including [^{99m}Tc]Tc-MIP-1404 and [^{99m}Tc]Tc-MIP-1405 (both of which utilize an imidazole with a carboxylate substitution), have favorable pharmacokinetic properties. Compared to [^{99m}Tc]Tc-MIP-1405, [^{99m}Tc]Tc-MIP-1404 has shown a greater uptake in the liver and spleen, owing to its higher ratio of carboxyl groups. The phase III clinical trials for [^{99m}Tc]Tc-MIP-1404, also known as Treforsta, have recently been completed [27]. Compared to [^{68}Ga]PSMA, delayed SPECT-CT imaging using [^{99m}Tc]PSMA can ensure the choice of subsequent treatment strategies [56,57]. Furthermore, scintigraphy with [^{99m}Tc]MDP is limited by factors, such as low PSA levels, long PSA doubling times, and osteolytic lesions. Thus, many examination results may be equivocal. In this regard, [^{99m}Tc]PSMA is superior to MDP and more sensitive for the detection of visceral metastases [58,59].

^{89}Zr-PSMA

Ligand internalization is a vital prerequisite for tracer accumulation in PCa lesions. Experimental data suggest that the internalization of PSMA ligands gradually increases over 24 h. Currently, the commonly used PSMA tracers have a short radioactive half-life, necessitating PET imaging within 3 h of injection. To overcome this limitation, a new ligand, ^{89}Zr-labeled PSMA tracer ([^{89}Zr]Zr-PSMA-Df) was explored. The long half-life of ^{89}Zr (77 h) and the prolonged ligand internalization period allow image acquisition several days after the tracer injection. Compared to [^{68}Ga]Ga-PSMA-11 and [^{18}F]F-JK-PSMA-7, [^{89}Zr]Zr-PSMA-Df shows a higher tumor-to-background ratio and increases the detection rate of metastatic lymph nodes near the ureter. Additionally, [^{89}Zr]Zr-PSMA-Df can detect [^{68}Ga]Ga-PSMA-11 or [^{18}F]F-JK-PSMA-7 intake-free lesions, thus improving the detection rate (57%) of biochemically recurrent lesions [60].

Most PSMA ligands described above are small-molecule inhibitors of PSMA. An 85-Kd vesicle, IAB2M, has also been developed. This molecule is a de-immunizing monoclonal antibody that binds to the extracellular region of PSMA. The performance of [^{89}Zr]Zr-df-IAB2M PET in detecting intra- and extra-prostatic lesions supports its use in clinical patient management for radical prostatectomy, pelvic lymphadenectomy, radiotherapy, and systemic therapy [61].

^{177}Lu-PSMA

Radioligand therapy (RLT) targeting PSMA effectively controls PCa progression at the mCRPC stage [62,63]. ^{177}Lu is a commonly used β radionuclide, and [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T have been used to treat mCRPC [64]. In one study, PSA levels decreased by 65% following [^{177}Lu]PSMA treatment, compared with a 37% PSA reduction after traditional treatment [65]. Although ligand studies for ^{177}Lu labeling are ongoing, PSMA ligands with a DOTA-BnSCN structure show higher uptake and internalization, whereas better tumor uptake and retention have been demonstrated for bromophenyl-modified ligands and PSMA ligands with linear linkers [66,67]. RLT can cause xerostomia due to the high intake of [^{177}Lu]PSMA by the salivary glands. Furthermore, the rapid excretion of [^{177}Lu]PSMA from the body results in ^{177}Lu-contaminated waste. To solve this problem, researchers proposed the introduction of Evans Blue dye into serum albumin to extend the circulation half-life of [^{177}Lu]Lu-PSMA-617 in vivo to obtain [^{177}Lu]Lu-EB-PSMA-617, which reached the maximum therapeutic effect at the lowest dose.

However, more than half of the patients with mCRPC treated with PSMA RLT ultimately failed treatment. The reasons for disease progression or lesion recurrence may include insufficient radiation dose delivery or radioresistance. One potential strategy for increasing tumor radiation doses is to extend the PSMA ligand circulation time. Tumor uptake was higher with PSMA-TO-1 than with PSMA-617 at all measured time points after 1h. The absorption of [^{177}Lu]Lu-PSMA-TO-1 was 26 times greater than that of [^{177}Lu]Lu-PSMA-617, suggesting long-term nephrotoxicity. Because PSMA-TO-1 is a long-circulating peptide, higher bone marrow doses are expected. While this higher dose could pose a greater risk of hematotoxicity and greater bone marrow exposure, dose delivery may be effective for treating bone marrow involvement [38].

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^{225}Ac-PSMA

^{225}Ac is an α radionuclide with a longer physical half-life and higher linear energy than α nuclides, and can cause DNA double-strand breaks and cell death. [^{225}Ac]PSMA is potentially highly effective against tumors. For example, lesions that do not respond to the [^{177}Lu]PSMA treatment can be eradicated by using [^{225}Ac]PSMA (Fig. 2). Additionally, [^{225}Ac]PSMA treatment can benefit patients with mCRPC who has developed diffuse red bone marrow infiltration and fail to respond to other therapies [68,69]. Although, xerostomia is one of the adverse effects of [^{225}Ac]PSMA treatment , the treatment is generally tolerated by the patients, and the incidence of xerostomia is reduced by applying ice [70,71]. Similar to ^{177}Lu, ^{225}Ac can be conjugated to PSMA ligands (PSMA-617, PSMA-I, PSMA-T, and PSMA-TO-1) and used for the treatment of mCRPC. The survival benefit conferred to mice treated with [^{225}Ac]Ac-PSMA-TO-1 was statistically significant compared with that observed in mice treated with [^{225}Ac]Ac-PSMA-617 [38].

Many other nuclides are under development, such as [^{18}F]F-PSMA-7Q [72], [^{111}In]In-PSMA-617 [73], [^{68}Ga]Ga-P16-093 [74], ^{68}Ga-NGUL [75], and dual-targeted nuclides, such as [^{64}Cu]Cu-FP-L1, which target both PSMA and fibroblast activator protein inhibitors (FAPI) [76].

NEPC Radionuclide Imaging and Therapy

PSMA-labeled radionuclides still play an important role in PCa. PCa cells express both adenocarcinoma and neuroendocrine differentiation markers. In contrast, this is not the case for NEPC, which expresses neuroendocrine differentiation only. Moreover, NEPC usually appears in the later stages of CRPC treatment and is characterized by small-cell morphology, downregulation of AR expression, and upregulation of neuroendocrine markers. In contrast to PCa adenocarcinoma, treatment-induced NEPC has aggressive tumor features, including large tumor size and a predisposition to bone and visceral metastases. Furthermore, treatment-induced NEPC has an inferior prognosis and is unresponsive to androgen deprivation therapy. The most common causes of NEPC development are the loss of the tumor suppressors RB1 and TP53 and the activation of oncogenic drivers, combined with significant epigenetic changes that further promote tumor proliferation and neuroendocrine lineage pathways [77]. In most NEPC cases, hormone depletion, p53 deletion, and lineage plasticity inhibit the PSMA gene, FOLH1. However, other molecular probes for NEPC differ from PSMA in prostate adenocarcinoma.

SSTR-2-Targeted Radionuclide Imaging and Therapy

There are five somatostatin receptor (SSTR) subtypes

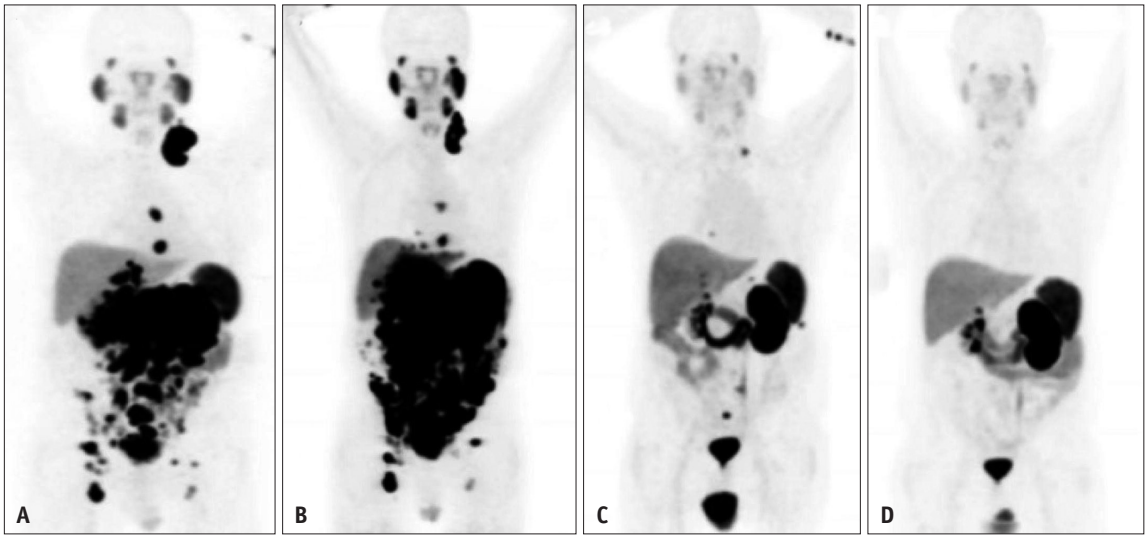

Fig. 2. [^{68}Ga]Ga-PSMA-11 positron emission tomography-computed tomography (PET-CT) scans of a patient with prostate cancer before and after radionuclide therapy. **A:** [^{68}Ga]Ga-PSMA-11 PET-CT imaging before radionuclide therapy. **B:** Progression is observed after 2 cycles of treatment with beta-emitting [^{177}Lu]Lu-PSMA-617. Promising treatment results after two **(C)** and three **(D)** cycles of treatment with α-emitting [^{225}Ac]Ac-PSMA-617. Reprinted with permission from Kratochwil et al. [68] (*J Nucl Med* 2016;57:1941-1944; https://doi.org/10.2967/jnumed.116.178673).

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(SSTRs 1–5). Of these, SSTR2 is expressed specifically in neuroendocrine tumors (NETs). SSTR is a powerful target for NET-targeted therapy. NEPC cells show elevated expression of SSTR-2 and downregulation of PMSA [77-79]. Many studies have found that NEPC lesions show high radioactive uptake in SSTR-targeted PET [80] but no radioactive uptake in PSMA-targeted PET [81]. High-affinity ligands for SSTR, including TOC, NOC, and TATE, can be used to target NETs. ^{68}Ga-labeled DOTA-TOC and DOTA-TATE have been widely used for the PET imaging of tumors. Additionally, peptide receptor radionuclide therapy (PRRT) with [^{90}Y]Y-DOTA-TOC and [^{177}Lu]Lu-DOTA-TATE can improve treatment efficacy for NETs [4,45].

CDCP1-Targeted Radionuclide Imaging and Therapy

Overexpression of the single-pass transmembrane protein, CUB domain-containing protein 1 (CDCP1), is significantly associated with phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene loss and a more aggressive PCa phenotype. CDCP1 expression was detected in 90% of mCRPC biopsies. To quantify the number of CDCP1 receptors per cell, researchers have used 4A06, a monoclonal recombinant human antibody that recognizes the ectodomain of full-length or cleaved CDCP1. The tumor-autonomous expression of CDCP1 in mCRPC can be detected using [^{89}Zr]4A06 PET. Moreover, [^{177}Lu]4A06 RLT inhibits and eliminates mCRPC lesions [82]. Therefore, combining CDCP1-targeted RLT with standard treatment for mCRPC could be a potentially more efficacious clinical treatment strategy.

NT-20.3-Targeted Radionuclide Imaging

High expression levels of neurohypotensin receptor subtype 1 (NTR1) are associated with neuroendocrine differentiation in PCa, which makes NTR1 a potential target for NEPC imaging. Recent studies have reported positive NTR1 expression in 91.8% of PCa tissues, including all PSMA-negative tissues. [^{68}Ga]Ga-DOTA-NT-20.3, can be used as a targeted radionuclide for the detection of NEPC because of its high affinity for NTR1 and favorable distribution and kinetics in the body [83]. In PC3 xenografts expressing NTR1, high-contrast [^{68}Ga]Ga-DOTA-NT-20.3 images indicate the potential to detect low or neuroendocrine differentiation in PCa. Furthermore, NT-20.3 exhibits high stability and retention within tumors, which is conducive to its application in PRRT for mCRPC at later stages.

[^{18}F]FDG-PET Imaging

Some high-grade aggressive NETs frequently lose SSTR expression. FDG is a glucose analog that shows a high level of uptake by cells with high glycolysis rates. [^{18}F] FDG-PET is widely used to detect tumors. The degree of [^{18}F]FDG uptake reflects the level of glucose metabolism in viable tumor cells, with highly aggressive malignancies showing higher levels of [^{18}F]FDG uptake [45,84]. Studies have demonstrated that NEPC cells show increased glucose uptake owing to the increased expression of glucose transporters. More glucose is brought into the tumor cells and is phosphorylated by hexokinase [81]. Importantly, glucokinase levels are 5-fold higher in PSMA-negative tumors than in AR-positive tumors, leading to increased uptake and deposition of [^{18}F]FDG within NEPC cells [81,85]. Research has found that eecurrent NEPC lesions show an increased [^{18}F]FDG uptake and a decreased PSMA expression. These lesions are characterized by high metabolic activity, rapid progression, and poor prognosis [86,87]. Although [^{18}F]-FDG-PET is inefficient in detecting PCa lesions, it can be beneficial in detecting NEPC lesions [88] (Fig. 3).

Other Molecular Probes for PCa

Fibroblast Activator Protein Inhibitors

Fibroblast activator protein (FAP) is a 97 kDa type II transmembrane serine protease that is expressed at low or undetectable levels in normal tissues but at high levels in a variety of cancers, including 90% epithelial tumors [89,90]. Recently, quinoline-based FAPIs have been developed as promising imaging probes for various solid tumors, including PCa. FAP-targeted radionuclide imaging and treatment can overcome tumor heterogeneity and the limitations associated with insufficient PSMA expression. However, their application may be limited to highly differentiated PCa [86]. Additionally, FAPI-targeted RLT has shown therapeutic potential in PSMA-negative mCRPC [91].

FSPG

L-glutamate is an unnatural amino acid that is upregulated in many cancers and can reflect tumor redox status and antioxidant capacity, and predict resistance to chemotherapy [92,93]. The glutamate derivative, (S)-4-(3-18F-fluoropropyl)-L-glutamate (FSPG), is rapidly excreted through the kidneys and has low background activity, providing high contrast for tumor imaging [93]. [^{18}F]-labeled FSPG ([^{18}F]FSPG) has been used in clinical imaging of

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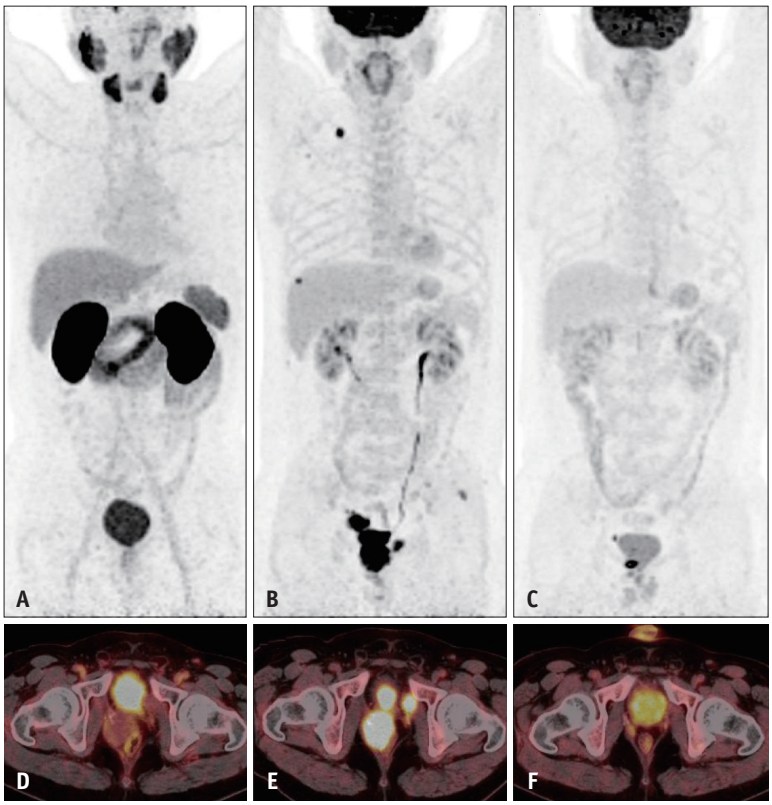

Fig. 3. Maximum intensity projection (MIP) of positron emission tomography (PET) and trans-axial fusion images of PET-computed tomography (CT) scans of a 53-year-old male with post-operative relapse of his prostate cancer. Al[^{18}F]F-PSMA PET-CT shows no uptake in the recurrent lesions **(A, D)**. [^{18}F]FDG PET-CT shows multiple lesions with high uptake throughout the body **(B, E)**. After six cycles of chemotherapy, [^{18}F]FDG PET-CT demonstrates that multiple lesions are significantly reduced in size and radioactive uptake **(C, F)**.

hepatocellular carcinoma, non-small cell lung cancer, PCa, and intracranial malignancies [94].

Gastrin-Releasing Peptide Receptor Antagonists

Although some NEPCs express little PSMA, they express GRPR. RM26 is a peptide skeleton-modified lactopin analog that serves as a high-affinity antagonist of GRPR, a member of the G protein-coupled receptor family of urotin receptors. Endogenous receptor expression is observed in the pancreas, whereas only low expression levels are detected in both normal and proliferative prostate tissues [7,95]. Studies have confirmed that [^{68}Ga]RM26-PET showed high specific uptake in tumors and a high tumor-to-background ratio [96,97]. [^{68}Ga]RM26-PET is of significant value for detecting primary and metastatic PCa lesions because GRPR expression is high in early-stage PCa. However, GRPR expression decreases as PCa progresses [98]. NOTA-DUPA-RM26 heterodimers that bind to both GRPR and PSMA are produced in PCa. These [^{68}Ga]- and [^{111}In]-labeled NOTA-DUPA-RM26 dimers can be used for simultaneous PSMA- and GRPR-targeted PET and SPECT imaging to improve the diagnostic accuracy of PCa [98,99].

NeoBOMB1 is a novel DOTA-coupled GRPR antagonist with a high affinity for GRPR and excellent in vivo stability. NeoBOMB1 can be labeled as [^{68}Ga] and [^{177}Lu]. Biodistribution studies with [^{68}Ga]NeoBOMB1 have shown high tumor uptake, leading to a clear visualization of the tumor on PET-CT scans. These data suggest that [^{177}Lu] NeoBOMB1 has strong specificity. It is also proven as a treatment for the currently known types of PCa, and has n a good tumor-kidney ratio [100].

SUMMARY

Radionuclide-labeled PSMA ligands are currently the most commonly used nuclide drugs in clinical practice. These drugs have replaced traditional imaging methods, allowing accurate TNM staging of PCa and providing a basis for the selection of a suitable treatment plan. Tracers excreted via the hepatobiliary route can highlight the bladder and periurethral lesions more clearly. Furthermore, promising progress has been made in the treatment of advanced mCRPC using [^{177}Lu]/[^{225}Ac]-PSMA.

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However, PSMA is not a perfect marker. There can be some physiological uptake of ligands and approximately 10% of primary PCa cases lack PSMA expression, which can arise from lesions with insufficient PSMA expression or from lesions developing into NEPC because of therapeutic AR resistance. Some NEPC targets have recently been used for NEPC imaging and treatment. Additionally, dual-targeting of PSMA and FAP by heterodimers has shown that combining different markers improved the specificity, sensitivity, and accuracy of PCa imaging and treatment. PRRT and RLT have opened new avenues for the treatment of NEPC. Furthermore, numerous radiopharmaceuticals and targeted molecular probes have continuously improved the detection rate of PCa lesions, and are being used for mCRPC, which will continue to be the focus of future research.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Weijing Tao. Funding acquisition: Weijing Tao. Methodology: Tianshuo Yang. Supervision: Weijing Tao. Writing—original draft: Luyi Cheng. Writing—review & editing: Jun Zhang, Feng Gao, Lingyun Yang.

ORCID iDs

Luyi Cheng
https://orcid.org/0000-0002-3382-3893
Tianshuo Yang
https://orcid.org/0000-0003-2272-8142
Jun Zhang
https://orcid.org/0000-0001-9761-2502
Feng Gao
https://orcid.org/0000-0002-8792-6257
Lingyun Yang
https://orcid.org/0000-0003-4479-5768
Weijing Tao
https://orcid.org/0000-0001-7262-9375

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