Lutetium-177 PSMA for prostate cancer; current developments and challenges

E.C.A. van der Sar, MSc[1]; B. de Keizer, MD, PhD[1]; J. Lavalaye, MD, PhD[2]; J.M.H. de Klerk, MD, PhD[3]; L.W. van Golen, MD, PhD[4]; W.V. Vogel, MD, PhD[4,5]; M.G.E.H. Lam, MD, PhD[1]; A.J.A.T. Braat, MD, PhD[1]

[1]Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, [2]Department Nuclear Medicine, st Antonius hospital, Nieuwegein, [3]Department Nuclear Medicine, Meander hospital, Amersfoort, [4]Department Nuclear Medicine, Netherlands Cancer Institute NKI-AVL, Amsterdam, [5]Department of Radiation Oncology, Netherlands Cancer Institute NKI-AVL, Amsterdam

Abstract

[^{177}Lu]Lu-PSMA has shown to be effective and safe in patients with metastatic castration resistant prostate cancer (mCRPC), leading to Food and Drugs Authorization (FDA) approval in the United States of America for [^{177}Lu]Lu-PSMA-617 in March 2022 and to European Medical Agency (EMA) approval in December 2022. In the Netherlands, [^{177}Lu]Lu-PSMA-I&T is reimbursed since August 2021 for the same indication. This illustrates that a lot has happened since our initial report on [^{177}Lu]Lu-PSMA in the previous therapy special edition of Tijdschrift voor Nucleaire Geneeskunde, five years ago. This review will summarize recent scientific developments on [^{177}Lu]Lu-PSMA radioligand therapy. The most notable and impactful prospective trials included the TheraP-, and VISION-trial investigating [^{177}Lu]Lu-PSMA-617 in mCRPC patients. They will be discussed in more detail. Furthermore, several technical aspects of this novel therapy, relevant to the nuclear medicine community will be discussed. As [^{177}Lu]Lu-PSMA is a relatively new therapy, many unknowns concerning patient selection, imaging biomarkers and response monitoring still exist. This review will provide a summary on these aspects and stresses the need for additional prospective validation studies.

Introduction

Most patients with prostate cancer can be treated with curative intent. However, the survival rates of prostate cancer depend on the stage of disease. Although the five-year survival rate for localized prostate cancer is 100%, it drops to 31% if distant metastases are present (1). Treatment options for men with advanced or metastatic castration resistant prostate cancer (mCRPC) mostly exist of new hormonal agents (e.g. enzalutamide and abiraterone) and chemotherapy (e.g. docetaxel and cabazitaxel). However, these therapies are associated with substantial side effects and in some patients it is contraindicated or not tolerated. Therefore, novel therapeutic strategies with improved outcomes and less side effects are desired.

With the introduction of the radioligand prostate specific membrane antigen (PSMA) a new 'theranostic' agent became available for prostate cancer. PSMA is a type II membrane glycoprotein (also called folate hydrolase I or glutamate carboxypeptidase II (GCPII)). The expression of PSMA is 100-1000 fold higher in prostate cancer cells in comparison to healthy tissue (2). This makes it an interesting target for both diagnostics and therapeutics. The first application using PSMA-ligands labelled with positron emitting isotopes allowed molecular imaging in vivo with PET(/CT), generally referred to as PSMA PET. Over the years, PSMA PET has proven to be more accurate in prostate cancer imaging with a higher diagnostic accuracy than conventional imaging (CT and skeletal scintigraphy) for the detection of prostate cancer lymph nodes and bone metastases: 92% (95% CI 88-95%) versus 65% (95% CI 60-69%), respectively (3). As a second step, PSMA-ligands were labelled with therapeutic isotopes, including ^{177}Lu. Radioligand therapy with [^{177}Lu]Lu-PSMA has shown to be effective and safe in patients with mCRPC in different multi-center, open-label, (randomized) trials (4-6). This led to the Food and Drugs Authorization (FDA) approval in the United states of America of [^{177}Lu]Lu-PSMA-617 (^{177}Lu-vipivotide teraxetan, PluvictoTM, Advanced Accelerator Applications USA, Inc. (AAA, a Novartis company; Millburn, NJ, USA)) for the treatment of metastatic prostate cancer since March 2022. Marketing authorization for the drug has been granted in August 2022 in the United Kingdom. In December 2022, the European medicines agency (EMA) approved [^{177}Lu]Lu-PSMA-617. In the Netherlands, despite the EMA

approval, PSMA-617 is currently not yet available for clinical use, while approval for reimbursement by health insurance companies is awaited. As an alternative and likely temporary solution, the comparable radiopharmaceutical, [^{177}Lu]Lu-PSMA-I&T has been reimbursed for men with mCRPC since August 2021 (figure 1). This review will summarize different leading developments on PSMA radioligand therapy and discuss further aspects of this novel therapy, with emphasis on current clinical and scientific efforts in the Netherlands.

Indication

Following the EANM procedure guidelines (7), patients are eligible for [^{177}Lu]Lu-PSMA if they have: 1) mCRPC and are exhausted or are ineligible for approved alternative options, 2) adequate organ function and, 3) show adequate radiotracer uptake on PSMA PET/CT prior to [^{177}Lu]Lu-PSMA therapy. The latter is fiercely debated, as it is based on previous literature on neuroendocrine tumour theranostics, in which uptake in de tumour sites must at least be higher than the physiological uptake in normal organs, including the liver. At present however, this will remain the key criterion on imaging for patient selection based on the VISION trial results. Table 1 represents the contraindications following the EANM guidelines.

Efficacy

Five years ago, in the previous edition of this journal's special issue (8), many small retrospective studies were available and since then numerous studies have been published. In the Netherlands the first clinical experience with small molecule [^{177}Lu]Lu-PSMA radioligand therapy was in 2016 at the Utrecht University Medical Center (9). Thirty consecutive patients with metastatic castration resistant prostate cancer (mCRPC) received 1-6 therapy cycles with 6 GBq [^{177}Lu]Lu-PSMA-617. After the first cycle, in 45% of the patients the analgesics could be decreased. During treatment, 57% of the patients had a maximum PSA decline of ≥ 50% and 24% of the patients even ≥ 90%. Toxicity was limited to Common Terminology Criteria for Adverse Events (CTCAE) grade I-II, most commonly xerostomia (17%). Median overall survival (OS) starting from the first therapy cycle was 11.3 (range 1.4-32.3) months during a median follow-up of 13.7 (9.8-32.3) months. Later, several multi-center prospective phase II and III trials followed, and the number of studies on [^{177}Lu]Lu-PSMA-617 rapidly increased

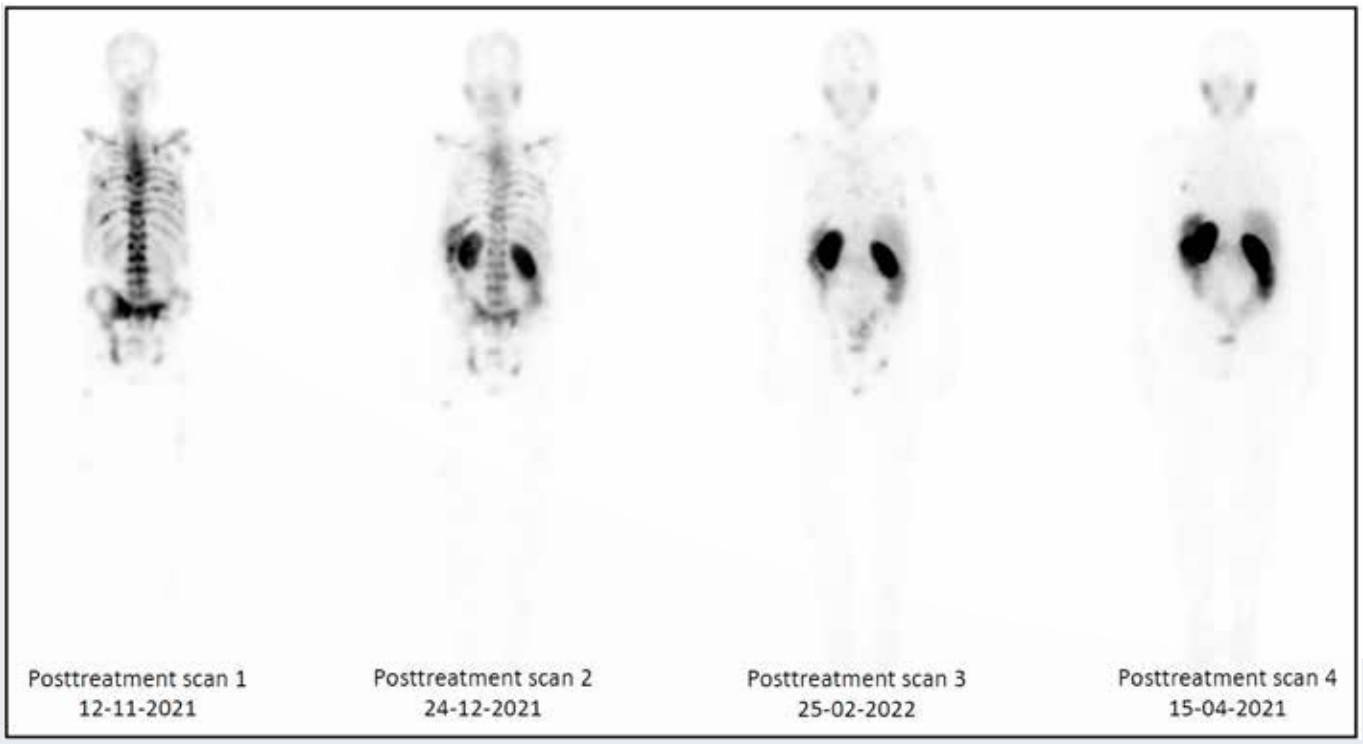

Figure 1. Example of response during [^{177}Lu]Lu-PSMA-I&T as shown on post-treatment scintigraphy. A 62 years old metastatic castration resistant prostate cancer (mCRPC) patient with baseline prostate specific antigen (PSA) of 399 ng/mL, received four cycles of 7.4 GBq [^{177}Lu]Lu-PSMA-I&T. He had a very good clinical response and was free of pain after his first treatment, which enabled him to start his work full-time again. A PSA decline to 1.6 ng/mL was observed.

Table 1. Contraindications for [^{177}Lu]Lu-PSMA therapy according to the EANM guidelines

1	Life expectancy < 6 months (ECOG performance status > 2); unless the main objective is alleviation of disease-related symptoms.
2	Unacceptable medical or radiation safety risk for isolation on a nuclear medicine therapy unit (if required by national regulations).
3	Unmanageable urinary tract obstruction or hydronephrosis. In patients with diagnosed or who are at high risk of urinary retention, [^{99m}Tc]Tc-MAG3 or [^{99m}Tc]Tc-DTPA renal scintigraphy should be considered as a baseline exam.
4	Progressive deterioration of organ function (GFR < 30 mL/min or creatinine > 2-fold upper limit of normal (ULN); liver enzymes > 5-fold ULN).
5	Myelosuppression: a. Total white cell count less than 2.5 × 10^9/L b. Platelet count less than 75 × 10^9/L
6	Conditions that require timely interventions (i.e. radiation therapy, surgery), e.g. spinal cord compression and unstable fractures. [^{177}Lu]Lu-PSMA may be performed afterwards upon patient's condition. Borderline cases should be evaluated within the multidisciplinary tumour board for the individual benefit-to-risk ratio.

after Novartis acquired Endocyte.

TheraP-trial

The first prospective, multi-center, open-label, randomized phase II study (TheraP) investigated the activity and safety of [^{177}Lu]Lu-PSMA-617 in men with mCRPC and PSMA PET positive disease, for whom cabazitaxel was considered the next appropriate standard treatment (6). Patients were randomly assigned in a 1:1 ratio. The intervention arm consisted of up to 6 cycles of 6.0-8.5 GBq [^{177}Lu]Lu-PSMA-617 every 6 weeks, the control arm received cabazitaxel (20 mg/m^2 intravenously every 3 weeks to a maximum of 10 cycles). A total of 200 men were randomly assigned, 101 patients in the intervention arm and 99 patients in the control arm. The intervention arm had similar median PSA-based progression-free survival (PFS) (interval from randomization to first evidence of > 25% PSA-progression and at least 2 ng/mL after 12 weeks) of 5.1 months. However, a delayed PSA-based progression was observed in the intervention arm (HR 0.60; 95% CI 0.44-0.83; p = 0.0017). Similar benefits were found for radiographic progression on CT according to the response evaluation criteria in solid tumours version 1.1 (RECIST 1.1) and prostate cancer clinical trials working group 3 criteria (PCWG3) (10) for bone lesions at skeletal scintigraphy (HR 0.64; 95% CI 0.46-0.88; p = 0.0070). Objective response according to RECIST 1.1 was observed in 49% (95% CI 33-56) in the [^{177}Lu]Lu-PSMA-617 arm versus 24% (95% CI 11-38) in the cabazitaxel arm (p = 0.019). A PSA-response of ≥ 50% PSA decline was noted in 66% (95% CI 56-75%) in the intervention arm versus 37% (95% CI 27-46%) in the control arm.

Three years later at ASCO 2022, the survival analysis was presented, in which OS in both arms were similar, approximately 19 months (HR 0.97; 95% CI 0.70-1.4; p = 0.99) (11). However, during follow up a high number of crossover and post-protocol therapies were reported.

VISION-trial

Largely in parallel, an international multi-center, open-label, randomized, phase III study (VISION-trial) investigated the efficacy and safety of [^{177}Lu]Lu-PSMA-617 plus protocol-permitted standard of care (ppSoC) in patients previously treated for mCRPC (with at least either enzalutamide or abiraterone, and a taxane; i.e. docetaxel or cabazitaxel), with a positive PSMA PET (4). Patients were randomly assigned in a 2:1 ratio. The intervention arm consisted of intravenous infusions of 7.4 GBq once every 6 weeks for four cycles and ppSoC, the control arm included ppSoC alone. ppSOC included hormonal treatment, not restricted to the approved hormonal treatments (e.g. abiraterone and enzalutamide), bisphosphonates, radiation therapy, denosumab, or glucorticoids. Treatment could be expanded up to a total of six cycles, in case patients showed evidence of response. A total of 831 patients were included, 551 patients in the intervention group and 280 patients in the control group. The intervention arm had a significant better median radiographic PFS of 8.7 months versus 3.4 months, defined according to PCWG3 (10) (HR 0.40; 99.2% CI 0.29-0.57; p < 0.001) and median OS of 15.3 months versus 11.3 months (HR 0.62; 95% CI 0.52-0.74; p < 0.001). Complete response rate according to RECIST 1.1 was 9.2% in the intervention arm and none in the control arm, a partial objective

response was noted in 41.8% in the intervention arm and 3% in the control arm. In comparison to TheraP-trial a lower PSA-response (≥ 50% PSA decline) was noted, 46.0% of the intervention arm and 7.1% in the control arm, caused by differences in patient selection. A PSA-response of ≥ 80% was noted in 33% of the intervention arm and 2% in the control arm.

PSMA I&T

The described studies applied the PSMA-617 ligand. At the same time, the alternative and largely comparable PSMA-I&T ligand was also evaluated in other studies. For [^{177}Lu]Lu-PSMA-I&T existing data consisted of retrospective studies only. Currently, an international, multi-center, phase III RCT is enrolling patients (SPLASH; NCT04647526; to be discussed in the final section).

Safety

Results from earlier retrospective studies were confirmed in the two above-mentioned prospective studies, in which the TheraP-trial revealed 33% grade 3-4 adverse events (according to CTCAE) in the intervention arm and 53% in the control arm. The most common side effects reported included fatigue (75%), dry mouth (60%), nausea (41%) and bone marrow suppression (thrombocytopenia (29%), anaemia (27%), neutropenia (11%), and leukopenia (11%)). No death was attributed to [^{177}Lu]Lu-PSMA-617 in the TheraP-trial.

In contrast to the TheraP-trial, in the VISION-trial, the incidence of adverse events of ≥ grade 3 was higher within the intervention arm (52.7% versus 38.0%). However, quality of life was not adversely affected. The most common adverse events in the intervention arm included fatigue (43.1%), dry mouth (38.8%), nausea (35.3%), and bone marrow suppression (thrombocytopenia (17.2%), anaemia (31.8%), lymphopenia (14.2%) and, leukopenia (12.5%)). Five adverse events that led to death were considered related to [^{177}Lu]Lu-PSMA-617 in the VISION-trial (bone marrow failure, subdural hematoma, intracranial hemorrhage, and pancytopenia in two patients).

Dosimetry

Biodistribution of [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T are quite similar, with high physiological accumulation in the lacrimal and salivary glands, kidneys, and small intestine; medium to low accumulation in the liver and spleen. Both are predominantly renally excreted. However, retention of [^{177}Lu]Lu-PSMA-617 is higher than of [^{177}Lu]Lu-PSMA-I&T, whilst they have a similar effective whole-body half-life, [^{177}Lu]Lu-PSMA-617 42 hours versus [^{177}Lu]Lu-PSMA-I&T 35 hours (12).

In a sub study of the VISION-trial, dosimetry was performed in 29 mCRPC patients who received up to six cycles of 7.4 GBq [^{177}Lu]Lu-PSMA-617 plus ppSoC every six weeks. SPECT/CT was preformed of the upper and lower abdomen at 2, 24, 48 and 168 hours after first administration (13). Blood and urine samples were collected throughout cycle one. Absorbed dose per unit activity (Gy/GBq) and cumulative estimated absorbed dose (Gy) over all 6 cycles (44.4 GBq cumulative activity) extrapolated from cycle one data were reported. The lacrimal glands received the highest absorbed dose per administered activity of 2.10 (±0.47) Gy/GBq, followed by the salivary glands and kidneys at 0.63 (±0.36) Gy/GBq and 0.43 (±0.16) Gy/GBq, respectively. These results are in line with earlier retrospective studies. Even though absorbed dose in lacrimal glands is the highest, incidence of related clinical toxicity is very low or non-existent, thus both salivary glands and kidneys are considered to be the dose limiting organs for [^{177}Lu]Lu-PSMA-617 treatment. For [^{177}Lu]Lu-PSMA-I&T a ~1.5x higher median kidney dose was observed in comparison to [^{177}Lu]Lu-PSMA-617 (14). However, reported clinically relevant toxicities remain similar (15). Fortunately, toxicity of salivary glands and kidneys is relatively low and predominantly transient, not affecting quality of life. Tumour dosimetry was not assessed in the sub-study of the VISION-trial.

Previous studies did investigate tumour dosimetry and a potential correlation to treatment outcome (biochemical response </≥ 50%). Violet et al. reported their results from a prospective cohort of 30 mCRPC patients, who received up to four cycles of [^{177}Lu]Lu-PSMA-617 (16). All patients had a screening [^{68}Ga]Ga-PSMA-11 PET/CT and SPECT/CT at 4, 24, and 96 hours after [^{177}Lu]Lu-PSMA-617. Administered [^{177}Lu]Lu-PSMA-617 dose was variable; based on tumour burden, patient's weight and renal function (mean 7.5 GBq/cycle range 4.4-8.7, SD 1.0). Non-responding patients had a significantly lower tumour dose of ~4 Gy than responders, ~12 Gy ($p < 0.01$). Regarding the administered dose, a pre-VISION single-center analysis evaluated two different administered doses of [^{177}Lu]Lu-PSMA-617 (6 GBq and 7.4 GBq) on safety and efficacy (5). No significant difference was found in change of kidney, liver, and blood cell parameters and no significant difference in PSA decline > 50% (35% vs. 54%, $p = 0.065$) or best PSA response (40.2% vs. 57.8%, $p = 0.329$). The median estimated survival and PSA-PFS also did not significantly differ between the 6.0 GBq and 7.5 GBq regimen (11.3 vs. 12.7 months, $p = 0.384$; and 9.5 vs. 12.3 months, $p = 0.258$). However, to date, prospective studies performing prospective dosimetry are lacking.

Discussion

This recap of recent developments (last 5 years) on PSMA radioligand

therapy has shown rapid adoption of a theranostic therapy by the (uro-) oncology community. Prior to [^{177}Lu]Lu-PSMA, all available therapies were either taxane-based or androgen receptor targeted treatments, thus the need for a new therapeutic mechanism was felt. In this respect, the TheraP- and VISION-trial had the most notable impact. [^{177}Lu]Lu-PSMA-617 has been proven to be safe, generally well tolerated and an effective therapy for men with mCRPC.
However, even though both trials provided paramount data, some issues are still debated. One issue to our interest, was the use of [^{68}Ga]Ga-PSMA-11 PET/CT for patient selection. In the VISION-trial 87% of all screened patients met the inclusion criterion (tumour uptake on [^{68}Ga]Ga-PSMA-11 PET > liver), which raised the question if pre-treatment PSMA PET/CT is worth the added effort and costs (17). Patients were excluded if they showed PSMA negative lesions (PSMA uptake ≤ liver parenchyma in any lymph node with a short axis of ≥ 2.5 cm, or in any metastatic solid-organ lesion with a short axis of ≥ 1.0 cm, or in any metastatic bone lesion with a soft tissue component with a short axis of ≥1.0). By using these criteria, VISION included 'predominant PSMA positive disease' patients. Thus, the scientific question remains whether patients with non-predominant PSMA positive disease with one or several PSMA negative lesion(s) could still benefit from [^{177}Lu]Lu-PSMA-617 therapy (figure 2). Patient selection in VISION was based on PSMA expression on [^{68}Ga]Ga-PSMA-11 PET/CT. In a sub-study of the VISION-trial, including the 551 patients from the intervention arm, high whole-body SUV_{mean} was the only consistent imaging parameter with improved outcomes across all clinical endpoints (i.e. only the quartile of patients with highest SUV_{mean} results). Unfortunately, imaging reconstruction and acquisition was non-standardized, thus many technical limitations were also present (17) (figure 3).
Hotta et al. investigated this particular issue in an international, multi-center retrospective study, in 301 patients with mCRPC treated with [^{177}Lu]Lu-PSMA-617 and divided the cohort in three 'expression groups' based on visual scores and semi-quantitative measures: high (> 80% of the lesions show higher uptake than the parotid glands), intermediate (neither "low" nor "high"), and low PSMA expression (> 80% of the lesions < uptake than the parotid glands) based on the [^{68}Ga]Ga-PSMA-11 PET/CT (18). The high accumulation group outperformed the intermediate and low groups regarding biochemical response (PSA decline ≥ 50%) 69.6%, 38.7%, and 16.7% (semi-quantitative measures: $p < 0.001$) in the high, intermediate, and low expression groups, respectively, and OS with

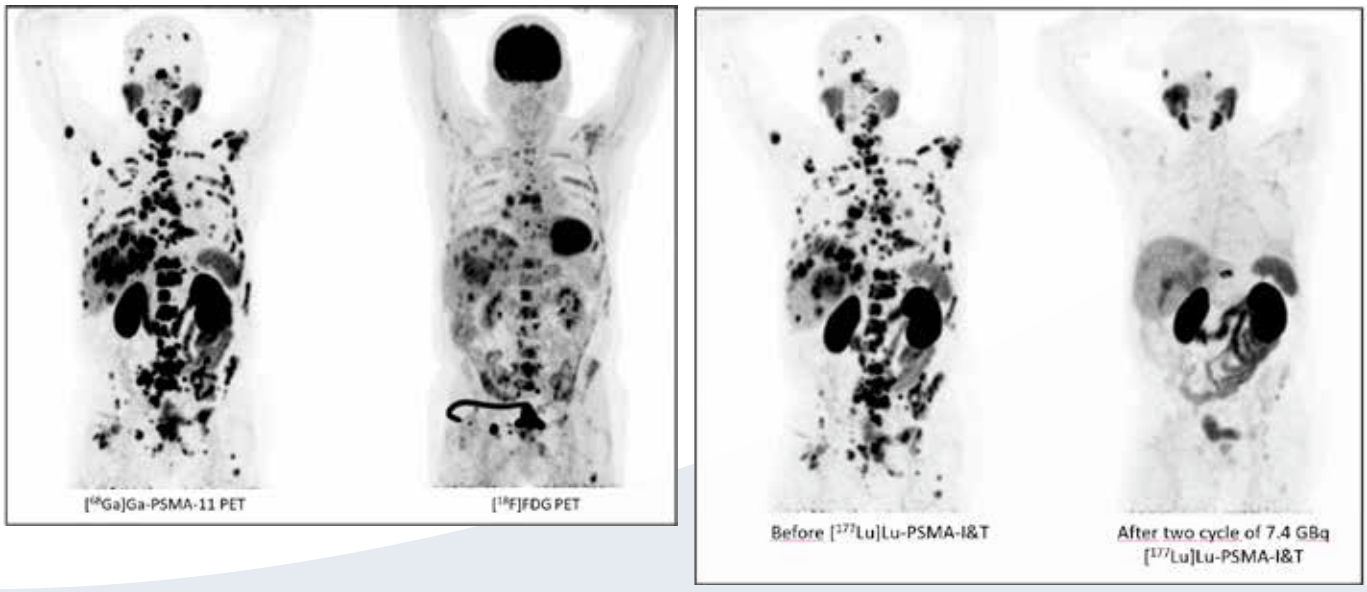

Figure 2. Maximum intensity projections pre- and post-treatment.
Maximum intensity projections (MIP) of a [^{68}Ga]Ga-PSMA-11 PET and [^{18}F]FDG-PET/CT in a 69 year old metastatic castration resistant prostate cancer (mCRPC) patient with baseline prostate specific antigen (PSA) of 105 ng/mL. The PET scans show high uptake of PSMA and moderate to low uptake of FDG.
[^{68}Ga]Ga-PSMA-11 MIP of the same patient before and after two cycles of 7.4 GBq [^{177}Lu]Lu-PSMA-I&T. The patient had a PSA decline to 0.91, a pain reduction from 8 to 1 following the VAS (visual analoque scale) pain score, and a quality-of-life gain of two points (5 to 7).

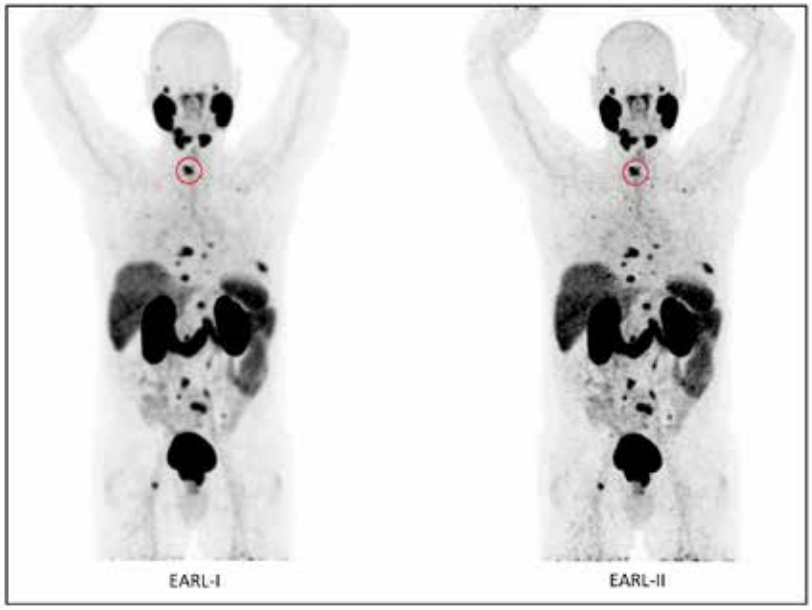

Figure 3. Follow-up [^{68}Ga]Ga-PSMA-11 PET in a 73 year old patient with metastatic castration resistant prostate cancer (mCRPC) and raising prostate specific antigen (PSA). Example of the influence of different reconstruction parameters and its effect on semi-quantitative measurements. Left: EARL-I reconstruction maximum intensity projection (MIP), with a maximum standardized uptake value corrected for lean body mass (SUL_{max}) of 5.41 of the indicated bone lesion (red circle). Right: EARL-II reconstruction MIP with a SUL_{max} of the same bone lesion of 6.81.

15.0 months in the high expression group versus 11.7 months in the intermediate plus low expression group (semi-quantitative measures: p = 0.013). These results suggest that uptake might be a valuable prognostic and predictive imaging-based biomarker, and that not all mCRPC disease within a patient has to be highly PSMA expressing. Additionally, the used visual and semi-quantitative measurements likely missed PSMA-negative disease, as visual assessments were based on maximum intensity projections only and semi-quantitative measures did not take PSMA-negative disease into account. To date, only one study pursued a lesion-based analysis, besides the general patient-based analyses that supported this hypothesis (19).

Van der Sar et al. found a clear accumulation-response relationship on a lesion-level (primary tumour, lymph node, bone or visceral metastasis) for $SUV_{peak/max}$ on pre-treatment [^{68}Ga]Ga-PSMA-11 PET/CT (reconstructed according to EARL1) in men with mCRPC receiving two cycles of [^{177}Lu]Lu-PSMA-617 treatment. Patients with a higher mean SUV_{peak} (> 14.87) at baseline had a better imaging-based response (based on PERCIST-like criteria) (p < 0.001), except for complete response, where a lower accumulation was found. The latter was probably a result of smaller lesions with less counts impaired by partial volume effects. The findings of van der Sar et al. strengthen the suggestion that mCRPC patients with some low uptake lesions could also benefit from [^{177}Lu]Lu-PSMA-617 therapy. In the study by van der Sar et al., no clear PSMA-negative disease was included (19).

Although most evidence on patient selection is based on [^{68}Ga]Ga-PSMA-11, not all centres have access to this radioactive isotope. There are currently several Fluor-18-based PSMA-ligands available for PET imaging that are in wide use in the Netherlands, including [^{18}F]PSMA-1007, [^{18}F]DCFPyL and [^{18}F]JK-PSMA-7. For these tracers, the uncertainty on thresholds that can predict response are even larger.

Considering PSMA-negative disease, some suggest using [^{18}F]FDG-PET/CT as an addition or surrogate for CT or MRI. Chen et al. (20) retrospectively evaluated the added value of [^{18}F]FDG-PET/CT compared to [^{68}Ga]Ga-PSMA-11 PET/CT in an in-patients comparison of 56 CRPC patients. [^{68}Ga]Ga-PSMA-11 PET/CT showed a higher detection rate and a higher number of positive lesions in comparison to [^{18}F]FDG-PET/CT, especially in patients with higher risk features (Gleason score ≥ 8 and PSA ≥ 7.9 ng/mL). However, in 23.2% (13/56) of the patients at least one lesion observed on the [^{18}F]FDG-PET/CT was not observed on the [^{68}Ga]Ga-PSMA-11 PET/CT. The clinical relevance of the increased detection rate however, remained unclear. Some suggested that patients with a PSMA-negative, but FDG-positive lesion will not have added value of [^{177}Lu]Lu-PSMA treatment (21). Khreish et al. (22) showed in a retrospective cohort of mCRPC patients that patients with at least one mismatch PSMA-/FDG+ lesion (17/29, 59%) had a significant shorter overall survival compared with patients without mismatch lesions (3.3 versus 6 months; p = 0.008). However, PSMA-/FDG+ mismatch in this study was determined on [^{18}F]FDG-PET/CT and [^{68}Ga]Ga-PSMA-11 PET with an interval of 4 weeks, and images were acquired after the second cycle of therapy (not at baseline, i.e. prior to initiation of [^{177}Lu]Lu-PSMA). Furthermore, patients were only selected for this analysis if they had

biochemically or clinically progressive disease after the second treatment (selection bias). Seifert et al. (23) concluded that less than 5% (3/98, 3%) of the mCRPC patients referred to [^{177}Lu]Lu-PSMA-617 therapy had a mismatch finding on pre-treatment PSMA-PET and [^{18}F]FDG-PET/CT. This raises the question if the combination of pre-treatment PSMA PET and FDG PET is really needed. Pathmanandavel et al. (24) recently reported the data from the phase I/II LuPIN-trial, including 65 mCRPC patients receiving up to six cycles of [^{177}Lu]Lu-PSMA-617 and a potential sensitizer (NOX66). In their study, [^{18}F]FDG-PET/CT did not have added value as prognostic factor for OS, whilst increased total tumour volume on [^{68}Ga]Ga-PSMA-11 PET/CT and PSA progression after treatment did (6 weeks after completing [^{177}Lu]Lu-PSMA-617 or when treatment ceased earlier because of clinical progression).

In the VISION-trial, the choice was made not to include [^{18}F]FDG-PET/CT for patient selection, in order to prevent potential operational complexity and costs (17). On the other hand, the TheraP trial excluded patients with PSMA-/FDG+ mismatch and metastatic disease was assessed semi-quantitatively (SUVmax > 10), which resulted in exclusion of one-third of screened patients (91/291). A small patient study (n=14) by Aberts et al. (25) showed that it is feasible to combine [^{18}F]FDG-PET/CT and [^{68}Ga]Ga-PSMA-11 PET/CT as part of a same day imaging protocol. However, with the data from Seifert et al. (23) in mind (<5% has PSMA-/FDG+ mismatch), cost-effectiveness is questionable and undetermined at this time.

Summarizing, pre-treatment PSMA PET can give added value for predicting [^{177}Lu]Lu-PSMA treatment response. Combining FDG PET with PSMA PET gives a higher detection rate of PSMA negative metastases, however the clinical relevance and cost-effectiveness for patient selection needs further investigation (26).

The second issue to our interest is the response evaluation. PSA for response evaluation has always been under debate for different lines of CRPC treatment (e.g. ^{223}Ra). Even with [^{177}Lu]Lu-PSMA not all patients with tumour progression show PSA progression (27). Both discussed trials (i.e. VISION and TheraP) used RECIST 1.1 and PCWG3 for radiological response assessment, being the most commonly used criteria, but subject to known flaws and limitations. Thus, new response criteria are eagerly being investigated. For molecular imaging with PSMA PET, several options are available for response evaluation: Positron Emission Tomography Response Criteria in Solid Tumours (aPERCIST), the PSMA PET Progression (PPP), and the Response Evaluation Criteria In PSMA-Imaging (RECIP) 1.0. A retrospective comparison study comparing all these different response criteria concluded that RECIP 1.0 identified the fewest patients with progressive disease and achieved the highest risk of death by progressive disease versus no progressive disease (28). The authors suggested that other classification methods tend to overcall progression. However, prospective validation studies evaluating the different response criteria are lacking (28) and these criteria have not been endorsed by the urogenital oncological community. The predominant reason is that response evaluation on PSMA PET alone is considered too limited, as low to intermediately active PSMA lesions may have responded, but are not account for in the response evaluation, while PSMA negative lesions might be missed.

Currently, there are six trials registered that investigate [^{177}Lu]Lu-PSMA in prostate cancer patients in the Netherlands, in various settings. These studies will be briefly described:

First, PROQURE (NCT05162573), a national, multi-center, phase I study, investigating tolerability of concurrent external beam radiotherapy and [^{177}Lu]Lu-PSMA-617 for node-positive prostate cancer in treatment naïve patients. The study opened in 2021 and is actively recruiting.

Second, PSMAddition (NCT04720157), an international, multi-center, open-label, randomized, phase III study investigating [^{177}Lu]Lu-PSMA-617 combined with androgen deprivation therapy (ADT) in hormone sensitive prostate cancer patients in comparison to standard of care. The study opened in 2021 and is actively recruiting.

Third, PSMAfore (NTC04689828), an international, multi-center, open-label, randomized, phase III study investigating [^{177}Lu]Lu-PSMA-617 in men with mCRPC, who already received ADT, but did not yet receive chemotherapy. The study opened in 2021 and recruitment has been closed.

Fourth, Bullseye 2 (NCT04443062) (29, 30), a multi-center, randomized, open-label, phase II study, investigating [^{177}Lu]Lu-PSMA-617 in men with recurrent hormone sensitive prostate cancer who are eligible for ADT. The study opened in 2020 and is actively recruiting.

Lastly, SPLASH (NCT04647526), an international, multi-center, open-label, randomized, phase III study, investigating [^{177}Lu]Lu-PSMA-I&T in men with mCRPC after second-line ADT. This study opened in 2021 and is actively recruiting.

The next step for PSMA radioligand therapy is the use of alpha emitters, e.g. actinium-225 PSMA ([^{225}Ac]Ac-PSMA). The high linear energy transfer in PSMA positive lesions causes more double-strand breaks and thereby potentially a higher efficacy than beta emitters (31). Currently, a single-center, phase I study is investigating [^{225}Ac]Ac-PSMA-I&T in mCRPC patients in the Netherlands (31).

Conclusion

[^{177}Lu]Lu-PSMA has shown to be safe and effective. It is reimbursed in the Netherlands in the salvage setting in mCRPC. Results of the currently recruiting studies in different settings are eagerly awaited. Furthermore, more evidence is needed for patient selection, imaging-based biomarkers and response monitoring.

e.c.a.vandersar@umcutrecht.nl ♦

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