PSMA Theranostics: A "Must Have" in Every Prostate Cancer Center. Illustration of Two Clinical Cases and Review of the Literature

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Introduction

A Concept of "Theranostics"

The term "theranostics", which is a combination of "therapy" and "diagnostics," was first coined by John Funkhouser in 1998.[1] In practice, it combines 2 radiolabeled ligands, 1 acting as a predictive biomarker and detecting specific features, such as receptors on cancer cells, and the other acting as a therapeutic agent, being supposed to destroy them, while sparing healthy cells. This concept helps physicians to properly select candidates most likely to benefit from targeted therapy in accordance with their "molecular profile" at a given time-point, minimizing side effects and improving their quality of life. The role of theranostics is increasingly important in delivering precision medicine to the individual patient. It provides a transition from conventional to personalized medicine, being a modern approach compared with empirical chemotherapy.[2]

Although the theranostics concept was first applied many decades ago by Saul Hertz, who successfully treated a patient suffering from hyperthyroidism with iodine-131 (^{131}I), it gained more attention recently with the results of the NETTER-1 study. This phase III study compared efficacy and safety of peptide receptor radionuclide therapy (PRRT) with lutetium-177 (^{177}Lu)-DOTATATE, a radiopharmaceutical that targets the membrane-bound somatostatin receptor of neuroendocrine tumors (NET), in combination with unlabeled octreotide acetate versus high-dose octreotide alone. The study demonstrated markedly longer progression-free survival (PFS) and significantly higher response rates in the study arm including PRRT in advanced midgut NET as compared with standard conventional therapy with cold somatostatin analogs ($p<0.001$).[3] Qualification for PRRT is based on noninvasive positron emission tomography (PET)/computed tomography (CT) imaging using gallium-68 (^{68}Ga) labeled somatostatin analogs, which confirms overexpression of somatostatin receptors on tumor cells as a prerequisite for subsequent targeted therapy.

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Prostate-Specific Membrane Antigen

Prostate-specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II, N-acetyl-α-linked acidic dipeptidase I or folate hydrolase, is a transmembrane protein overexpressed on the vast majority of prostate cancer (PCa) cells.[4] PSMA PET/CT may revolutionize PCa management. Because of the high-binding affinity of small molecule ligands to this antigen, PSMA PET/CT characterizes PCa lesions with high diagnostic accuracy, both in the context of re-staging of disease in biochemical relapse after radical treatment, as well as even more and more often in primary staging before definitive therapy. As to the former clinical indication, PSMA PET is capable of detecting small disease foci at very low or even undetectable serum levels of prostate-specific antigen (PSA).[5,6] According to a recent extensive analysis of 635 patients with relapse, PSMA-directed imaging helped to localize recurrence in 38% of patients with PSA < 0.5 ng/mL, 57% with PSA between 0.5 and 1.0 ng/mL, and 84% with PSA between 1.0 and 2.0 ng/mL, respectively.[7] Pathological focal uptake of ^{68}Ga-PSMA was reported in lymph node metastasis (LNM) measuring only 2.4 mm in a restaged patient.[8] For more information about the utility of re-staging with PSMA PET/CT we refer to the meta-analysis of Perera et al.[9]

In patients newly diagnosed, PSMA PET/CT scans can outline a subcohort with regional lymphatic involvement and/or distant metastatic spread in a substantial portion of patients with intermediate- and high-risk PCa, as recently shown,[10] and thus outperforms conventional staging modalities, such as the combination of CT and bone scintigraphy.[11]

PSMA PET/CT also plays a pivotal role in the management of patients with metastatic castration-resistant prostate cancer (mCRPC), a lethal form of disease. The majority of these patients present with remarkably high tracer uptake of the lesions because PSMA expression rises with de-differentiation, Gleason score (GSC), and in hormone-refractory disease.[12] This makes PSMA an excellent target for systemic, radioligand therapy (RLT), which has been established in many centers worldwide.[13-15] There have been several studies based on non-randomized cohorts of patients with mCRPC treated with ^{177}Lu-labeled PSMA ligands demonstrating very promising response rates with acceptable toxicity. The therapy is currently being implemented in a growing number of centers in Europe and beyond. Results of the VISION (NCT03511664) and TheraP trials (NCT03392428) are highly anticipated, as they might confirm the effectiveness of PSMA RLT in patients with mCRPC with positive impact on survival rates.

In this manuscript we would like to present 2 clinical cases of patients with PCa in whom PSMA theranostics played a vital role in clinical management. In patient 1, newly diagnosed with high-risk PCa, preoperative PSMA PET/CT revealed—apart from the primary tumor—metastases in pelvic lymph nodes (LN), including those located in regions inaccessible by surgery. Patient 2, with mCRPC and multiple PSMA avid LNMs and bone metastases, underwent PSMA-directed RLT with very good biochemical and clinical response. We also present a review of the current literature concerning PSMA theranostics in these 2 clinical settings, ie, primary staging of PCa and PSMA RLT of mCRPC.

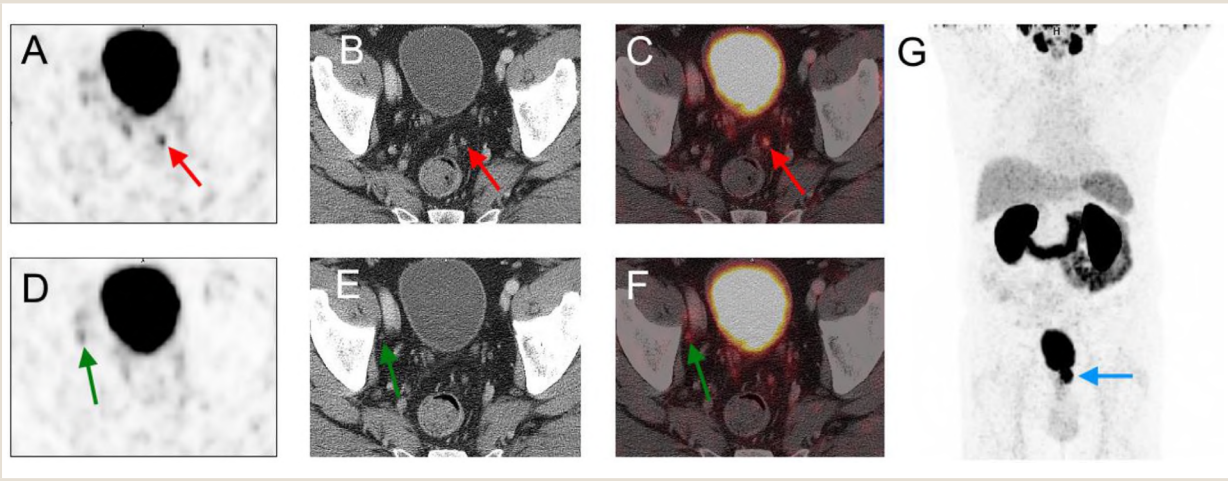
Clinical Case 1. PSMA PET/CT in Primary Staging of PCa

A 64-year-old patient diagnosed with high-risk PCa (GSC 5 + 5 = 10, initial PSA value of 10.5 ng/mL) in March 2017, detected by transrectal ultrasound-guided biopsy underwent primary staging with PSMA PET/CT imaging in April 2017. Imaging was performed 60 minutes after intravenous injection of 170 MBq of ^{68}Ga-PSMA I&T (imaging and therapy) (2-3 min emission time per bed position), with full-dose, contrast-enhanced CT covering the region from the base of the skull to the proximal thighs. No adverse events including allergic reactions were observed after the administration of the radiotracer and contrast media.

Imaging revealed high, pathological tracer uptake of the primary tumor (SUVmax 44.8), as well as focal uptake in a small, 4-mm left perirectal LN (SUVmax of 5.0), highly suspicious for metastasis (Figure 1A-C). Two weeks after PSMA PET/CT the patient underwent radical prostatectomy with extended pelvic LN dissection, as routinely performed in patients with increased risk of nodal involvement according to the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) guidelines.[16-18] The patient was deemed eligible for surgery as the conventional, non-PSMA CT imaging showed pelvic LNs below the size threshold of 8 mm in short-axis considered malignant.

Postoperative histopathology confirmed presence of PCa in both lobes of the prostate (GSC 10, ISUP 5 [International Society of Urohisto-Pathologists]) with two 3-mm micrometastases in the right obturatory LNs, with faint tracer uptake detected only in retrospective analysis (Figure 1D-F). The PSMA-positive left perirectal LN was not resected because of its deep mesorectal localization, although an attempt was made to remove it. Because of a persistently elevated PSA level, measuring 0.8 ng/mL, the patient was referred for PSMA PET/CT imaging in June 2017 with the intention to plan salvage radiotherapy. PSMA PET/CT revealed progression of the aforementioned left perirectal LN, now measuring 7 mm and having clear focal uptake (SUVmax 13.8), with suspicion of another, PSMA-positive (SUVmax 16.7) perirectal LN metastasis on the right side, measuring only 4 mm (Figure 2). Proper target volume delineation was based on CT contouring to deliver a dose of 69.3 Gy to the prostate bed (and LNs), and 45.9 Gy to the pelvic lymph drainage area (a total of 33 fractions with single doses of 1.7/2.1 Gy, between July and September 2017), with simultaneously integrated boost of the PET-avid foci (Figure 2D). The 2 PSMA-positive perirectal LNs, especially the 4-mm on the right side, but also the enlarging 7-mm on the left side, might not have received the additional radiation dose if the treatment planning had been based solely on the abdominal CT scan because both nodes did not exceed the critical threshold of 8 mm (concerning malignancy). PSA at the beginning of radiation therapy was 1.8 ng/mL and dropped to 0.16 ng/mL in January 2018. In mid-2018, the patient started additional androgen deprivation therapy (ADT) with gonadotropin releasing hormone agonist (leuprolide). Re-staging with ^{18}F-PSMA-1007 PET/CT was performed in January 2020 with a PSA of 0.34 ng/mL, revealing 2 foci of pathological tracer uptake, highly consistent with recurrent LN metastases: para-aortic, measuring 4 mm (SUVmax 34.3), and left perirectal (SUVmax 8.1), with no clear

Figure 1 Clinical case 1. ^{68}Ga-PSMA I&T PET/CT of a 64-year-old patient with high-risk prostate cancer (Gleason score 10) performed for primary staging before scheduled radical prostatectomy. Apart from pathological tracer uptake in the primary tumor of the prostate (blue arrow, maximum intensity projection image [MIP], SUVmax 44.8, G) consistent with malignant infiltration, imaging revealed focal uptake in a small left perirectal lymph node, measuring 4 mm, SUVmax 5.0, highly suspicious for metastasis (red arrows, cross-sectional images, A-C). Postoperative histopathology confirmed the presence of two 3-mm micrometastases in the right obturatory lymph nodes, with faint tracer uptake found only in retrospective analysis (green arrows, cross-sectional images, D-F).



CT-correlate (Figure 3). In March 2020, in addition to ADT, the patient began treatment with apalutamide (a pure androgen receptor antagonist), which resulted in a PSA drop to 0.04 ng/mL (September 2020).

This case shows the utility of PSMA-guided theranostics in management of PCa with persistently elevated PSA levels after initial treatment. It may not only guide salvage radiotherapy to the prostate bed but also to untypically located small LNs, eg, perirectal, harboring metastases, potentially increasing PFS and overall survival (OS).[19]

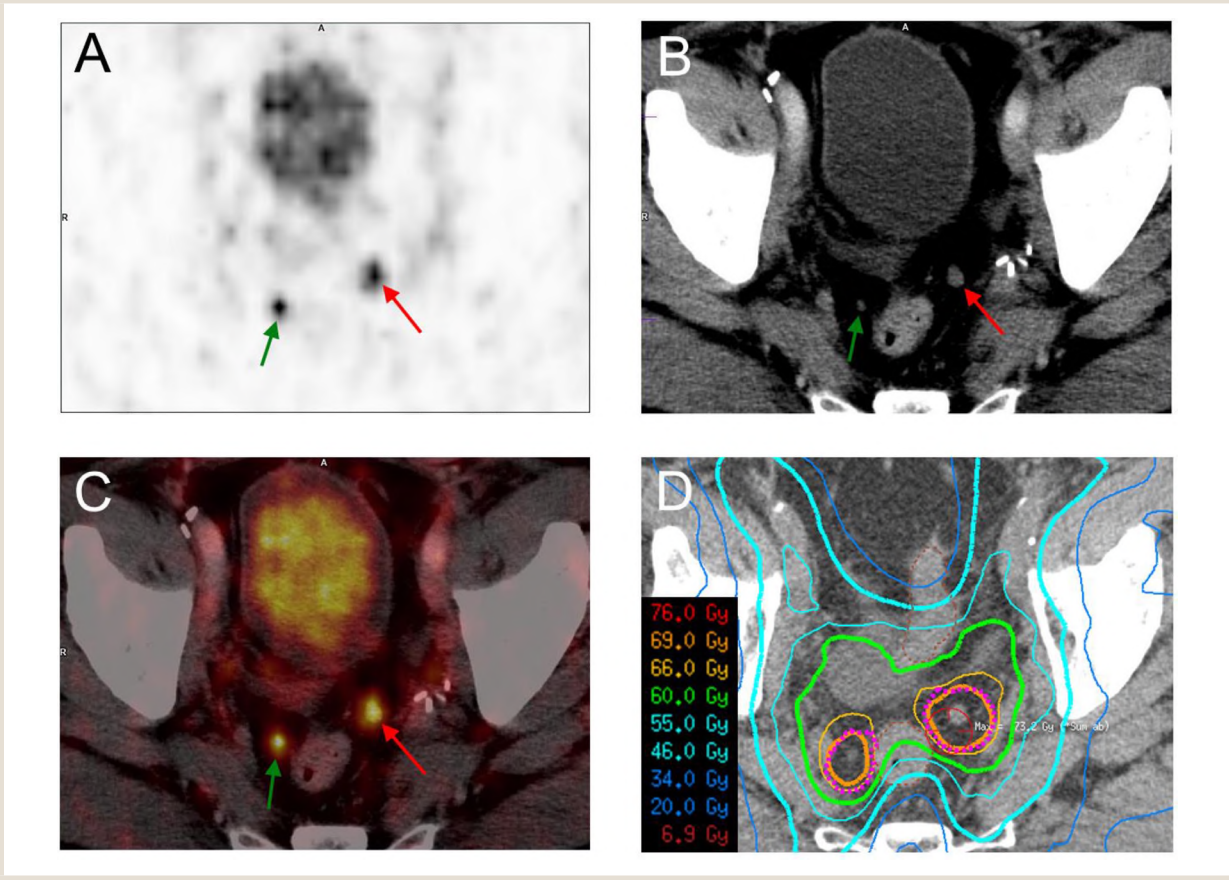
Clinical Case 2. PSMA PET/CT Theranostics in the Qualification and Monitoring of RLT of mCRPC

The second patient, diagnosed with PCa (GSC 9, ISUP 5) in November 2012 at the age of 76 years, with initial PSA of 15.8 ng/mL, started primary hormonal therapy with bicalutamide as first-line treatment owing to advanced metastatic disease. In August 2015 he underwent prophylactic irradiation of both mamillae. By September 2015, after choline PET/CT imaging revealed local recurrence, with metastatic pelvic (iliac) and retroperitoneal LNs, complete androgen deprivation was introduced. From May 2016 he was treated with abiraterone, however, treatment was ended in September 2016 because of side effects. Systemic therapy was continued with enzalutamide until March 2018, then terminated owing to progression. Docetaxel-based chemotherapy was contraindicated because of diabetic polyneuropathy. A recommendation of the institutional multidisciplinary tumor board was to apply ^{177}Lu-PSMA RLT.

The patient fulfilled all inclusion criteria consistent with the guidelines of German Society of Nuclear Medicine, ie, histopathological confirmation of PCa, unresectable metastases, castration-resistant disease, other on-label options of treatment of mCRPC completed or contraindicated, progression of disease by PSA level and imaging, PSMA-positive lesions confirmed in pretherapeutic ^{68}Ga-PSMA PET/CT imaging, white blood cell count > 3000/μL, platelet count > 75,000/μL, creatinine < 2-fold the upper limit of normal (ULN), AST (aspartate aminotransferase) and ALT (alanine aminotransferase) < 5-fold ULN, and no myelosuppressive therapy within 6 weeks prior to RLT. The decision for RLT was made in accordance with the Declaration of Helsinki, paragraph 37 for "Unproven Interventions in Clinical Practice" and German compassionate use regulations. The patient gave written informed consent to undergo RLT with subsequent follow-up.

Baseline ^{68}Ga-PSMA PET/CT imaging revealed progression of disease (compared with previous choline PET/CT imaging), with the appearance of multiple new PSMA-positive LN and bone metastases (a key condition for the initiation of PSMA RLT). The first 2 cycles of RLT (with 6.0 and 6.2 GBq of ^{177}Lu, respectively) were administered in September and October 2018, respectively, at the PSA level of 1640 ng/mL. Re-staging performed in December 2018 revealed morphologic partial response of LN and bone metastases (according to RECIST), with a concurrent PSA decrease of > 80%. Another 2 cycles of RLT (December 2018 and March 2019) resulted in nearly complete imaging response of LN and skeletal lesions (Figure 4) and very good biochemical response (PSA decrease > 95%). The cumulative dose of radiopharmaceutical given in 4 cycles was 24.5 GBq. No important adverse effects of the treatment were reported. The next recommendation of tumor board after completion of RLT was "watch and wait." Unfortunately, the patient was lost to follow-up. At the end of February 2020 the patient succumbed.

Figure 2 Clinical case 1. The follow-up ^{68}Ga-PSMA I&T PET/CT scan performed 2 months after radical prostatectomy due to persistently elevated prostate-specific antigen level (0.8 ng/mL), with the intention to plan salvage radiotherapy, showing progression of the aforementioned left perirectal lymph node, now measuring 7 mm, SUVmax 13.8 (red arrows, cross sectional images, A-C), with another perirectal lymph node on the right side, measuring 4 mm, SUVmax 16.7 (green arrows, cross sectional images, A-C). Proper target volume delineation of the pelvic lymph drainage area was based on CT contouring with simultaneously integrated boost of the PET-avid spaces (delineated by pink dotted lines, D).



Although the exact cause of death in this patient was not established, the residual tumor after RLT completion (PSA 80 ng/mL), potentially PSMA-negative, may have contributed to disease progression. Nevertheless, almost 1 year of survival after PSMA RLT would probably have not been achieved if the patient had received only palliative care.

Review of the Literature

PSMA PET/CT for Primary Staging of PCa

A diagnosis of PCa requires a clinical decision regarding treatment and its potential scope. In case of intermediate- and high-risk PCa (according to D'Amico classification) precise primary staging of disease is of utmost importance because it allows to tailor the therapy to the extent of disease.[16,18] Conventional imaging, such as CT and bone scan, routinely performed in this clinical setting, yields unsatisfactory results, with limited accuracy of detecting LN and bone metastases, usually present in disseminated forms of disease. PSMA-guided theranostics has successfully broken this limitation. In a recent meta-analysis (8 studies, 274 patients) the overall PSMA PET positivity rate in patients with newly diagnosed PCa was 74%. In a series of retrospective and prospective analyses of diagnostic efficacy of PSMA PET/CT for detecting regional LN metastases, the weighed sensitivity and specificity was 59% and > 90%, respectively.[20] An important prospective randomized multicenter study of the impact of ^{68}Ga-PSMA PET/CT imaging for staging high-risk PCa prior to curative-intent surgery or radiotherapy (proPSMA study) has now been completed.[11] It provides high-quality data confirming that PSMA PET/CT inherits superior accuracy than the combination of CT and bone scanning. In total, 302 men were randomly assigned to conventional imaging or to PSMA PET/low-dose CT before treatment of high-risk PCa. PSMA PET/CT had greater accuracy (92% vs. 65%), sensitivity (85% vs. 38%), and specificity (97% vs. 91%) compared with conventional imaging.[11] Management changes occurred in 5% of patients follow-

Figure 3 Clinical case 1. Re-staging with ^{18}F-PSMA-1007 PET/CT performed more than 2 years after salvage radiotherapy and initiation of androgen deprivation therapy because of prostate-specific antigen recurrence (0.34 ng/mL), revealed 2 foci of pathological tracer uptake, highly consistent with recurrent lymph node metastases: para-aortic, measuring 4 mm, SUVmax 34.3 (red arrows, cross-sectional images, A-C; maximum intensity projection image [MIP], G), and left perirectal, SUVmax 8.1, with no clear CT-correlate (green arrows, cross-sectional images, D-F; MIP, G).

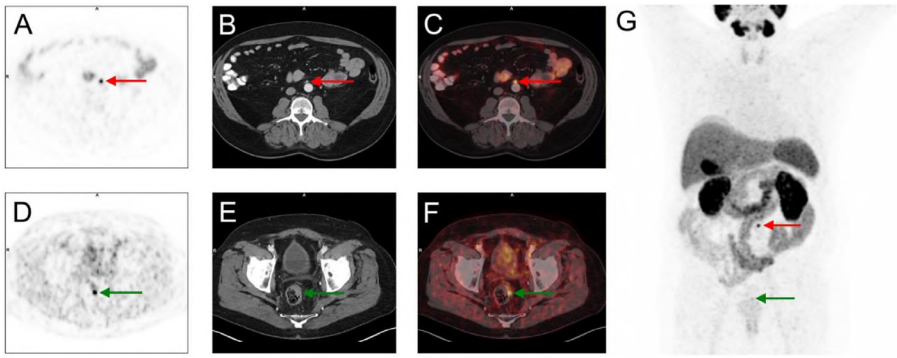
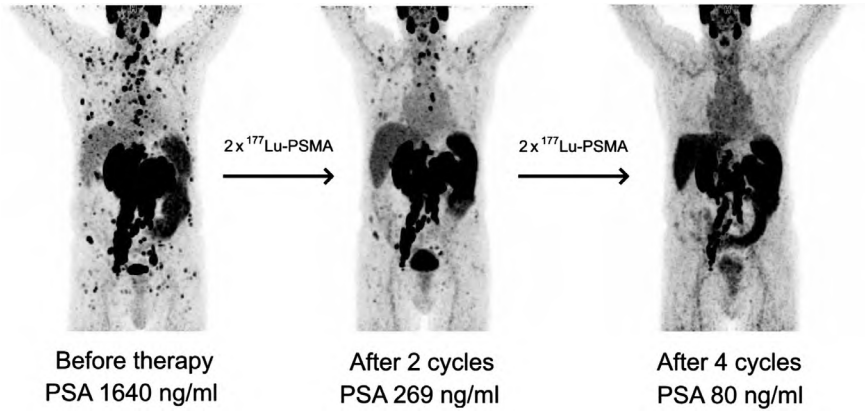


Figure 4 Clinical case 2. The baseline and 2 follow-up ^{68}Ga-PSMA PET/CT scans of the patient with metastatic castration-resistant prostate cancer (Gleason score 9) showing partial (after 2 cycles of ^{177}Lu-PSMA radioligand therapy [RLT]) and nearly complete (after 4 cycles of RLT) imaging response of lymph node and bone metastases, with very good biochemical response (prostate-specific antigen [PSA] value decrease > 95%).



ing conventional imaging, and in 27% following PSMA-directed imaging. Hence the nuclear medicine physicians are more and more often being encouraged to be embedded in PCa multidisciplinary teams.[21]

In an interesting study analyzing the efficacy of primary T-staging in patients suspected of PCa, the patient-based detection rate of multiparametric magnetic resonance imaging (mpMRI), PSMA PET/CT, and PSMA PET/mpMRI was 66%, 92%, and 98%, respectively.[22] These data show that hybrid PSMA PET/mpMRI, commercially available in an increasing number of centers, conveys additional value to mpMRI alone.

Various PSMA Tracers

PSMA tracers can be labeled with various radioisotopes. The clinical breakthrough was achieved with the development of ^{68}Ga-labeled PSMA ligands. The PSMA PET ligand most often used in clinical practice is ^{68}Ga-PSMA-11, also referred to as ^{68}Ga-PSMA HBED or ^{68}Ga-PSMA HBED-CC. It shows excellent binding affinity to PSMA and highly efficient internalization rate into PCa cells.[23] ^{68}Ga-PSMA I&T also shows high-binding capacity to PSMA, with the advantage of having a therapeutic equivalent (^{177}Lu-PSMA I&T), which has an analogous chemical structure. The challenges of ^{68}Ga-based imaging include relatively high

costs per dose and limited number of examinations owing to small yields per elution from gallium generators (approximately 1.1-1.2 GBq, in practice allowing to perform 3 PSMA studies a day). A solution to this problem could be cyclotron-based ^{68}Ga production, however, the radionuclide's short half-life (68 min) limits distribution radius. Alternatively, fluorinated PSMA ligands are more and more often used. This group comprises various compounds, such as ^{18}F-DCFBC, ^{18}F-DCFPyl, ^{18}F-PSMA-1007, of which the last one has very low urinary excretion, which is favorable for primary tumor assessment.[24,25] Additionally, the use of fluorine-18 (^{18}F) has physical advantages because of shorter positron range, which translates into higher resolution of PET images (^{18}F has a mean positron range of 0.27 mm in soft tissue, as compared with 1.5 mm for ^{68}Ga).[26] Technetium-99m (^{99m}Tc)-labeled PSMA small-molecule inhibitors, eg, ^{99m}Tc-MIP-1404, are a potential alternative, if PET technology is not feasible,[27] however, single photon emission computed tomography (SPECT) has lower spatial resolution and sensitivity than PET. Of note, ^{99m}Tc-labeled tracers also enable more efficient radioguided surgery of PCa,[28] whereas ^{18}F-guided interventions using gamma detection probes can result in relatively high background counts and potentially lower efficacy of tumor detection.[29]

To sum up, ^{68}Ga remains the most commonly used radionuclide for PSMA diagnostic and theranostic indications, therefore a high yield gallium production process is expected to appear to reduce costs and cover high demand, with a valuable alternative of fluorinated ligands.

PSMA Radioligand Therapy

PSMA RLT has shown promising antitumor activity in advanced PCa. With small exceptions, such as that described in the work by Sathekge et al.[30] who recently presented the results of actinium-225 (^{225}Ac)-PSMA-617 therapy in chemotherapy-naïve patients, this treatment is offered to patients who suffer from progressive, advanced, or end-stage disease and to those who have exhausted or are ineligible for other, EMA/FDA approved treatment options.[31] Most of the data are based on retrospective, non-randomized, single-center trials with limited numbers of patients. A multicenter analysis was carried out in Germany, including 145 patients with mCRPC treated with ^{177}Lu-PSMA-617.[13] Optimistic results of these observational studies allow us to propose hypotheses about the efficacy of PSMA RLT and its positive impact on patients' survival rates. Here we present an overview of PSMA-targeted therapy, its historical background, and future perspectives.

Short Historical Background. First attempts of using PSMA as a target for radionuclide therapy were made shortly after the conjunction of a humanized monoclonal antibody J591 (huJ591) against the extracellular domain of PSMA with beta(-) emitting ^{177}Lu in 2005.[32] Unfortunately, because of unfavorable pharmacokinetics of ^{177}Lu-DOTA-huJ591 and its diagnostic equivalent labeled with zirconium-89 (half-life, 78.41 h) this research was discontinued. New promise emerged with the development of small-molecule inhibitors of PSMA. Their structure is most often based on the chemical motif *glutamate-urea-glutamate* or *glutamate-urea-lysine*, which binds to the catalytic domain of PSMA. The first clinically used molecules ^{123}I-MIP-1072 and ^{123}I-MIP-1095 were introduced in 2008 and showed rapid and high uptake in PCa lesions. Hence the idea to substitute diagnostic ^{123}I with therapeutic ^{131}I and to test these small molecule ligands in targeted therapy for PCa appeared. Indeed, the radiopharmaceutical presented long-lasting tumor accumulation and a therapeutic response with respect to PSA levels, and control of symptoms in most patients.[33] Among 28 patients who received ^{131}I-MIP-1095 as end-of-line therapy and were assessed within 3 months after 1 cycle of treatment (mean activity, 4.8 GBq; range, 2.0-7.2 GBq) a PSA decrease by $\geq$ 50% was observed in 60.7% of patients and by $\geq$ 75% in 25% of the population, respectively.[33] A considerable reduction of tumor mass was observed in many patients, with an average time to PSA rise of 126 days (range, 62-469 d). The reported side effects comprising xerostomia and thrombocytopenia observed in some patients were transient. However, a milestone was reached in 2012 with the invention of PSMA ligands dedicated for PET imaging labeled with ^{68}Ga and their therapeutic analogs coupled with ^{177}Lu and ^{225}Ac, which appeared soon thereafter. The most common theranostic twins currently studied are ^{68}Ga-PSMA-11/^{177}Lu-PSMA-617 and ^{68}Ga/^{177}Lu-PSMA I&T. ^{177}Lu has several advantages over ^{131}I: its synthesis is easier, it has lower proportion of gamma-radiation, which may result in shortening of hospital admission times, and lower toxicity as compared with ^{131}I.

Overview of ^{177}Lu-Labeled PSMA Ligands. After the development of ^{177}Lu-PSMA-617 at the German Cancer Center in Heidelberg, many German nuclear medicine departments started using this radiopharmaceutical in a series of patients with end-stage mCRPC. This led to the publication of a German multicenter study, which showed a PSA decline of > 50% and an overall response rate of 45% in the treated population.[13] Other centers were encouraged by these promising, preliminary results and gained their own experience with ^{177}Lu-PSMA therapy. Response rates and other main clinical observations of these single-center, one-arm trials are summarized in Table 1 .

The data published so far show biochemical response rates (> 50% PSA decrease) between 30% and 64.5%, with acceptable toxicity, usually transient thrombocytopenia, leukopenia, and usually mild anemia. In a recent meta-analysis, the pooled proportions of any PSA decline was 68%, and those with a greater than 50% PSA decline was 34.45%.[34] The treatment may cause xerostomia, which usually resolves after 3 to 4 weeks. In most centers, to minimize the risk of xerostomia, patients receive cool packs applied to the salivary glands, starting from 30 minutes prior to ^{177}Lu-PSMA infusion and continuing for 4 hours thereafter.[13] Of note, a considerable percentage of patients (up to 30%) who do not respond to the first cycle of treatment, may present late response after second or third cycle of RLT.[35] Complete biochemical and radiographic remissions are rare (~1%), even in patients with less advanced disease.[36,37]

The results of currently ongoing, prospective, phase III VISION trial, which is supposed to end in August 2021, are highly anticipated. In the study, 2 arms of patients with advanced PCa are being evaluated: the first arm receiving best standard of care (BSC) + ^{177}Lu-PSMA-617, whereas the second arm receiving BSC only. It may be the first randomized controlled trial to show a

Table 1 Overview of the Studies Reporting on ^{177}Lu-PSMA Radioligand Therapy

Author(s)	Number of Pts Treated (n)	Number of PSMA RLT Cycles per Pt (range)	Any PSA Response	PSA Response > 50%	PSMA Imaging Response	Symptoms Control	Toxicity	Side Effects	Median PFS (mo)	Median OS (mo)	Remarks
Ahmadzadehfar et al. 2015[60]	10	1	70%	30%			1 pt with grade III/IV hematotoxicity	Occasionally fatigue and dry mouth			
Kratochwil et al. 2016 (177Lu)[61]	30	2 (1-3)	70%	43%	Positive response in 10/11 pts	Stabilization of pts well-being; fairly stable body weight	Rarely, grade I/II anemia/ leucopenia/ thrombocytopenia	Sporadically xerostomia, nausea, fatigue			
Yadav et al. 2017[62]	31	1-4	70.9% 22/31 (mean baseline PSA 275 ng/mL dropped after 1 cycle to 141.75 ng/mL)	64.5%	CR 2/6; PR 3/6; PD 1/6 (PERCIST 1)	Clinical response 67.7% (21/31) pts; mean analgesic score[a] decreased from 2.5 to 1.8 after therapy	2 pts with grade I/II hemoglobin toxicity	No xerostomia or dry mouth	12	16	
Heck et al. 2016[63]	19	1-4	PSA decrease ≥ 30% in 56% pts	33%	PD 32%; SD 63%; CR 5%	58% pts with complete resolution or reduced pain	Grade I/II anemia in 6/19 pts; grade I/II thrombocytopenia in 5/19 pts	Grade I/II dry mouth in 7/19 pts	5.8		^{177}Lu-PSMA I&T used
Kulkarni et al. 2016[36]	80	1-7	76.3%	57.5%	CR 5/58; PR 12/58; SD 23/58	QoL essentially improved in symptomatic pts	Grade III/IV hematologic toxicity in 3.4% pts (among pts heavily pretreated with chth and ^{223}Ra)	Most commonly mild fatigue over a few days after therapy	10.7		^{177}Lu-PSMA I&T and ^{177}Lu-PSMA-617 with comparable response and toxicity profiles
Baum et al. 2016[64]	56	1-5	80.4%	58.9%	PR 56%; SD 8%; PD 36% (EORTC)	Decrease of pain in 33.3% (2/6) pts	9 pts with grade I/II leukocytopenia (treated with long-term chth before RLT)	2 pts with mild xerostomia after 3 and 4 cycles, with spontaneous resolution within 3 mo	13.7	> 28	^{177}Lu-PSMA I&T used
Fendler et al. 2017[65]	15	2	47% pts with PSA decrease ≥ 30%	60%	PR 27%; SD 40%; PD 20% (RECIST 1.1)	QoL improved in 53%; pain responded well or completely in 47%	1 pt with grade III anemia; 1 pt with grade III leukocytopenia	1 pt with grade III nausea; mild/transient xerostomia in 47%			

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Table 1 (*continued*)

Author(s)	Number of Pts Treated (n)	Number of PSMA RLT Cycles per Pt (range)	Any PSA Response	PSA Response > 50%	PSMA Imaging Response	Symptoms Control	Toxicity	Side Effects	Median PFS (mo)	Median OS (mo)	Remarks
Grubmüller et al. 2019[66]	38	3 (all pts)	73.7%	47.4%	CR 5.3%; PR 57.9%; SD 21.1%; PD 15.8% (based on change of PSMA TTV)						
Rahbar et al. 2018[35]	71	3 (all pts)	66%	56%							29% of nonresponders to first cycle responded to further cycles of RLT
Bräuer et al. 2017[67]	59	3 (1-7)	91%	53%					4.5	8	
Rahbar et al. 2017[13]	145	1-4	60% (data from 99 pts)	45% (data from 99 pts)	45% PR; 28% SD; 25% PD; 2% CR (data from 47 pts)		10% grade III-IV anemia; 4% grade III-IV thrombocytopenia; 3% grade III-IV leukopenia	8% mild to moderate xerostomia; 6% mild to moderate nausea			German multicenter study (12 nucl. med. dep.)
Hofman et al. 2018[15]	30	1-4	97%	57%	CR 10%; PR 30%; SD 3%; PD 27%	Clinically meaningful improvements at all time points	13% grade III/IV thrombocytopenia (possibly attributed to RLT)	87% grade I dry mouth; 50% grade I/II nausea; 50% grade 1-2 fatigue	7.6	13.5	Phase II trial; decline in PSA ≥ 50% associated with longer OS (17.0 mo) and PFS (9.9 mo) vs. PSA decline < 50% (OS 9.9 mo, PFS 4.1 mo)
Ahmadzadehfar et al. 2017[68]	100	3 (1-8)	69%	38%						15	PSA decline > 14% associated with longer OS of 22 mo vs. 7.3 mo, if PSA decline ≤ 14%

Abbreviations: chth = chemotherapy; CR = complete response; I&T = imaging and therapy; nucl. med. dep. = nuclear medicine department; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; pts = patients; QoL = quality of life; RLT = radioligand therapy; SD = stable disease; TTV = total tumor volumes.
[a]Analgesic scoring according to the 5-point EORTC (European Organisation for Research and Treatment of Cancer) protocol: 0 no analgesics, 1 nonopiate analgesics taken occasionally, 2 nonopiate analgesics taken regularly, 3 opiate analgesics taken occasionally, 4 opiate analgesics taken regularly.

survival benefit after PSMA RLT and to further justify and support the concept of theranostics.[38]

Recently, the first results of a randomized phase II TheraP trial were presented, comparing ^{177}Lu-PSMA-617 (LuPSMA) to cabazitaxel in men with mCRPC progressing after docetaxel.[39] The preliminary data show that PSA response rate (decrease > 50%) was higher in patients assigned to LuPSMA than to cabazitaxel arm (66% vs. 37%, respectively). Also, at a median follow-up of 11.3 months, LuPSMA significantly improved PSA PFS (p=0.007). OS data remain immature.

Details of PSMA-directed RLT procedure using ^{177}Lu-labeled PSMA compounds are described in the European Association of Nuclear Medicine (EANM) guidelines prepared by Kratochwil et al.[14]

PSMA Targeted Alpha Therapy

The future of radionuclide therapy for PCa seems to be PSMA targeted alpha therapy (TAT). Alpha radiation is characterized by a much higher linear energy transfer (LET) (50-230 keV/μm), which yields a greater potential for inducing unrepairable, double-strand DNA breaks in cancer cells, as compared with beta particles (LET of 0.2 keV/μm), which usually induce sparse ionization events, individual DNA lesions, and repairable single-strand DNA breaks. Hence TAT is anticipated to cause more mutations in cell genome and have increased cytotoxicity as compared with beta radiation.[31,40] Alpha radiation has also the potential to efficiently eradicate hypoxic tumor cells, as well as tumor cells that are resistant toward beta- and gamma-radiation, and treatment with cytostatic drugs.[41]

The idea to use alpha-emitting isotopes for endo-radiotherapy is not new. Successful attempts to use radium-223 (^{223}Ra) against cancer cells have been shown in a series of preclinical data.[42] A few clinical trials involving ^{223}Ra have also been completed, of which ALSYMPCA—a phase III, randomized, double-blind, placebo-controlled study—proved significant survival benefit in patients with mCRPC receiving ^{223}Ra-chloride + BSC versus BSC alone, median OS, 14.9 versus 11.3 months, respectively (p<0.001).[43] However, in Era-223 trial abiraterone in combination with ^{223}Ra raised safety concerns, as it was associated with a higher number of fractures and deaths than in the control arm of abiraterone + placebo, which was the reason to unblind the study prematurely.[44] The wider application of calcium analogs, such as ^{223}Ra, in the treatment of mCRPC is limited by the fact that this bone-seeking agent targets only newly forming bone or osteoblastic lesions. It does not target, however, osteolytic lesions or extraosseous disease, eg, nodal or visceral metastases. For that reason, more specific radioligands of PCa tissue were highly desired. Discovery of PSMA pathed the way to deliver alpha emitting isotopes more selectively to the tumor. First clinical application of ^{225}Ac-PSMA-617 in 2 patients with mCRPC as salvage therapy was presented by the Heidelberg group.[45] The radiopharmaceutical showed remarkable antitumor activity leading to complete metabolic and radiographic remission, although both patients presented with multiple metastatic disease (1 with diffused red marrow infiltration, the other with peritoneal carcinomatosis and liver metastases) and had exhausted or were not eligible for any other available treatment options.

The safety and efficacy of ^{225}Ac-PSMA-617 TAT was first investigated by the Heidelberg[31] (Figure 5) and the Pretoria group.[30,46] The efficacy of this novel treatment turned out to be clearly higher than that of ^{177}Lu-PSMA RLT, resulting in biochemical response rates (> 50% PSA decline) in 39% to 82% vs. 30% to 64.5% for ^{177}Lu (Table 2). ^{225}Ac TAT is characterized by minimal bone marrow toxicity, which can be achieved because of the exceptionally low range of alpha particles (50-100 µm), as compared with beta particles (1000-10,000 μm), acting mainly within malignant cells after internalization of the PSMA-ligand complex into the cytosol. An obstacle yet to overcome is to reduce the percentage of other important side effects that substantially lower quality of life, namely dry mouth and dry eye syndromes. They are usually mild (grade I/II), however, in some individuals may lead to severe xerostomia, being a main reason for toxicity-related treatment discontinuation. Recently, Khreish et al.[47] suggested that a single course of tandem therapy with low-activity ^{225}Ac-PSMA-617/full-activity ^{177}Lu-PSMA-617 may safely enhance response to PSMA-guided RLT in men with late-stage/end-stage mCRPC while minimizing xerostomia severity.

Other alpha emitters targeting PSMA being currently under investigation include bismuth-213 (^{213}Bi), astatine-211 (^{211}At), and thorium-227 (^{227}Th). First clinical use of ^{213}Bi-PSMA-617 was reported by Sathekge et al.[48] in 1 patient with mCRPC. After 2 doses of the radiopharmaceutical with a cumulative activity of 592 MBq, the patient presented with a remarkable molecular imaging response and partial biochemical response (decrease in PSA level from 237 to 43 μg/L).

^{211}At- and ^{227}Th-labeled PSMA conjugates have been tested preclinically and exhibited promising antitumor activity in mice bearing PCa xenografts.[49,50] ^{227}Th (half-life of 18.7 d) forms stable conjugates with monoclonal antibodies, which have been already tested in preclinical studies in PCa xenograft models. Another advantage of ^{227}Th is that it decays via alpha particle emission to ^{223}Ra, which releases 4 more alpha particles.[51]

A remaining challenge is the availability of proper alpha emitters, with ^{225}Ac (half-life of 9.9 d) being produced in only 2 centers in the world (Oak Ridge, USA and Karlsruhe, Germany). Alternatively, ^{225}Ac can be obtained from high-energy proton accelerators, but the production is not established in any known department yet. ^{213}Bi (half-life of 46 min) is potentially available from generator, although its therapeutic index seems inferior to that of ^{225}Ac.[52] ^{211}At (half-life of 7.2 h) has favorable nuclear decay characteristics, resulting in 100% alpha particle emission,[51] however, its production in nuclear reactors and extraction from other byproducts requires much effort. ^{227}Th can be obtained in large amounts via beta(-) decay of ^{227}Ac, which is a product of irradiation of ^{226}Ra by thermal neutrons in nuclear reactors.[41]

Limitations and Challenges of PSMA-Directed Therapy

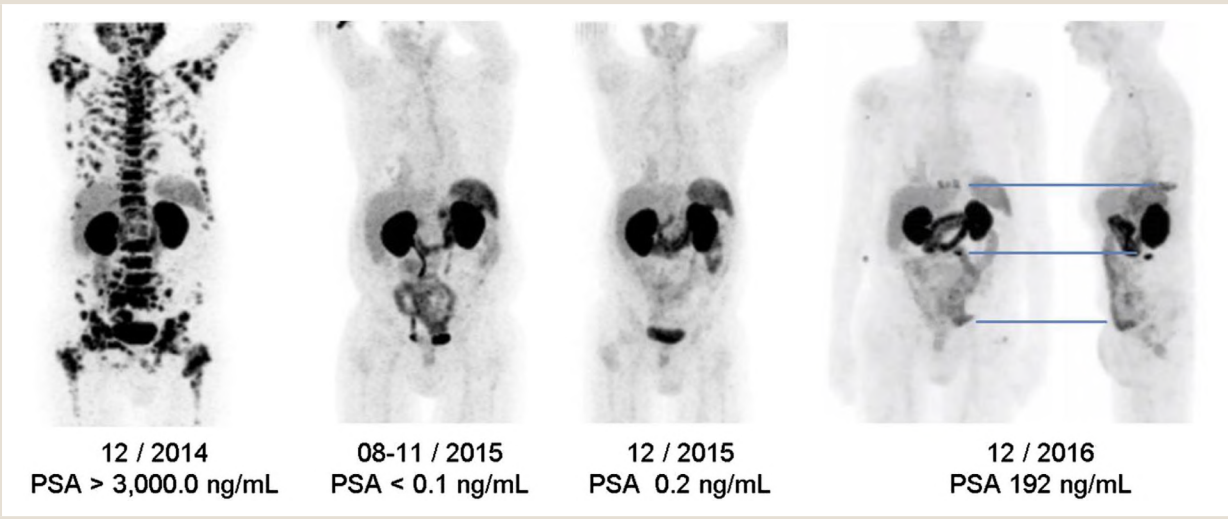
The main limitations of PSMA-directed RLT are dose-limiting organs, such as salivary glands, kidneys, and bone marrow. Some solutions for lowering the absorbed doses delivered to salivary glands

Table 2 Overview of PSMA Targeted Alpha Therapy Studies

Author(s)	Number of Pts Treated (n)	Number of PSMA TAT Cycles per Pt	Any PSA Response	PSA Response > 50%	PSMA Imaging Response	Symptoms Control	Toxicity	Side Effects	Median PFS (mo)	Median OS (mo)	Remarks
Kratochwil et al. 2017[69]	14	1-4	75% (100% for the activity > 50 kBq/kg of ^{225}Ac-PSMA-617)					1 pt with combined grade II thrombocytopenia/leucopenia in the 200 kBq/kg group		8.5	Optimal activity: 100 kBq/kg of ^{225}Ac-PSMA-617 per cycle every 8 wks
Kratochwil et al. 2018[31]	40	31 with 3 cycles; 11 with > 3 cycles; 9 with < 3 cycles	87% (33/38)	63% (24/38); CR in 13% (5/38)	50% (19/38) PR			10% pts discontinued treatment owing to xerostomia	7	12	CR in PSA and PSMA imaging in 13% (5/38) pts
Sathekge et al. 2019[30]	17	Median 3 (2-6)	88%	82% pts with PSA decrease ≥ 90% (7 pts with PSA < 0.1 ng/mL)	15/17 pts with >50% reduction in tracer avidity of metastases (11 pts with complete resolution of all lesions)		1 pt with grade II anemia before treatment required blood transfusion after first cycle; 1 pt with 1 functional kidney deteriorated from grade III to IV renal toxicity	All pts with grade I/II xerostomia; no grade III xerostomia or discontinuation of therapy because of dry mouth			Chemotherapy naïve mCPRP pts; possibility to reduce salivary toxicity by de-escalation of administered activities in consecutive cycles
Sathekge et al. 2020[46]	73	Median 3 (1-8); (17 with 1 cycle; 18 with 2 cycles; 14 with 3 cycles; 11 with 4 cycles; 9 with 5 cycles; 3 with 6 cycles; 1 with 8 cycles)	83%	70%	CR in 29% (21/73) (PSMA avidity of lesions after therapy similar to blood pool)		22 pts with grade I/II; and 5 pts with grade III anemia; 15 pts with grade I-II, 3 with grade III, and 2 with grade IV renal toxicity	85% grade I/II dry mouth (including 4 pts with dry eye and dysgeusia)	15.2	18	Side effects prevalent in pts with superscan
Yadav et al. 2020[70]	28	Median 3 (1-7)	78.6%	39%	CR 9% (2/22); PR 45.4% (10/22); SD 9% (2/22); PD 36% (8/22)	Significant decrease in VAS and analgesic score, with a concordant improvement in KPS and ECOG status ($p \leq 0.001$)	1 pt with grade III anemia	Most commonly transient fatigue (50%) followed by grade I/II xerostomia (29%)	12	17	54% (15/22) pts refractory to prior ^{177}Lu-PSMA-617 RLT

Abbreviations: CR = complete response; ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky Performance Status; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; pts = patients; RLT = radioligand therapy; SD = stable disease; TAT = targeted alpha therapy; VAS = Visual Analog Scale.

Figure 5 Complete metabolic remission of a patients with metastatic castration-resistant prostate cancer with extensive tumor burden after 4 cycles of ^{225}Ac-PSMA-617 targeted alpha therapy, with tumor control lasting 1 year and duration of clinical benefit lasting more than 2 years. Abbreviation: PSA = prostate-specific antigen. (*This research was originally published in Kratochwil C, et al. Targeted a-therapy of metastatic castration-resistant prostate cancer with 225 Ac-PSMA-617: swimmer-plot analysis suggests efficacy regarding duration of tumor control. J Nucl Med 2018;59:795-802. Copyright 2018 Society of Nuclear Medicine and Molecular Imaging.*)



have already been suggested and include cooling with icepacks[53] or intraparenchymal injection with botulinum toxin.[54] Mannitol and 2-PMPA have been used to reduce kidney-absorbed dose.[55,56] Also, to protect organs at risk, it may be reasonable to de-escalate therapeutic activity in second and consecutive cycles because of so-called tumor sink effect.[57] It results from the fact that physiological uptake in normal tissues is dependent on tumor load, which may shrink considerably after first cycle of therapy. Therefore maintaining constant therapeutic activity in further treatment cycles would result in an increasing radiation burden of vulnerable organs. The earlier observation was reported for salivary glands toxicity after PSMA TAT.[31]

Hematological toxicity is a challenge in patients with diffuse bone marrow infiltration because this organ is particularly sensitive to PSMA RLT. A recommendation of EANM for these patients is PSMA TAT because of shorter range of alpha particles and potentially more favorable microdosimetry to red marrow,[14] however, according to a recent multicenter retrospective study, diffuse bone marrow involvement should not be treated as an exclusion criteria for PSMA RLT because the treatment was associated with acceptable safety in this challenging cohort of patients.[58]

Although radionuclide therapy for mCRPC is usually offered as a last salvage therapeutic option, it may sometimes overlap with chemotherapy or antihormonal treatment. The effect of concomitant therapies is so far little explored. For instance, it was recently reported that pretreatment of mCRPC with enzalutamide could potentially enhance the effect of PSMA-guided therapy because it upregulates the PSMA expression in the tumor even in patients having previously progressed on enzalutamide.[59] This important observation should be considered when qualifying patients for PSMA RLT. Further pre- and clinical research is highly warranted in this field.

Future Perspectives

PSMA theranostics has a potential to become a game changer for diagnosis and therapy for PCa. Its remarkable ability to localize disease foci in early stages of biochemical relapse after definitive treatment and to detect lesions that escape detection by conventional imaging during primary staging may prolong survival rates or even increase the cure rates of PCa.

The therapeutic application of small molecule ligands of PSMA conjugated with ^{177}Lu or ^{225}Ac brings hope to patients with metastatic PCa who are at the stage of castration-resistance and are not eligible for other treatment options. However, full knowledge about long-term efficacy and safety of radioligand and alpha targeted therapy still requires prospective, multicenter trials, a few of which concerning ^{177}Lu-PSMA are currently under way: VISION and TheraP mentioned earlier, and LUTECTOMY (NCT04430192), PRINCE (NCT03658447), LuPARP (NCT03874884), UpFrontPSMA (NCT04343885). It should also be emphasized that—given the appropriate training, the longstanding experience regarding RLT in oncologic diseases, such as NETs, pheochromocytomas, or lymphomas, and the expertise in modern molecular theranostics—PSMA-directed RLT should preferably be carried out (in close collaboration with their partners in uro-oncology) by nuclear medicine physicians. It is them who play a central role in qualifying candidates for therapy, administering the isotope, and monitoring patients throughout the process.

Conclusion

In the authors' opinion, the already existing data are sufficient to recommend that PSMA theranostics should be considered a valuable toolkit in every clinical center dealing with PCa.

Disclosure

The authors have stated that they have no conflicts of interest.

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