short review

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Theranostics in prostate cancer

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Summary This review summarizes current evidence of "theranostics" for patients with prostate cancer. Prostate-specific membrane antigen (PSMA) is a glycoprotein which can be labeled with positron-emitting tomographic (PET) tracers like fluorine-18, gallium-68, or copper-64 and can be labeled with beta emitters like lutetium-177 to treat patients with metastatic castration-resistant prostate cancer (mCRPC). PSMA PET/CT has been shown to be superior to computer tomography (CT) and bone scintigraphy in accuracy, sensitivity, and specificity in the evaluation of metastatic tumor sites and may change treatment management. However, outcome studies showing an improvement in progression-free survival (PFS) and/or overall survival (OS) after management change is missing. PSMA PET/CT is highly recommended in prostate cancer patients with biochemical recurrence (PSA >0.2 ng/ml). Patients presenting with high PSMA expression in PSMA PET/CT may be favorably treated with ^{177}lutetium-617. In the TheraP study, a multicenter phase 2 trial, patients with mCRPC were randomly assigned to receive either ^{177}lutetium-617 or cabazitaxel. The results indicate fewer treatment-related adverse events in patients treated with ^{177}lutetium-617, an improvement in PSA response, but no improvement in OS after 36 months follow-up. In the VISION trial, a phase 3 international study, patients with mCRPC were randomly assigned to receive either ^{177}lutetium-617 and standard of care (SOC) or SOC alone. At 12 months, radiographic PFS or PSA-PFS was 18% in patients treated with ^{177}lutetium-617 and 3% in patients treated with SOC alone. The real status of ^{177}lutetium-617 in the sequel of treatment regimens remains unclear and additional studies are therefore warranted.

Keywords Prostate neoplasms · PSMA PET/CT · ^{177}Lu-PSMA-617 · Radioligand therapy · Nuclear medicine

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Introduction

In general, nuclear medicine has become one of the leading disciplines in personalized medicine, meaning in vivo molecular imaging and molecular directed treatment of patients with one molecular target. This combined approach is called "theranostics".

In 1941, Dr Samuel Hertz was the first to apply beta-emitting radioactive iodine-131 (^{131}I) to treat patients with thyroid cancer [1]. Well-differentiated thyroid cancer and its metastases can be easily visualized with radioactive gamma-emitters like ^{131}I or ^{123}I using a conventional gamma camera or with a positron-emitting tracer like ^{124}I using a more sophisticated positron-emission tomography (PET) device.

In recent years, prostate-specific membrane antigen (PSMA) became an interesting molecular target in nuclear medicine for specific molecular imaging and for specific treatment of patients presenting with advanced metastatic castration-resistant prostate cancer.

PSMA is a type II transmembrane glycoprotein receptor containing about 750 amino acids. In benign prostatic cells, it is localized to the cytoplasmic and apical part of the prostate epithelium. As malignant transformation occurs, PSMA is commonly transferred from the cytoplasm to the luminal surface of

the prostatic ducts, where it presents a large extracellular domain to ligands [2]. The biological function of PSMA remains unclear, but it is hypothesized to have a transport function because PSMA ligands are internalized through endocytosis. Furthermore, research suggests a 100- to 1000-fold increase in PSMA expression in prostatic adenocarcinoma versus benign prostatic tissue [3, 4].

PET/CT imaging with PSMA

In nuclear medicine, PET/CT imaging has become widely available over the last two decades and has become a standard of choice for imaging in patients with cancer. In comparison to conventional nuclear medicine using gamma-emitters, PET/CT offers a much better spatial image resolution of 4 mm and image fusion with the CT component facilitates image interpretation.

PSMA molecules can be labeled with short-lived positron-emitting tracers like fluorine-18, gallium-68, or copper-64 (physical half-lives range between 110 min and 12.8 h) and whole-body PET/CT scans can be easily recorded with the patient in the supine body position within 20–30 min after intravenous (IV) injection of the radiolabeled compound. There is no evidence that one of these tracers is superior to the others; however, direct comparative studies in individual patients in literature are rare. There is only one study indicating that the sensitivity of ^{18}F-PSMA-11 was not inferior to ^{68}Ga-PSMA-11 in prostate cancer patients for primary staging and in patients with biochemical PSA recurrence [5]. In the last 2 years, the US Food and Drug Administration (FDA) approved ^{68}Ga-PSMA-11 and a PSMA ligand ^{18}F-pifluolastat (Pylarify®, Progenics Pharmaceuticals, Inc., N. Billerica, MA, USA) for routine clinical application. In Europe, European Medicines Agency (EMA) approval is still pending.

Multiparametric magnetic resonance imaging (MRI) is validated for the detection of clinically significant prostate cancer, although patients with negative or equivocal MRI undergo biopsy for false-negative concerns. The additive value of PSMA PET/CT was shown in a prospective multicenter study in 156 patients with PI-RADS 3–5 [6]. PSMA PET/CT showed PSMA expression in 73% of patients and were positive in 81% in the combined PSMA/MRI evaluation. Combined MRI/PSMA PET/CT improved the negative predictive value compared with MRI alone with 91% versus 72%, test ratio = 1.27 (1.11–1.39, $p < 0.001$). The sensitivity was improved at 97% versus 83% ($p < 0.001$); however, specificity was reduced at 40% versus 53% ($p = 0.011$). In addition, 5 patients (4 with ISUP 2 and 1 with ISUP 3) were missed with PSMA PET/CT and MRI indicating the necessity of an additional biopsy.

PSMA-targeted imaging has been extensively investigated for primary staging and restaging of prostate cancer patients; most of these studies were single-center studies and did not include histological verification of metastatic sites visualized by PSMA PET/CT. For primary staging, the sensitivity for detection based on individual lesions ranged from 33 to 92% and the specificity ranged from 82 to 100% [7]. In a recent publication with patients with histologically proven prostate cancer, initial staging was planned and patients were randomly assigned to conventional imaging with CT and bone scanning or to ^{68}Ga PSMA-11 PET/CT. First-line imaging was done within 21 days following randomization. Patients crossed over unless three or more distant metastases were identified. PSMA PET/CT demonstrated a 27% (95% CI 23–31) greater accuracy than that of conventional imaging at 92% (95% CI 88–95) versus 65% (95% CI 60–69; $p < 0.0001$). The sensitivity for primary staging was reported to be 85% (95% CI 74–96) for PSMA PET/CT as compared to only 38% (95% CI 24–52) for conventional imaging; the specificity was 98% (95% CI 95–100) for PSMA PET/CT and 91% (95% CI 85–97) for conventional imaging [8].

The clinical impact of PSMA-PET/CT in the detection of pelvic lymph nodes prior to radical prostatectomy or local radiotherapy was addressed in the OSPREY trial, a prospective phase 2/3 multicenter trial with ^{18}F-DCFPyL [9]. The poor sensitivity of only 40% in the detection of histologically proven metastatic pelvic lymph nodes and the sensitivity of 60% in the detection of lymph nodes greater than 0.5 cm in size means that PSMA-PET/CT cannot be recommended in general for initial staging. The low sensitivity of 40% in pelvic lymph nodes was also reported in another prospective phase 3 trial with ^{68}Ga-PSMA-11 [10]. The clinical value of PSMA PET/CT was shown in the CONDOR study, a multicenter phase 3 trial [11]. In patients presenting with biochemical recurrence of PSA ≥ 2 ng/ml and normal or only suspected morphological recurrence on conventional imaging, PSMA PET/CT showed a sensitivity of 91% in the detection of histologically proven metastases. Clinical management was changed in 64% of patients after the PSMA PET/CT was obtained. Another international multicenter trial included more than 1000 prostatic cancer patients with biochemical recurrence (PSA > 0.2 ng/ml and normal results in conventional radiological and scintigraphic bone imaging) and showed PSMA-expressing lesions in PSMA PET/CT in 65% of patients investigated [12]. A positive scintigraphic result was more likely to be reported in patients with a Gleason score of 7 or higher ($p < 0.001$, 95% CI 1.25–1.65), in patients who were initially treated with local ablative radiotherapy ($p < 0.001$, 95% CI 1.42–1.76) and in patients with a mean PSA doubling time less than 10 months ($p < 0.001$, 95% CI 0.97–0.99) or in patients with an increased PSA value ≥ 4 and below 10 ng/ml ($p < 0.001$, 95% CI 1.47–1.97) at the time of the PSMA PET/CT. Fig. 1 shows the association between a positive PET/CT scan result and the Gleason score of patients, and Fig. 2 illustrates the association between

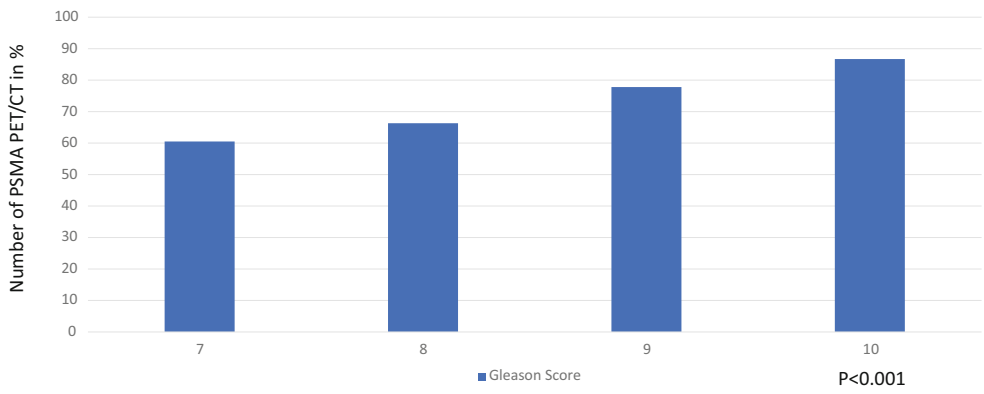

Fig. 1 Association between prostate-specific membrane antigen (*PSMA*)-positive PET/CT scans (%) and Gleason score

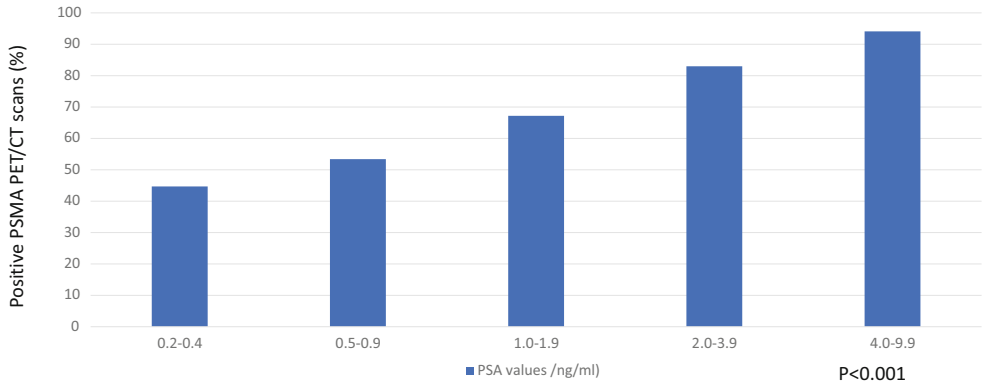

Fig. 2 Association between prostate-specific membrane antigen (*PSMA*) PET/CT-positive results and prostate-specific antigen (*PSA*) values

PSMA PET/CT and PSA values. A treatment modification was reported in 57% of patients after the PSMA PET/CT information was obtained. However, a limitation of this study was that no PSMA-positive lesions were confirmed by biopsy. PSA as the main predictor of a positive PSMA PET/CT scan was also reported in another multicenter study with more than 2000 patients with biochemical PSA recurrence with 44.8% PSMA-positive scans at PSA < 0.25 ng/ml up to 96.2% at PSA > 10 ng/ml, $p < 0.001$ [13]. A recently published prospective study in patients with newly diagnosed prostate cancer and with pathological confirmation of PSMA-positive scan results reported a malignancy in 74% of taken biopsies. In a second group of patients with biochemically recurrent disease, the malignancy rate was even higher with 89% [14].

In general, PSMA PET/CT is more accurate for staging than CT and bone scan for high-risk disease but to date no outcome data exist. However, one additional limitation must be understood is that PSMA expression is not present in prostate cancer patients only. In literature, several other malignant tumors like hepatic cell cancer, bladder cancer, renal cell carcinoma, breast cancer, non-small lung cancer, adrenocortical cancer, colon cancer, neuroendocrine tumors, celiac ganglioma, multiple myeloma, atypical meningioma and glioma, central nervous system (CNS) lymphoma, acute lymphocytic leukemia and lymphoma, osteosarcoma, thyroid cancer, melanoma, but also nonmalignancies like hemangiomas, bone disease like Paget's disease and osseous fibrosis or inflammation may be associated with a PSMA expression high enough to be visualized by PSMA PET/CT [15]. Even in patients after radical prostatectomy with a PSA value < 0.05 ng/ml may show false-positive results [16]. Therefore, in unclear findings, additional biopsy is mandatory to rule out secondary malignancies.

Table 1 Indications for PSMA PET/CT (from [17], shortened and adapted by the author)

Biochemical recurrence of PSA after radical prostatectomy (RPE) or after local ablative radiotherapy (PSA > 0.2 ng/ml)
To select patients for PSMA–radioligand therapy
Primary staging after a negative conventional imaging (CT, MRI, bone scan) and high clinical suspicion of metastases

PSMA prostate-specific membrane antigen, *PET/CT* positron emission tomography/computer tomography, *PSA* prostate specific antigen, *CT* computer tomography, *MRI* magnetic resonance imaging

Table 1 summarizes possible indications for PSMA PET/CT imaging in prostate cancer patients and the recommendations were published in a guideline in a joint effort between The European Association of Urology and The European Association of Nuclear Medicine and Metabolic Imaging in 2022 [17].

Targeted treatment with PSMA

Beta-emitting radioisotopes, such as lutetium-177 (^{177}Lu), are one of the favored types of radioisotopes

with a relatively long physical half-life of 6.6 days, permitting delivery of a high radiation dose to prostate cancer cells. After binding of ^{177}Lu-PSMA on the cell surface of PSMA-expressing tumor cells, an internalization process of the radiocompound into the cytoplasm of tumor cells will cause apoptosis of tumor cells by DNA double strand cleavage in the cell nucleus. The short maximal tissue penetration of only 2 mm minimizes the radiation burden to normal tissues improving overall drug compatibility. In general, this treatment can be offered as outpatient or inpatient care, depending on national legal regulations.

In the last 2 years, two multicenter randomized clinical trials in patients with mCRPC receiving ^{177}Lu-PSMA-617 were published [18, 19]. The TheraP study was a phase 2 multicenter trial in patients with mCRPC after treatment with docetaxel and a rising PSA or a PSA >20 ng/ml [18]. All patients included showed a PSMA-positive PET/CT scan and had at least one lesion with a very high PSMA tracer uptake as expressed by a standardized uptake value (SUVmax) >20 and no uptake in a concomitant ^{18}F-FDG PET/CT, which may indicate poor differentiation of individual tumor lesions. All 200 patients with an ECOG performance of 0–2 were randomized in a 1:1 fashion, receiving either 8.5 GBq with a lowering of the dosage by 0.5 GBq every 6 weeks up to 6 cycles in total, or cabazitaxel 20 mg/m^2 every 3 weeks with up to 10 cycles. Primary endpoint of the study was PSA response rate, defined as the proportion of patients in each group with a PSA reduction ≥50% from baseline. Secondary endpoints included overall survival (OS), progression free survival (PFS), PSA progression-free survival, objective tumor response, and pain response. A PSA reduction >50% was reported in 66% (95% CI 56–75) of patients treated with ^{177}Lu-PSMA-617 as compared to 37% (95% CI 27–46, $p<0.001$) of patients treated with cabazitaxel. The secondary endpoint risk of tumor progression could be improved by 37% (HR 0.63; 95% CI 0.45–0.85; $p=0.002$). At 12 months, a radiographic PFS or a PSA PFS was reported in 19% (95% CI 12–27) of patients treated with ^{177}Lu-PSMA-617 as compared to only 3% (95% CI 1–9) of patients treated with cabazitaxel. However, the median PFS showed no difference with 5.1 months (3.4–5.7) in patients treated with ^{177}Lu-PSMA-617 and 5.1 months (2.8–6.0) in patients treated with cabazitaxel. Treatment-emergent adverse events (TEAE) grade 3 or 4 were reported in 54% of patients treated with cabazitaxel and in 33% treated with ^{177}Lu-PSMA-617. The most frequently reported adverse events in patients treated with ^{177}Lu-PSMA-617 were thrombopenia, anemia, and fatigue. Table 2 shows the TEAE in both treatment groups in more detail. The OS results were presented separately at ASCO 2022 and showed no statistical difference in the two groups. The median follow-up time was then 36 months and the OS reported was 19.1 months in patients with ^{177}Lu-PSMA-617 and 19.8 months in patients treated with cabazitaxel (NS). A subgroup analysis including 61 patients, who were not included in the published study because of low PSMA expression in the PSMA PET/CT or a positive ^{18}F-FDG PET result and who then received either cabazitaxel or ^{177}Lu-PSMA-617, showed an OS of only 11.0 months at the 36 month follow-up [20].

Table 2 Treatment-emergent adverse events in patients receiving either cabazitaxel or ^{177}Lu-PSMA-617

Term	Cabazitaxel (*N*= 85)		Lu-PSMA (*N*= 98)	
	G1–2 %	G3–4 %	G1–2 %	G3–4 %
Neutropenia (±fever)	5	13	7	4
Thrombocytopenia	5	0	18	11
Dry mouth	21	0	60	0
Diarrhea	52	5	18	1
Dry eye	4	0	30	0
Dysgeusia	27	0	12	0
Neuropathy (motor or sensory)	26	1	10	0
Fatigue	72	4	70	5
Nausea	34	0	40	1
Anemia	13	8	19	8
Vomiting	12	2	12	1
TOTAL (all AEs)	40	54	54	33

Discontinuations for toxicity occurred in 1/98 (1%) Lu-PSMA vs 3/85 (4%) cabazitaxel-treated
There were no Lu-617 PSMA-related deaths
AE adverse event, *G* grade, *Lu-PSMA* ^{177}Lutetium-PSMA-617

The VISION trial became the first international multicenter phase 3 trial randomizing in a 2:1 fashion to treat patients with ^{177}Lu-PSMA-617 and standard of care (SOC) as compared to patients treated with SOC alone. SOC was defined by each study center and could include hormonal treatment including abiraterone and enzalutamide, bisphosphonates, denosumab, radiation therapy, or glucocorticoid at any dose [19].

A total of 831 patients with mCRPC who already received at least one taxane and at least one androgen receptor signaling inhibitor prior to study inclusion were included in the study. All patients had a positive PSMA PET/CT scan, showed adequate major organ function and bone marrow function, and an ECOC performance status of 0–2 was reported. Primary endpoints of the study were radiographic PFS and OS; secondary endpoints included objective response rate (OR), biomarkers, health-related quality of life and pain scores, and safety and tolerability issues. The median rPFS was 8.7 months in the patients treated with ^{177}Lu-PSMA-617 and SOC as compared to 3.4 months in patients treated with SOC alone. The risk of radiographic progression was reduced by 60% (HR 0.40; 99.2% CI 0.29–0.57; $p<0.001$). The median OS was 15.3 months in patients treated with ^{177}Lu-PSMA-617 and SOC as compared to 11.3 months in patients treated with SOC alone. The risk of death was reduced by 38% with a HR 0.62 (95% CI 0.52–0.74, $p<0.001$). Secondary endpoints like OR indicated

a complete radiographic response in 17 patients (9.2%) treated with ^{177}Lu-PSMA-617 and SOC and no patient treated with SOC alone. The time to first symptomatic skeletal event was reported after a median of 11.5 months in patients with ^{177}Lu-PSMA-617 and SOC as compared to 6.8 months in patients treated with SOC alone. The HR was 0.50 (95% CI 0.40–0.62, $p<0.001$). A drop of PSA values of more than 50% from baseline after treatment with ^{177}Lu PSMA-617 and SOC was reported in more than 79% of patients as compared to 9% in the control group. In addition, the evaluation of quality of life and bone pain intensity scores favored treatment with ^{177}Lu-PSMA-617 and SOC as compared to SOC alone. Subgroup analysis indicated that patients receiving an additional androgen receptor blocking agent, patients with impaired liver function, presence of liver metastases, an ECOG score of 2, or older patients (>65 years) had no negative effect on the treatment response. TEAEs grade 3–5 were more commonly reported in patients with ^{177}Lu-PSMA-617 + SOC with 28% as compared to 4% in patients receiving SOC alone. Fatigue, bone marrow suppression, and renal effects were the most frequently reported grade 3–5 side effects. There were 5 TEAEs leading to death in patients treated with ^{177}Lu-PSMA-617 + SOC indicating the importance of a tumor board with all medical disciplines like urology, pathology, radiology, radio-oncology, and nuclear medicine included prior to treatment decision to select patients properly for the best individual treatment available. The limitation of this study was that no long-term side effects were reported, due to the short observation period of only 30 days after radioligand therapy, and in addition, there was no direct comparison to a taxane or an androgen receptor signaling inhibitor. However, in March 2022 the FDA approved ^{177}Lu-PSMA-617 (Pluvicto™, Advanced Accelerator Applications, Milburn, NJ, USA) for the treatment of mCRPC followed by treatment with at least one taxane and one androgen receptor signaling inhibitor and evidence of disease progression in conventional imaging and high PSMA expression in PSMA PET/CT. Post hoc subgroup analyses presented at ASCO 2022 showed that the number of prior androgen-receptor blocking agent lines and the number of taxane lines had no negative effect on rPFS and on OS after treatment with ^{177}Lu-PSMA-617 [21]. In addition, neither bone health agents nor prior radiotherapy had an effect on the outcome. Interestingly, patients who presented a high PSMA expression in the PSMA PET/CT scan with a SUVmax >10 showed a median OS of 21 months as compared to patients with a SUV <6 with a median OS of 14.5 months. Additional prospective studies are warranted to clarify whether a SUVmax >10 in PSMA PET/CT could really serve as a predictive or prognostic biomarker in mCRPC.

Perspective—a brief outlook in ongoing clinical trials with ^{177}Lu-PSMA-617

There are currently several additional clinical trials looking for the real status of ^{177}Lu-PSMA in the sequel of multiple treatment strategies and regimens in patients with mCRPC including chemotherapy, androgen receptor signaling inhibitors, PARP inhibitors, and antibodies. The PSMAddition trial (NCT04720157) is a phase 3 international multicenter study in patients with hormone-sensitive metastatic prostate cancer and will answer the efficacy of ^{177}Lu-PSMA-617 plus SOC as compared to SOC in an earlier disease course. In total, 1126 patients will be included and in case of radiographic disease progression, a crossover to treat with ^{177}Lu-PSMA-617 is allowed. Another phase 3 clinical trial, the PSMAfore trial (NCT04689828) will compare the efficacy of ^{177}Lu-PSMA-617 versus androgen-receptor directed therapy in progressive mCRPC. The potential of ^{177}Lu-PSMA-617 prior to radical prostatectomy is being addressed in the LuTectomy (NCT04430192), a phase 1/2 study. All these studies are already recruiting, and first results should be available in the coming years.

Conclusion

In patients with prostate cancer, PSMA PET/CT has been shown to be more sensitive and specific in detecting PSA biochemical-recurrent disease as compared to conventional imaging (CT and bone scan). In patients with mCRPC, the results of initial phase 2 and phase 3 clinical trials indicated that ^{177}Lu-PSMA-617 was better tolerated, had less toxic adverse events compared to taxane-based chemotherapy, and showed an improvement in rPFS and OS as compared to treatment with SOC alone. However, additional prospective randomized clinical trials are warranted to address where the greatest benefit of ^{177}Lu-PSMA-617 will be in the sequel of different treatment options.

Take home message

- PSMA PET/CT is highly recommended in prostate cancer patients with biochemical PSA recurrence >0.02 ng/ml.
- In patients with metastatic castration-resistant prostate cancer after one taxane line and one androgen-receptor signaling line, ^{177}Lu-PSMA-617 offers a better adverse event profile compared to cabazitaxel with no statistical difference in overall survival.

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Merck and received travel fees from IPSEN, Novartis, Merck, Sanofi-Genzyme and Siemens.

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