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Prostate-specific membrane antigen (PSMA)–ligand positron emission tomography and radioligand therapy (RLT) of prostate cancer

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Abstract

From a clinical perspective, prostate-specific membrane antigen (PSMA) is a valuable target for both diagnosis and radioligand therapy (RLT) of prostate cancer. The term 'specific' has been used to characterize a histologic hallmark of overexpression in the membrane of most prostate cancer. Many PSMA ligands have been developed since the previous decade and have been used in several clinical trials and clinical studies. However, procedure, specification, protocol, interpretation criteria, radiation dose, and cost-effectiveness of PSMA ligands have not been fully explained. Regardless of worldwide use of promising PSMA-ligand PET and RLT, it has not been approved in Japan. Expedited introduction of PSMA-ligand PET and RLT to Japan and implementation of clinical study are eager for many patients with prostate cancer.

Key words: PET, PET/CT, PSMA, prostate cancer, prostate-specific membrane antigen

Introduction

From the clinical perspective, prostate cancer shows the first prevalence in most countries and has been a global concern. The disease extent of prostate cancer at the time of initial diagnosis is mostly limited—that is, the presence of disease is suspected when the serum prostatic specific antigen (PSA) is elevated and the symptoms are present when the disease is already at an advanced stage after initial treatment—and as a rule there are no specific imaging methods or biomarkers to diagnose extent of disease except for PSA. Although treatment for patients with castration-resistant prostate cancer (CRPC) with more recently developed oral agents has improved quality of life, the group of CRPC has remained fatal after long duration of disease whether due to progression of systemic metastasis including the lymph node, bone, liver, and lungs. Prostatic specific membrane antigen (PSMA) is a valuable target for both diagnosis and therapy of prostate cancer. A series of PSMA ligands has been developed since previous decade.

PSMA ligands

Since PSMA is overexpressed on the surface of prostate cancer, various targeting PSMA ligands have been developed (Table 1). PSMA monoclonal antibodies with different radionucleotides were introduced both for intracellular and extracellular domains of PSMA (1), (Fig. 1). To obtain fast blood clearance and specific accumulation, PSMA antibody fragments were also developed as PSMA–PET ligands; however, significant kidney uptake and retention were also found to be a limitation for clinical use. Small molecular inhibitors of PSMA have been introduced to be recognizing enzymatic site and has been developed for clinical studies. There are three types of small molecular inhibitors based on the zinc-binding portions: phosphorous-based, thiol-based, and urea-based (2). The phosphorous-based type is considered gold standard binding phosphonate core to two zinc ions located in the active domain of PSMA. The difference between phosphorous-based type and thiol-based type depends on polarity. On the other hand, the urea-based type is internalized into cell after binding to the active domain of PSMA.

Table 1. Current diagnostic PSMA ligand

Isotope	Target	Imaging agent
^{89}Zr		
	Monoclonal antibody	^{89}Zr-DFO-7E11
	Monoclonal antibody	^{89}Zr-DFO-J591
	Antibody fragment	^{89}Zr-Cys-Db
^{64}Cu		
	Monoclonal antibody	^{64}Cu-DOTA-3/A12
	Monoclonal antibody	^{64}Cu-DOTA-3/F11
	Monoclonal antibody	^{64}Cu-DOTA-3/E7
^{111}In		
	Antibody fragment	^{111}In-JVZ007-cys
^{99m}Tc		
	Antibody fragment	^{99m}Tc-J591Cdia
	Small molecule inhibitor	^{99m}Tc-MIP-1404
	Small molecule inhibitor	^{99m}Tc-MIP-1405
	Small molecule inhibitor	^{99m}Tc-DUPA
^{68}Ga		
	Antibody fragment	^{68}Ga-THP-scFv
	Small molecule inhibitor	^{68}Ga-rhPSMA
	Small molecule inhibitor	^{68}Ga-THP-PSMA
	Small molecule inhibitor	^{68}Ga-PSMA-11
	Small molecule inhibitor	^{68}Ga-PSMA-I&T
^{18}F		
	Small molecule inhibitor	^{18}F-SFB
	Small molecule inhibitor	^{18}F-CTT-1298
	Small molecule inhibitor	^{18}F-CTT-1057
	Small molecule inhibitor	^{18}F-DCFBC
	Small molecule inhibitor	^{18}F-DCFPyL
	Small molecule inhibitor	^{18}F-YC-88
	Small molecule inhibitor	^{18}F-PSMA-1007
	Small molecule inhibitor	^{18}F-rhPSMA-7.3
	Small molecule inhibitor	^{18}F-FSU-880

Positron emission tomography–computed tomography (PET/CT) imaging of prostate cancer

Recent advance of PET tracers using PSMA provides us a more accurate diagnosis of prostate cancer both at staging and in biochemical recurrence after radical prostatectomy or radiation therapy (Table 2). Detection of tumor regions with PSMA–PET/CT shows higher detection rate compared to other conventional imaging modalities. Several PSMA–PET tracers have been developed to date demonstrating significant detection rate of prostate cancer. They have different chemical structures and radiolabeled with many different radioisotopes including ^{11}C, ^{18}F, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{99m}Tc, ^{68}Ga, ^{177}Lu, ^{44}Sc, ^{64}Cu, ^{111}In, ^{86}Y, ^{90}Y, ^{225}Ac, ^{213}Bi, and ^{211}At. At first, ^{68}Ga was introduced only available for generator use. However, technical advance enables us to produce this under cyclotron use. ^{18}F and ^{68}Ga are major radioisotopes for PSMA tracers. ^{18}F has 110 min half-life and is suitable for in-house or delivery setting, but ^{68}Ga has 68 min half-life and can be available for generator use in most institutions.

Table 2. Clinical application of PSMA–PET/CT

Primary staging	Comparison with mpMRI is preferable because low spatial resolution and artifact given by excreted tracer
Secondary staging	Accuracy depends on serum PSA level
Diagnosis of biochemical recurrence	Accuracy depends on serum PSA level, Biochemical progression-free survival
Treatment planning	Delineation of CTV to include potential occult tumor for SRT
Response evaluation	RLT with alpha- or beta-emitting radionucleotides

Abbreviations: PSMA, prostatic specific membrane antigen; mpMRI, multiparametric magnetic resonance imaging; PSA, prostate specific antigen; CTV, clinical target volume; SRT, stereotactic radiotherapy; RLT, radioligand therapy.

^{18}F-labeled PSMA–PET ligands

Fluorine-18 is the most prevailing imaging isotope with positron emission yield of 97%. In 2008, the first ^{18}F-labeled ligand N-[N-(S)-1,3-dicarboxypropyl]carbamol]-4-[^{18}F]fluorobenzyl-L-cysteine (^{18}F-DCFBC) (Fig. 2) was introduced (3). ^{18}F-DCFPyL (Fig. 3) was developed as second generation demonstrating five times higher Ki than ^{18}F-DCFBC (4). The biodistribution was noted with 36.6%ID/g after 4 h in PC-3 PIP mice. Chen and the colleagues introduced ^{18}F-YC-88 which exhibited favorable kidney uptake of 47.6%ID/g compared to ^{18}F-DCFPyL (5). ^{18}F-labeled to DKFZ-PSMA-617 which was originally developed for ^{68}Ga-ligand was introduced as ^{18}F-PSMA-1007 (Fig. 4) (6). Biodistribution was 8.0%ID/g for tumor at 1 h

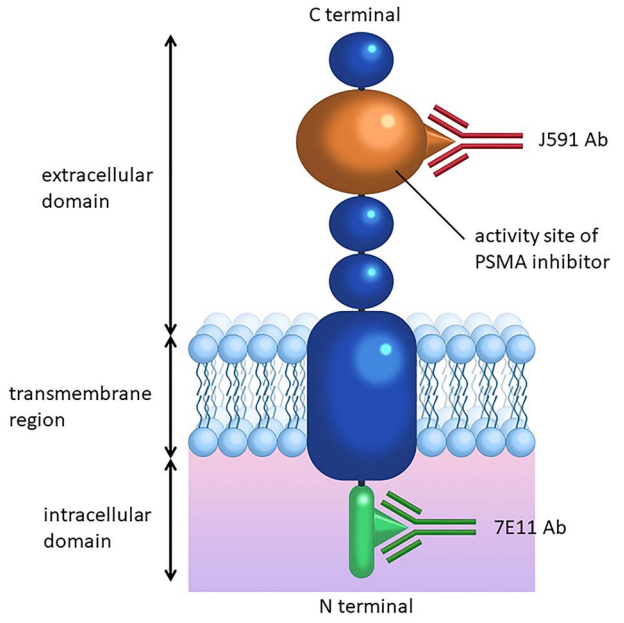
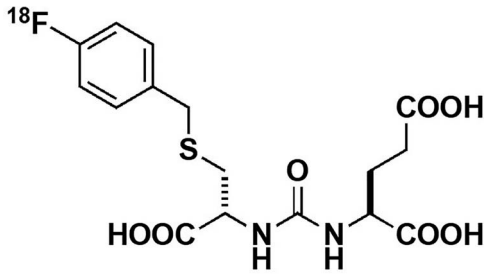


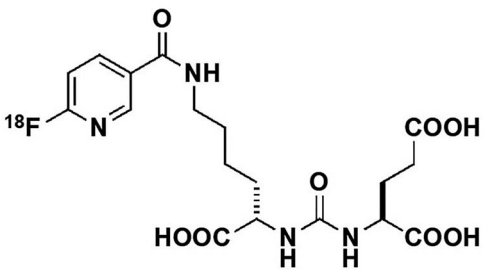
Figure 1. Molecular structure of prostate-specific membrane antigen (PSMA). Prostate-specific membrane antigen (PSMA) monomer has three domains. J591 antibody binds to activity site of extracellular domain which has 707 amino acids. 7E11 antibody binds to intracellular domain which has 19 amino acids. The homodimeric form of PSMA has enzymatic activity as glutamate carboxypeptidase II or folate hydrolase.



^{18}F-DCFBC

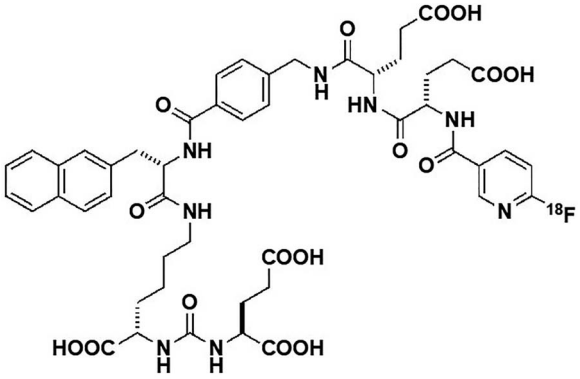
Figure 2. Chemical structure of ^{18}F-DCFBC.

in LNCaP tumor-bearing mice. The comparability of ^{177}Lu-PSMA-617 and ^{18}F-PSMA-1007 in tumor and normal organ uptake was noted. Kelly and the colleagues developed ^{18}F-labeled ligands as lead compounds of RPS-040 and RPS-041 demonstrating biodistribution of 14.3%ID/g in tumor (7). Behr and the colleagues developed ^{18}F-ligand targeting phospharamidate core as ^{18}F-CTT1057 showing the same biodistribution to urea-based PSMA-targeted ligands with low exposure to the kidneys and salivary glands (8). Radiohybrid PSMA (rhPSMA) ligands were developed as theranostic agents with fast ^{18}F synthesis and labeling with radiometals. ^{18}F-rhPSMA-7.3 demonstrated high tumor uptake and low kidney uptake in human study (9). Saga and the colleagues developed ^{18}F-FSU-880 sharing the same binding moiety as ^{68}Ga-PSMA-11 (10).



^{18}F-DCFPyL

Figure 3. Chemical structure of ^{18}F-DCFPyL.



^{18}F-PSMA-1007

Figure 4. Chemical structure of ^{18}F-PSMA-1007.

^{68}Ga-labeled PSMA–PET ligands

^{68}Ga-labeled inhibitor of PSMA of urea-based ligands having DOTA chelator was firstly introduced. Tumor uptake in biodistribution demonstrated 3.78%ID/g at 30 min post injection. Eder and the colleagues developed ^{68}Ga-PSMA-HBED-CC which possessed both DOTA and HBED-CC chelating moieties having a tumor uptake of 7.70%ID/g in biodistribution (11). Consequently, they identified higher tumor uptake of 8.22%ID/g with dimerizated HBED-CC chelators (12). ^{68}Ga-PSMA-HBED-CC and ^{68}Ga-PSMA-11 are the same material. Weineisen and the colleagues introduced coupled chelators with DOTAGA and DOTA demonstrating tumor biodistribution of 4.95%ID/g as ^{68}Ga-PSMA I&T and 7.96%ID/g as ^{177}Lu-PSMA I&T 1 h after injection (13). PSMA-617, which contains a urea-binding motif coupled to a DOTA chelator, was developed for imaging and therapy (6). Tumor uptake value was 8.47%ID/g for ^{68}Ga-PSMA-617 and 11.2%ID/g for ^{177}Lu-PSMA-617, respectively (14). Gourni and the colleagues developed another ligand using NODAGA chelating ^{68}Ga, ^{64}Cu, and ^{111}In (15).

Comparison of ^{18}F-labeled PSMA–PET ligands

Treglia and the colleagues described the results of systematic review and meta-analysis based on six studies (16–22). They compared

Table 3. Clinical use of PSMA ligands (Oct 2019)

18F-PSMA ligands		Organization or company	Clinical phase
1	^{18}F-DCFPyL	Progenics Pharmaceuticals	Phase 3
2	^{18}F-PSMA-1007	ABX	Clinical study
3	^{18}F-CTT1057	Novartis (AAA)	Phase 1
4	^{18}F-rhPSMA-7.3	Blue Earth Diagnostics	Phase 1
5	^{18}F-FSU-880	Kyoto University	Phase 2
^{68} Ga-PSMA ligands		**Organization or company**	**Clinical phase**
1	^{68}Ga-PSMA-11	Telix Pharmaceuticals	Phase 3
2	^{68}Ga-PSMA-617	Novartis (Endocyte)	Clinical study
3	^{68}Ga-PSMA-I&T	Technical University of Munich	Clinical study
PSMA ligands for RLT		**Organization or company**	**Clinical phase**
1	^{177}Lu-PSMA-617	Novartis (Endocyte)	Phase 3
2	^{225}Ac-PSMA-617	Novartis (Endocyte)	Phase 1
3	^{177}Lu-TX591	Telix Pharmaceuticals	Phase 2
4	^{177}Lu-PSMA-R2	Novartis (AAA)	Phase 1/2
5	^{227}Th-PSMA-TTC	Bayer	Phase 1

Abbreviation: RLT, radioligand therapy.

three different fluorinated PSMA–PET ligands for detection of biochemical recurrent prostate carcinoma. On the basis of a sub-group analysis, the pooled detection rate of F-PSMA-1007, F-DCFPyL, and F-DCFBC were 89% (95% CI: 72–98%), 81% (74–87%), and 60% (48–72%), respectively. F-PSMA-1007 demonstrates highest detectability of these three ligands. However, there is no study to compare the detection rate directly between three PET tracers to date. The authors also suggested that limitations contained availability of only six studies, and their results were lack of verification by histologic confirmation. F-PSMA-1007 and F-DCFPyL are developed under clinical trials in Europe and the USA, respectively. Other fluorinated PSMA–PET ligands are also under clinical phase I study, and the results will be out in the near future (Table 3).

Comparison of ^{68}Ga-labeled PSMA–PET ligands

There were no evidence demonstrating the results of direct comparisons between ^{68}Ga-labeled PSMA–PET ligands. ^{68}Ga-PSMA-HBED-CC is the most widely used small molecular inhibitor, and evidence supporting its use in CRPC or advanced PC has been described to date. Perera and the colleagues conducted a meta-analysis to demonstrate updated data based on a total of 37 articles including 4790 patients ((23), Table 4). Diagnostic accuracy of ^{68}Ga-labeled PSMA–PET/CT depends on serum PSA level. The pooled estimate positivity was 33% (confidence interval [CI], 16–51%) for prescan PSA of <0.2 ng/ml, 45% (39–52%) for 0.20–0.49 ng/ml, 59% (50–68%) for 0.50–0.99 ng/ml, 75% (66–84%) for 1.00–1.99 g/ml, and 95% (92–97%) for >2.00 ng/ml. On the basis of secondary staging purpose, overall estimates of positivity comprised of prostatic bed (28%), pelvic lymph nodes (38%), extrapelvic lymph nodes (13%), bone (22%), and distant viscera (5%). The detectability of recurrent tumor in prostatic bed was significantly higher in patients who underwent radiotherapy (52%) compared to prostatectomy (22%).

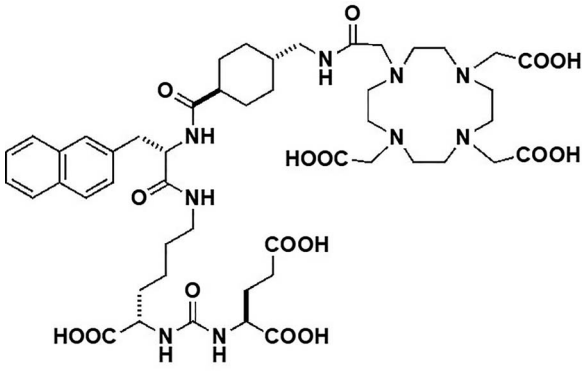


Figure 5. Chemical structure of PSMA-617. ^{68}Ga and ^{177}Lu can bind to PSMA-617.

On the pathologic basis of lesion by lesion, the summary sensitivity and specificity to detect primary tumor within prostate were 75 and 99%, respectively.

Clinical utility

Biochemical recurrence

PSMA–PET/CT is highly sensitive for detecting regional and distant metastases of prostate cancer at low serum PSA level. For patients with serum PSA level lower than 1 ng/ml, standard care imaging is insensitive for detecting recurrence. Detection of focus in biochemical recurrence after prostatectomy offers long-term biochemical control after introduction of salvage radiotherapy. Calais and the colleagues

Table 4. Large-scale clinical studies of PSMA–PET/CT

References	Year	Study design	Type of patients evaluated	Tracer	Study objectives	Study results
Treglia et al. (16)	2019	Meta-analysis of 6 studies	BRPCa (n = 645)	^{18}F-PSMA	Perform a meta-analysis about the DR of ^{18}F-PSMA–PET/CT in BRPCa patients	DR 81% (per patient analysis) 86% for PSA $\geq$ 0.5 ng/ml 49% for PSA $<$ 0.5 ng/ml
Perera et al. (23)	2019	Systematic review of 37 studies	Advanced prostate cancer (n = 4790)	^{68}Ga-PSMA	Provide updated data on the predictors of a positive ^{68}Ga-PSMA–PET with sensitivity and specificity and additionally to identify locational patterns of PSMA-avid lesions in the setting of prostate cancer staging in both primary and biochemical recurrence situations	Positive ^{68}Ga-PSMA–PET in BRPCa patients 33% for PSA 0.0–0.19 ng/ml 45% for PSA 0.2–0.49 ng/ml 59% for PSA 0.5–0.99 ng/ml 75% for PSA 1.0–1.99 ng/ml 95% for PSA $\geq$2 ng/ml NSD: Gleason sums $\leq$7 and $\geq$ 8 Primary staging (per node analysis): sensitivity 75% and specificity 99%

Abbreviations: BRPCa, biochemical recurrent prostate cancer; DR, detection rate; NSD, no significant difference.

conducted a randomized phase III trial of salvage radiotherapy with or without PSMA–PET/CT investigating its potential benefit on clinical outcome (24). Their hypothesis was that the incorporation of PSMA–PET/CT to salvage radiotherapy can improve a 5-year progression-free survival by 20%. PSMA–PET/CT can offer precise patient selection for salvage radiotherapy by improving the coverage of the recurrent lesions in the pelvic radiation field and by excluding patients with metastasis where salvage radiotherapy would not be curative. Calais and the colleagues will randomize a total of 193 patients for control arm with standard salvage radiotherapy and for intervention arm with PSMA–PET/CT prior to salvage radiotherapy planning: NCT03582774 (24). The primary endpoint is the success rate of salvage radiotherapy measured as biochemical progression-free survival. The results of the study will lead potential benefit of PSMA–PET/CT for the management of biochemical recurrence in prostate cancer. Recent advance in kit-based ^{68}Ga-labeling, ^{68}Ga-THP-PSMA was introduced to be suitable tracer for patients with biochemical recurrence greater than serum PSA 2.0 ng/ml (25).

Diagnostic accuracy of PSMA–PET and bone scan index

Bone is the common site of distant metastasis in patients with prostate cancer of advanced stage. Bone scintigraphy (BS) using ^{99m}technetium–methylene diphosphate (^{99m}Tc-MDP) or ^{99m}technetium-hydroxymethylene diphosphate (^{99m}Tc-HMDP) plays an important role to detect bone metastasis in CRPC. Zacho and the colleagues demonstrated that bone scan index (BSI) was an independent risk factor for the time from initiation of androgen deprivation therapy to CRPC and one of the prognostic factors (26). However, prognostic evaluation by BS alone is not satisfactory because of the presence of extraosseous metastases and limited spatial resolution. Anand and colleagues observed BSI reproducibility and dependence on the scanning speed of bone scan and suggested that standardization of scanning speed was needed to obtain image counts above 1.5 million prior to prospective BSI studies (27). However, standardization has not been applied for prospective studies to date. PSMA–PET/CT doesn't depend on four different types of bone metastases: lytic/lucent, sclerotic, mixed and without any morphologic abnormalities which often complicate assessment of bone metastasis by BS. It has been proposed that in patients with CRPC of advance stage, BS has a lower sensitivity for detecting distant metastasis when compared with PET/CT using PSMA ligands.

Diagnosis accuracy of PSMA–PET/CT and PSMA–PET/MRI

PSMA–PET/CT has been shown to be more accurate than conventional imaging to assess both osseous and extraosseous metastasis in CRPC. Accurately co-registered functional and morphologic data sets generated by integrated imaging systems provide us accurate diagnosis of metastasis in CRPC. The integrated whole-body PET/MRI also enables us to perform a functional and morphologic imaging for CRPC. From initial report describing comparison between PSMA–PET/MRI and PSMA–PET/CT, PSMA–PET/MRI was more accurate than PSMA–PET/CT in patients with local recurrence (28). With regard to metastatic CRPC, PSMA–PET/MRI does not seem to provide a considerable benefit as compared with PSMA–PET/CT (29). Although small nodal or bone metastasis can be easily detected by PSMA–PET/MRI, the clinical utility of PSMA–PET/MRI with comparison to PSMA–PET/CT in metastatic CRPC has not been fully elucidated.

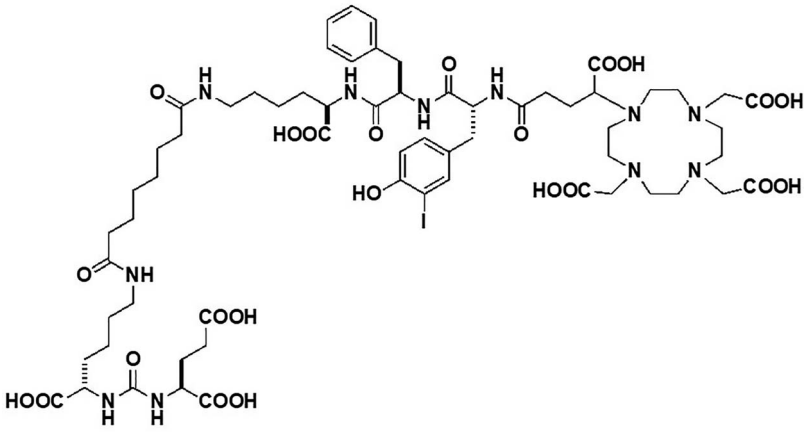


Figure 6. Chemical structure of PSMA-I&T. ^{68}Ga and ^{177}Lu can bind to PSMA-I&T.

Table 5. Summary of efficacy of 177Lu-PSMA RLT in large-scale clinical studies

References	Year	Study design	Radioligand	Patient characteristics	TEAE	Response	Survival
Rahbar et al (20)	2017	Retrospective, 12 centers, Germany	^{177}Lu- PSMA-617 2–8 GBq/cycle Total 248 cycles	PSMA-avid mCRPC, 145 patients (median age 73 years) Prior Tx: AA 64%, ENZ 52%, CTx 54%, ^{223}Ra 17% Mets: bone 87%, LN 77%, liver 20%, lung 14%	Grade 1/2 Xerostomia 8%, Nausea 6% Grade 3/4 Anemia 10%, Thrombo-cytopenia 4% Leukopenia 3%	PSA decline ≥50%, 45% PSA response Good: ≥3 cycles Bad: visceral mets, elevated ALP	NA
Heck et al. (31)	2019	Retrospective, single-center, Germany	^{177}Lu- PSMA-I&T 7.4 GBq/cycle Every 6–8 weeks Total 319 cycles	PSMA-avid mCRPC, 100 patients Prior Tx ≥3 regimens 57% Mets: bone 96%, LN 87%, viscera 35%	Grade 1/2 Xerostomia 24% Fatigue 20% Loss of appetite 10% Diarrhea 7% Grade 3/4 Anemia 9% Thrombocytopenia 4% Neutropenia 6%	PSA decline ≥30%, 47% ≥50%, 38% ≥90%, 11%	Median PFS 4.1 months Median OS 12.9 months Prognostic factors Good: PSA decline≥50% Bad: visceral mets, rising LDH

Abbreviations: PSMA, prostate-specific membrane antigen; RLT, radioligand therapy; TEAE, treatment-emergent adverse events; mCRPC, metastatic castration-resistant prostate cancer; Tx, therapy; AA, abiraterone acetate; ENZ, enzalutamide; CTx, chemotherapy; mets, metastases; LN, lymph node; ALP, alkaline phosphatase; NA, not available; PFS, progression-free survival; OS, overall survival.

Radioligand therapy (RLT)

Response and safety of RLT using urea-based PSMA inhibitors has demonstrated the potential for expanded therapeutic options for metastatic CRPC. Baum and the colleagues reported response and safety in 56 metastatic CRPC using ^{177}Lu-PSMA-617 (Fig. 5) (30). The response to ^{177}Lu-PSMA-617 demonstrated 80.4% decline of serum PSA levels and median progression-free survival of 13.7 months. Heck and colleagues described the efficacy of ^{177}Lu-PSMA-I&T (Fig. 6) in patients with metastatic CRPC (31). The response to ^{177}Lu-PSMA-I&T demonstrated over 30% decline of serum PSA levels in 47% of patients and progression-free survival of 4.1 months. Although high accumulation of kidney and parotid glands is noted in these agents, overall the use is safe and effective. The results of large scale clinical studies are summarized in Table 5. Kratochwil and colleagues described response and safety of ^{225}Ac-PSMA-617 for metastatic CRPC (32). The results demonstrated PSA decline in 87% of patients after 3 cycles. ^{213} Bi and ^{211}At using urea-based PSMA inhibitors have been also developed. Sathekge and

Table 6. False-positive conditions of PSMA–PET in the diagnosis of prostate cancer

Physiological uptake	
Head and neck	Lacrimal gland, parotid gland, submandibular gland
Abdomen	Liver, spleen, kidney, small bowel, ureter
Pelvis	Urinary bladder, myometrium
Other	Sympathetic ganglia (cervical, celiac, sacral ganglia)
Benign condition or disease	
Granuloma	Granulation tissue, keroid, sarcoidosis, active tuberculosis, anthracosis
Inflammation	Nodular fasciitis, bronchiectasis
Bone disorder	Paget's disease, fibrous dysplasia, healing bone fracture
Benign tumor	Meningioma, neurogenic tumor (schwannoma), hemangioma of liver, hemangioendothelioma of liver, adrenal adenoma, pancreatic serous cystadenoma, pancreatic neuroendocrine tumor
Soft tissue tumor	desmoid tumor, intramuscular myxoma
Other	Amyloidosis
Malignant tumor	
Brain	Glioblastoma multiforme
Head and neck	Salivary gland ductal carcinoma, squamous cell carcinoma of oropharynx, thyroid carcinoma
Chest	Pulmonary adenocarcinoma, breast carcinoma
Abdomen	Hepatocellular carcinoma, renal cell carcinoma, gastrointestinal stromal tumor, urothelial carcinoma, colorectal carcinoma
Hematologic malignancy	Malignant lymphoma, multiple myeloma

colleagues reported therapeutic efficacy in patients with metastatic CRPC with ^{213} Bi-PSMA-617 (33). ^{211}At is a favorable pure alpha-emitting radionucleotide because its daughter gives excessive dose with 7.2-h half-life. Kiess and colleagues developed ^{211}At-DCAtBzL which improved survival of tumor bearing mice (34).

Pitfalls of PSMA–PET/CT

PSMA–PET/CT is promising for the management of prostate carcinoma; however, it also has pitfalls for clinical applications. False positive findings are noted in up to 10% of patients in which etiology is non-specific or unclear (35). False negative findings are known as tumors less than spatial resolution of PET/CT (5 mm). Neuroendocrine prostate cancer can't be identified on PSMA–PET/CT (36). Furthermore, most PSMA–PET tracers show high specificity for lesion detection, while their sensitivity depends on serum PSA level. Benign pathologies identified on PSMA–PET/CT comprised of granulomatous diseases, benign bone disorders, benign tumors, and soft-tissue tumors (36) (Table 6). PSMA is type II glycoprotein originally identified in prostatic epithelium and overexpressed in the surface of prostate carcinoma cells. This glycoprotein is encoded by the folate hydrolase 1 (*FOLH1*) gene. However, this antigen also exists in other human tissues and carcinoma cells (37). Regardless of being 'prostate-specific', there are many malignant diseases which demonstrate positive PSMA–PET/CT (Table 4). Tumors exhibiting PSMA overexpression are associated with microenvironment of neovascularization. Since PSMA functions as folate hydrolase 1, these tumors are activated in folate metabolism. Actually, these tumors are also possible indications of another PSMA theranostics because insufficient information exists to recommend these situations.

Conclusions

PSMA-ligand PET can contribute diagnosis of prostate cancer in several clinical applications including initial staging, secondary staging, detection of biochemical recurrence, treatment planning, and response evaluation. To this end, further research is required to determine diagnostic utility with PSMA-ligand PET for prostate cancer with consideration given to the imaging study procedure, imaging protocol, image interpretation criteria, radiation dose, and cost-effectiveness against the yield of information. Regardless of worldwide use of promising PSMA-ligand PET, it has not been approved in Japan. Expedited introduction of PSMA-ligand PET to Japan and implementation of clinical study are eager for many patients with prostate cancer.

Conflict of interest statement

None declared.

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