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Prostate Cancer Theranostics With ^{177}Lu-PSMA

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This review paper highlights the transformative role of PSMA-targeted diagnostics and therapy in prostate cancer management, particularly focusing on ^{177}Lu-PSMA-617, approved by the FDA and EMA for metastatic castration-resistant prostate cancer (mCRPC) patients post-chemotherapy and ARPI treatment. Originating from the VISION trial's success, this paper navigates the current radioligand therapy (RLT) indications, emphasizing practical patient selection, planning, and treatment execution. It critically examines Lu-PSMA's comparative effectiveness against cabazitaxel and Ra-223, addressing decision-making dilemmas for mCRPC treatments. Furthermore, the paper discusses Lu-PSMA in chemotherapy-naïve patients and its application in hormone-sensitive prostate cancer, underlined by ongoing global studies. A significant concern is Lu-PSMA's long-term safety profile, particularly nephrotoxicity risks, necessitating further investigation. The possibility of Lu-PSMA rechallenge in responsive patients is explored, stressing the need for comprehensive analyses and real-world data to refine treatment protocols. Conclusively, PSMA-targeted therapy marks a significant advance in prostate cancer therapy, advocating for its integration into a multimodal, patient-centric treatment approach. The review underscores the imperative for additional comparative studies to optimize treatment sequences and outcomes, ultimately enhancing long-term prognosis and disease control in prostate cancer management.

Introduction

The FDA and EMA approved radioligand therapy using [177Lu]Lu-PSMA-617 (Lu-PSMA) for treating metastatic castration-resistant prostate cancer patients, following at least one line of ARPI and at least one line of taxane-based chemotherapy. This approval was based on the results of the VISION trial, which were published in the New England Journal of Medicine in 2021.[1] The timeline from the first case report published on Lu-PSMA therapy[2] and the first original paper on this topic[3] to the publication of the VISION trial was a record in our field. It took only 6 years, a duration not comparable to the lengthy approval process for PRRT of neuroendocrine tumors using Lu-DOTATATE.[4,5]

In this review paper, we will not discuss the basics of diagnostics and therapy using PSMA. We recommend the following paper for this.[6] However, we will cover the current indications for radioligand therapy based on the VISION trial and provide a practical approach for patient selection, therapy planning, and execution. We will discuss some important issues relevant in this field, such as the role of Ra-223 in the era of radioligand therapy or should we use cabazitaxel or Lu-PSMA?

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The Current Indication of Radioligand Therapy Using Lu-PSMA

The recommended indication for Radioligand Therapy (RLT) using Lu-PSMA is derived from the study protocol of the VISION trial.[1] This trial focused on patients with advanced metastatic Castration-Resistant Prostate Cancer (mCRPC) who had undergone at least one line of taxane-based chemotherapy and one line of therapy with an Androgen Receptor Pathway Inhibitor (ARPI). Eligible patients, identified with PSMA-positive lesions on Ga-68-PSMA PET/CT scans, were randomly assigned in a 2:1 ratio into two groups. In one group, patients received up to six cycles of Lu-PSMA therapy every 6-8 weeks, combined with Standard of Care (SoC), while the control group received only SoC. The SoC could not incorporate chemotherapy, immunotherapy, radium-223 (Ra-223), or investigational drugs, as per the study protocol. The key endpoints were radiologic progression-free survival (rPFS) and overall survival (OS).

Treatment continued until radiographic progression, intolerable toxicity, lack of clinical benefit, or the need for non-authorized treatment. In this study, 551 patients received RLT and 280 were in the SoC group. The combination of Lu-PSMA and SoC significantly improved both rPFS (median, 8.7 vs. 3.4 months; Hazard Ratio (HR) for progression or death, 0.40; $P < 0.001$) and OS (median, 15.3 vs. 11.3 months; HR for death, 0.62; $P < 0.001$) compared to SoC alone. These positive outcomes, anticipated from several previously published retrospective analyses, led to the treatment's approval.[7-11]

Lu-PSMA vs. Cabazitaxel

The main question is how we should make decisions from now on for patients who have been treated with first-line chemotherapy using docetaxel and could still be treated with cabazitaxel. According to the VISION study, about 45% of patients received second-line chemotherapy in both study arms.[1] Therefore, the question arises: which therapy is better for the patients, RLT or second-line chemotherapy?

Based on retrospective published studies, patients who received prior chemotherapy, especially second-line chemotherapy, showed a shorter OS compared to patients without any prior chemotherapy or only with a history of just one line of chemotherapy.[7,12] In the phase 2 TheraP trial,[11] patients with advanced mCRPC, previously treated with first-line chemotherapy and ARPI, were randomized in a 1:1 ratio into two groups. One group received up to six cycles of RLT, and the other up to ten cycles of chemotherapy using cabazitaxel. The primary endpoint of the study was the PSA response rate, with PFS, OS, and toxicity as secondary endpoints. In this study, 101 patients received cabazitaxel, and 99 received Lu-PSMA.

The 66% of patients in the Lu-PSMA group showed a PSA decline of more than 50%, compared to only 37% in the cabazitaxel group ($P < 0.0001$). However, a recently published study from the same group reported no significant differences in OS between these two groups.[13] Whether these results are due to 20% of participants assigned to cabazitaxel and 32% assigned to Lu-PSMA subsequently being treated with the alternative regimen, or because both treatments have similar OS, is unclear. There is a need for phase 3 study. Although both therapies could be administered after first-line chemotherapy, the toxicity rate of Lu-PSMA is significantly lower than that of cabazitaxel, and there is a greater improvement in the quality of life of patients undergoing RLT compared to those receiving cabazitaxel.[11]

Lu-PSMA vs. Ra-223

Ra-223 remains an approved alpha therapy for the treatment of mCRPC patients.[14] According to the latest recommendation from the EMA,[15] it can be used in patients with symptomatic bone metastases without visceral metastasis who have undergone two previous treatments (e.g., two lines of ARPI or one line of ARPI and one line of chemotherapy), or in those who cannot receive other treatments. However, it must not be used concurrently with abiraterone acetate.[15]

Although the use of Ra-223 is continuously declining, it still has some indications, such as in patients with renal insufficiency, those who avoid chemotherapy without contraindications for it, in patients without favorable response to RLT and theoretically in patients with very low PSMA uptake. Retrospective analysis has shown that administering Lu-PSMA therapy after Ra-223 is safe and does not increase hematotoxicity.[16] Moreover, there is no negative impact on OS of patients who received Ra-223 therapies prior to RLT compared to those who only received RLT.[7,8] The safety of this combination has been recently reaffirmed by the RALU study.[17,18]

Lu-PSMA vs. PARP Inhibitors

In 2020, the FDA approved the first second-line treatment for mCRPC with altered DNA repair genes, specifically for patients whose cancer was no longer responding to earlier hormone therapy.[19] Later, in May 2023, the FDA approved the combination of olaparib with abiraterone and prednisone for the treatment of patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC.[20] This approval was for patients who had progressed following prior treatment with enzalutamide or abiraterone.

At the time of the VISION study, therapy with a PARP inhibitor like Olaparib was not approved, and therefore, prior therapy with Olaparib is not included in the approval criteria for RLT. Currently, there is no data showing the safety of RLT following PARP inhibitor therapy. However, based on our daily experience, a history of PARP inhibitor treatment prior to RLT does not seem to increase the toxicity rate.

There is an ongoing phase 1 dose-escalation and dose-expansion study (NCT03874884) designed to evaluate the

safety and tolerability of olaparib in combination with Lu-PSMA in patients with mCRPC.

Patient Selection

Patients are referred to Nuclear Medicine for PSMA-RLT from various specialties, including urology, oncology, and radiation oncology. As mentioned earlier, currently, patients should have been treated with at least one line of ARPI and one line of chemotherapy, normally with Docetaxel. PSMA-RLT can also be performed for patients for whom chemotherapy is contraindicated, which is very small group of patients. The results of the PSMAfore study presented at the ESMO conference demonstrated significant benefits of PSMA-RLT compared to changing the ARPI regimen.[21] The outcomes of this study will be discussed later in the paper.

Another important aspect is the examination of the patient's blood count and renal function. According to the joint EANM/SNM guideline,[22] myelosuppression is a relative contraindication for RLT, with WBC < 2.5/nl, ANC (absolute neutrophil count) < 1.5/nl, and platelets < 75/nl. However, it should be noted that these cutoffs are only recommended values, and each patient should be evaluated individually for therapy. In some cases, even with lower platelet counts and diffuse bone marrow infiltration (i.e., super scan), PSMA-RLT can be beneficial for the patients by reducing the tumor load and in turn allows bone marrow expansion.[22,23] Creatinine levels more than twice the upper limit of normal (ULN) or a GFR of less than 30 ml/min are also relative contraindications for RLT. Presence of significant renal obstructive disease should be ruled out prior to PSMA-RLT, which can be done by renal scintigraphy. Any significant urinary stasis, if possible, should be resolved before the start of PSMA-RLT.

The Definition of PSMA Positive and Negative Disease

PSMA expression, which can be measured non-invasively by PSMA-PET, is correlated with the dose delivered by PSMA-RLT and thereby its therapeutic efficacy.[24] To ensure that patients benefit from PSMA-RLT and to in turn increase the likelihood of positive trial results, certain criteria have been used to define PSMA positive disease. In the early prospective trial of Hofman et al., a minimum PSMA uptake of 1.5 times liver activity was requested in all metastases. In addition, FDG-PET was performed to rule out PSMA negative, FDG positive disease, which is discussed in detail below.[25] However, the retrospective application of this relatively high PSMA-uptake threshold to data from routine clinical practice could not identify a significant difference in survival time; this indicates that a lower threshold on liver uptake can be sufficiently identify PSMA-RLT candidates.[26]

A similar criterion was also used by the phase III VISION trial, which required that PSMA uptake has to be higher than liver on ^{68}Ga-PSMA-11 scans in all metastases.[1] This criterion has also been integrated into the PROMSIE V2.0 framework for PSMA-PET reading.[27] Measurable disease was a nodal lesion greater than 25 mm or greater than 10 mm for visceral lesions or the soft tissue component of bone lesions.[28] Importantly, one measurable PSMA negative lesion usually leads to exclusion from therapy.[28] This is built on the idea that a dedifferentiated tumor cell clone, e.g., neuroendocrine dedifferentiation, can rapidly become the dominant one and lead to fulminant disease progression, which is not targetable by PSMA-RLT. This has been described for liver metastases, which are therefore important to detect before the start of PSMA-RLT.[29]

Despite these widely applied criteria, stricter regimens are applied by some groups. The phase II TheraP trial requested an SUVmax of $\geq$ 20 in any metastasis and $\geq$ 10 in all metastases that are measurable (i.e., $\geq$ 10 mm). However, given the not significant survival benefit when compared to cabazitaxel, it is not clear if such high thresholds to define eligibility to PSMA therapy are needed.[11,13]

Parotid and Spleen Uptake

Salivary glands show higher physiological uptake then liver and spleen, which are used to define the minimally needed uptake to refer a patient to PSMA-RLT.[27] If most metastases of patients treated with PSMA-RLT show uptake that exceeds the parotids, the outcome is especially favorable.[30] Therefore, the PROMISE V2.0 framework has proposed a 4-point scale, which include below or equal to blood pool (0), above blood pool but below or equal to liver,[1] higher than liver but below or equal to parotid glands[2] and finally higher than parotid glands.[3,27] Patients with uptake higher than liver are usually eligible for PSMA RLT and those with uptake exceeding parotid uptake are likely to have a favorable outcome.[30] This in line with outcome prognostication based on SUV measurements in PSMA PET (see next section).

The frequently used PSMA-1007 tracer has a liver dominant excretion, which is why the liver is not a suitable reference organ for those scans. To overcome this limitation, the spleen has been proposed as reference instead.[27,31] However, the spleen is not present in all patients and the spleen uptake can also exceed the liver uptake in PSMA-1007, which is why the sole reliance on the numerical measurement is difficult. Rather, a combination of different physiological uptakes, e.g., spleen, parotid glands, etc. and SUV measurements is advisable to assess therapy eligibility.

The Prognostic Value of PSMA Imaging

The PSMA uptake measured on PSMA PET can predict response to therapy and is a prognosticator of the outcome.[26] It was shown than the maximum uptake on PSMA PET is not a relevant predictor, but the average uptake is.[26,32] This seems to be in line with the biological understanding, as the efficacy of PSMA RLT in all metastases should be more dependent on the average than peak uptake. An analysis of the first prospective Melbourne trial of Lu-PSMA therapy patients revealed than an average uptake on PSMA PET greater than SUV 10 was associated with higher biochemical

response rated.[32] This cutoff was defined by identifying the best threshold to statistically separate the patients with regards to overall survival and is therefore influenced by the inclusion criteria of the trials. Still, the threshold was corroborated by the TheraP trial, which could also show that high average PSMA uptake was predictive of response.[33]

Similarly, an additional analysis of the phase III VISION trial data in 548 patients could show that patients with an average SUV showed better response and longer overall survival.[34] Still, it is difficult conclude that patients with lower uptake, such lower than the average uptake of SUV 10, will not sufficiently benefit from PSMA RLT. This could be answered by comparing the outcome of patients who have or have not received PSMA RLT stratified by PSMA expression and might be addressed in future trials.

The Role of New Software

Various approaches have been proposed to facilitate the analysis of PSMA-PET to assess therapy eligibility. For example, semi-automated reading of PSMA-PET with qPSMA or related enabled the quantification of the total tumor volume and uptake parameters.[35,36] This led to the description of uptake patterns such as low average PSMA expression or presences of low PSMA expression lesions despite high average uptake.[26] Also, those approaches enabled the quantification of the PSMA-PET derived total tumor volume, which has also been shown to be a statistically significant prognosticator of response.[37] In line with the PROMISE V2.0 framework that proposed organ specific and total tumor volumes to quantify response to therapy, multivariable risk models assessed by machine learning for tumor delineation result in promising accuracy for the prediction of overall survival time in prostate cancer patients.[37] This seems especially useful for the response assessment (see below). However, in routine clinical practice, manual analysis of individual lesions and visual assessment of the PSMA-PET MIP prevails.

FDG-PET in the Context of Lu-PSMA Therapy

The role of FDG-PET for the management of patients treated with PSMA RLT is twofold. First, it is employed to rule out PSMA negative, FDG positive disease. This has been used by the first prospective landmark trials of the Melbourne group and has been adopted by other departments as well.[25,38] To simplify the patient management, the VISION study omitted to use FDG-PET in addition to PSMA-PET, which is accordingly now the current standard procedure in most nuclear medicine departments.[28] In line with the simplification of patient selection, it was shown that the additional use of FDG-PET over PSMA-PET only resulted in a neglectable fraction of patients, in which mismatch findings have not been discovered by PSMA-PET and CT alone.[31] Therefore, the relevance to detect PSMA negative disease might be of neglectable relevance.

Second, FDG-PET can be used to assess the risk of patients treated with PSMA RLT. It was shown that the FDG-PET extracted tumor volume was a negative prognosticator of overall survival time.[32,33] Also, it was associated with inferior response to therapy. Therefore, future studies might discover distinct phenotypes of patients by the integrated analysis of uptake seen on FDG- and PSMA-PET (Fig. 1).

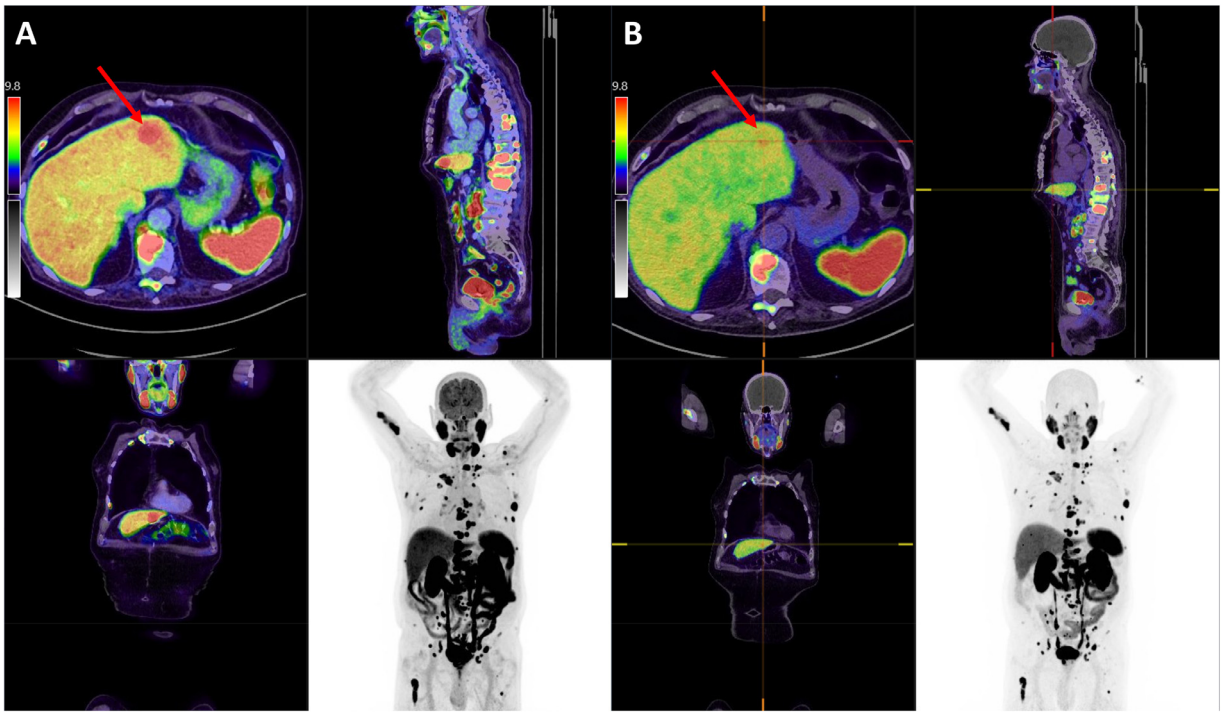

Figure 1 Exemple of a patient who was refferred for PSMA-RLT. In the dual scan with FDG (A) and 18F-PSMA (B), a liver metastases presented FDG-positive but PSMA-negative (red arrows).

PSMA-SPECT

Due to the inherently lower spatial resolution and signal-to-noise ratio of SPECT vs PET, in the setting of biochemical relapse ^{99m}Tc- PSMA SPECT/CT only achieves comparable detection rates to PET/CT at higher PSA levels.[39] Nevertheless, in a comparison of ^{99m}Tc- vs ^{68}Ga-PSMA all nodes > 10 mm which equals the definition of measurable disease in the VISION and TheraP trials were also detected by PSMA-SPECT/CT.[40] Confirmatively, a lower detection rate of tiny lesions but equal tumor-to-background ratios of detectable lesions were reported between ^{99m}Tc-iPSMA SPECT/CT and ^{18}F-PSMA-1007 PET/CT.[41] In an intra-individual comparison of ^{99m}Tc-MIP-1404 and ^{68}Ga-PSMA-11 in patients evaluated for eligibility to ^{177}Lu-PSMA therapy, the tumor-uptake (median SUV_{max} 18.2 vs. 17.3) as well as parotid gland SUV_{max} and tumor-to-parotid gland ratios were not significantly different.[42]

When tailoring patients for or against Lu-PSMA therapy we are not searching for small lesions but are rather assessing the PSMA positivity of known (> 10 mm) metastases. Consequently, PSMA-SPECT can be a good alternative to PSMA-PET for treatment stratification or as a prognostic biomarker.

Implementation of Therapy

Radiopharmaceuticals are to be handled and administered exclusively by authorized individuals in facilities that comply with national regulations. These facilities must have a valid radioactive material license, specifically for activities involving 177Lu. The treatment facility should be equipped with qualified personnel, radiation safety measures, and established procedures for waste management, contamination handling, accidental spill response, and prevention of contamination spread.

The administration of Lu-PSMA, along with subsequent care, follow-up, and coordination, should be under the responsibility of a nuclear medicine specialist. This specialist must work closely with the referring and other involved physicians in the patient's care. Prior to therapy, it is mandatory for the nuclear medicine specialist to discuss the technical and clinical aspects of the treatment with the patient.

Prior to administration of Lu-PSMA an adequate hydration is of enormous importance.[22]

Hydration Protocol

1. Intravenous infusion:
   - Duration: Begin 30 minutes prior to administration and continue for several hours afterward.
   - Solution: 500-1000 ml of 0.9% saline.
   - Rate: 250 ml/hour.
2. Oral hydration (For compliant patients):
   - Guidance: Patients should be encouraged to consume a significant amount of fluids.
   - Duration: Continue for the next 1-2 weeks.

The patients should be encouraged to intake enough fluids. Prior to administration of the Lu-PSMA and at the time of discharging of the patient, patients should be pointed this out.

A co-medication is not although mandatory, it can help for better tolerating of the therapy. Following medication could be combined with the RLT.

1. Prophylactic antiemetic therapy:
   - Medication example: Ondansetron.

Some patients could have some nausea and seldom vomiting, a few hours after administration of Lu-PSMA. A prophylactic antiemetic therapy can enhance the tolerability of RLT. Normally one dose is enough. It is especially helpful in countries in which patients get this therapy in a out-patient setting and the patients do not have access normally to a doctor at the evening.

2. Corticosteroids therapy
   - Indications:
   - Mandatory for metastases involving the brain, spine, or other areas with a risk of painful or obstructive swelling.[22]
   - Administration:
   - Permitted based on patient's need and physician's discretion.
   - Examples:
   - Dexamethasone, typically 4 mg, administered over 5 days.

Or prednisolone 40 mg for 2-4 days and then tapering within 8-10 days. In patients with diabetes blood sugar should be controlled more often as usual.

3. Furosemide: Some groups inject 40 mg of furosemide after the administration of Lu-PSMA.[43] Although there is no evidence for this approach, in patients with non-obstructive urinary stasis it may help to reduce the radiation dose to the kidneys. Changing in the body position from lying to sitting or walking some steps after administration may help also to reduce the radiation amount to the kidneys.

Cooling of the salivary glands is a subject of controversy. Despite these controversies, we still recommend cooling the salivary glands with ice packs from 30 minutes prior to the injection and continuing for up to 4 hours afterward. This approach can reduce the uptake of Lu-PSMA and lower the probability of xerostomia.[44-46]

For the administration of the radioactivity using a three-way stop cock is recommended. Through one way the normal saline could be administered and through another way the Lu-PSMA. Normally it can be injected as a short injection over a period of more than 30 seconds. When you do not use a three-way stop cock, use a 10 ml saline flush to ensure

the patency of the IV line prior to therapy. After injection of Lu-PSMA, administer at least 20 ml saline.[22]

According to the VISION trial, an activity level of 7.4 GBq (+/- 10%) per cycle for 6 cycles has been found to be effective and safe.[1] However, the activity level can be adjusted in special cases. For example, in patients with reduced renal function, it can be lowered to 4-5 GBq. Generally, a higher activity level can be considered during the initial cycles due to the 'tumor sink effect', which results in less uptake in non-target organs.[47] In cases of a favorable response, the activity level could be reduced to 6 GBq. This amount is also considered effective based on the results of several retrospective analyses.[7-9] The time interval between the cycles is 6-8 weeks.

Some clinics administer Lu-PSMA as an infusion within 30 minutes same as infusion of Lu-DOTATATE. Which method is better is unclear; however, a short injection is easier for the patients and personal.

At least one post-therapeutic whole-body scan should be performed, ideally not earlier than 2 hours post-injection.[22] Delaying the imaging time can enhance image quality and reduce radiation exposure to personnel. Performing SPECT/CT scans is also recommended. This imaging approach offers two benefits: firstly, it aids in documenting the therapy as a form of quality control, and secondly, the images obtained after each treatment cycle can be utilized for evaluating the effectiveness of the therapy. As long as the radioligand therapy is performed for in-label use, performing dosimetry is not recommended.[22]

Follow-Up PET Scans

The diagnostic follow- up of patients treated with PSMA RLT is difficult, as patients are in advanced disease stages with the risk of PSMA-PET negative progression and/or PSA negative disease. Therefore, many departments use a combination of biochemical and imaging follow up to monitor patients.

When should we really do a follow-up PET scan in patients with PSA response and in patients without any response according to PSA?

The phase III VISION trial relied on repeated CT and bone scans to measure response to PSMA-RLT.[1] In clinical routine, PSMA-PETs are performed to monitor the patients longitudinally, often every two cycles of PSMA-RLT. The neglection of PSMA-targeted imaging over conventional CT and bone scans seems to be primarily caused by the lack of clear PSMA-PET response criteria. PCWG3.0 criteria do not consider PSMA-PET for response assessment, which is why it was not possible to use PSMA-PET in a phase III trial.[48] However, the PROMISE V2.0 framework for PSMA-PET reading proposed the total tumor volume and frameworks such as PPP and RECIP for response assessment (see below).[27,49,50] Still, given the opportunity of post treatment imaging by Lutetium whole body scintigraphy and SPECT, it is unclear if interim PSMA-PET has higher diagnostic accuracy compared to post therapy imaging. To fulfill the promise of personalized medicine through theragnostics, it seems mandatory not only to monitor PSA levels or initiate a scan in case of disease progression, but to use PSMA-targeted imaging for a detailed analysis of the patient's condition. With PSMA-RLT moving to less advanced disease staging, PSMA-PET targeted imaging seems also mandatory to decide on the ideal follow up treatment.

How Should This Scan Be Evaluated?

Follow-up PSMA-targeted imaging is primarily analyzed manually in routine clinical practice. It was shown that the volumetric reduction of PSMA positive tumor is a prognosticator of the survival time, but the PSMA expression must be considered to not erroneously interpret dedifferentiation as response.[51] For advanced disease, the PROMISE V2.0 framework recommends the RECIP method, which can also be used without quantification of the tumor on a visual basis.[27,50] RECIP assists in the integration of volumetric changes and accordance of new lesions. For example, a decline in PSMA volume greater than 30% but the occurrence of new lesions is rated as RECIP-SD and a PSMA volume increase greater than 20% without new lesions is also classified as RECIP-SD, whereas a 30% decline in volume without new lesions is classified as RECIP-PR (Fig. 2). It was shown that the RECIP framework provides complementary information to PSA response, which underscores the importance of PSMA-targeted imaging for PSMA-RLT.[50]

In routine clinical practice, tools like visual RECIP might be useful to assess response to therapy, but the application of such frameworks to post therapy imaging is not elucidated to date.[52] Also, visual RECIP seems only to serve as surrogate parameter and quantitative assessment of the tumor burden as continuous metric should enable higher accuracy. Therefore, future studies should investigate PSMA targeted imaging for response assessment.

Repeated Lu-PSMA Therapy

According to our experiences since 2014, patients with an excellent response to Lu-PSMA can be considered for a new series of Lu-PSMA as a rechallenge.[1] To date, there are no systematic analyses of patients receiving a second series of LuPSMA. Real-world data on the now-approved Lu-PSMA will likely provide more insight into this question.

Lu-PSMA Therapy for Chemotherapy-Naïve Patients

As previously mentioned, the VISION phase III trial demonstrated a significant increase in survival for patients with mCRPC who had been previously treated with at least one line of chemotherapy and at least one line of ARPI.[1] Prospective comparative studies of Lu-PSMA versus chemotherapy are not yet available. Barber et al.[12] conducted a retrospective study comparing the clinical outcomes of Lu-PSMA therapy

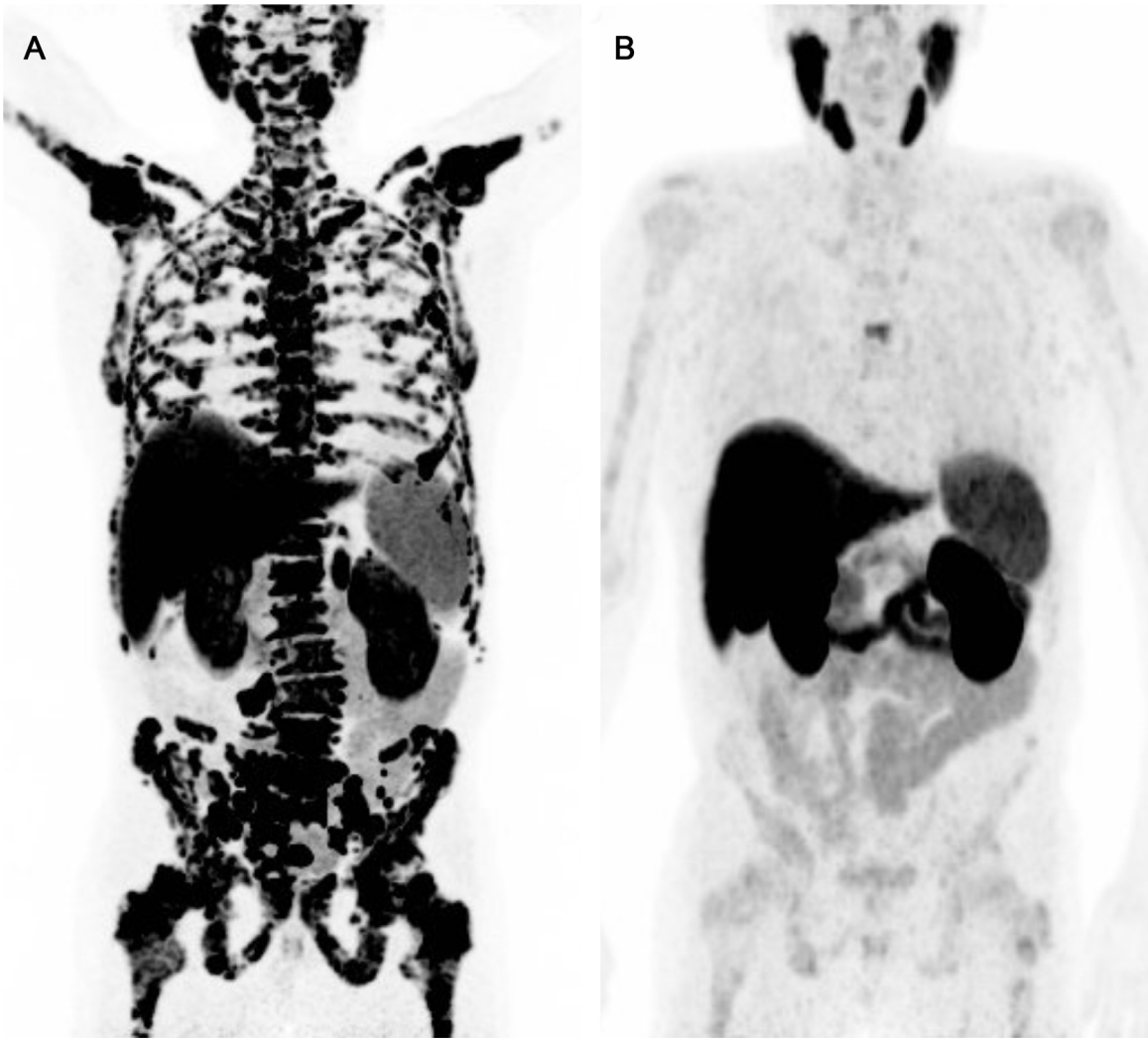

Figure 2 The 73 y/o patient with a spectacular partial response to two cycles of Lu-PSMA. 18F-PSMA-PET/CT demonstrates the tumor load before (A) and one moth after the second cycle (B). During that time PSA dropped from 121 ng/ml to 1.3 ng/ml.

in taxane chemotherapy pretreated and taxane-naïve patients with mCRPC. In the chemotherapy-naïve group, patients showed an OS of 27.1 months versus 10.7 months in chemotherapy-pretreated patients. The major limitation of this retrospective analysis is the heterogeneous cohorts and the significant differences between the two groups. Notably, approved therapies such as abiraterone or enzalutamide were not administered to a large portion of patients (62%) in the chemotherapy-naïve group.

TheraP is the only comparative study of Lu-PSMA with second-line taxane chemotherapy cabazitaxel in an Australian phase II study by Hofman et al.[38] In total, 98 patients received Lu-PSMA and 85 received cabazitaxel. A PSA response with a reduction of $\geq$ 50% was reported in 66% of the Lu-PSMA group compared to 37% in the cabazitaxel group, with Lu-PSMA showing a lower Grade 3/4 toxicity profile.

The PSMAfore trial, a randomized phase III study of Lu-PSMA versus ARPI change in chemotherapy-naïve mCRPC, was recently presented at the European Society of Medical Oncology.[53] The primary endpoint of the study was rPFS. The authors reported a significantly longer rPFS of 12.2 months for Lu-PSMA versus 5.9 months for the ARPI change. The high crossover rate (84%) will complicate the analysis of OS at later follow-up stages.

The weaknesses of the PSMAfore trial were recently discussed by Rahbar et al. in the Journal of Nuclear Medicine.[54] In this editorial, the authors highlighted the need for a comparative study of Lu-PSMA and chemotherapy to determine which treatment offers the best option and value for patients. Probably, a randomized and fully crossover study of Lu-PSMA and Docetaxel will answer the question of which sequence performs better for patients.

Lu-PSMA Therapy in Hormone Sensitive Prostate Cancer (hsPC)

Currently, several prospective studies are underway worldwide at the early stages of prostate cancer. Particularly in

metastasized hormone-sensitive prostate cancer (mhsPC), PSMAddition (NCT04720157) is a significant phase III trial comparing Lu-PSMA therapy plus standard of care (ADT + an ARPI) to standard of care alone in therapy-naïve mhsPC patients. The primary endpoint of the study is radiographic progression-free survival (rPFS), with OS as a key secondary endpoint.

On the other side of the globe, two Phase II trials are currently recruiting in Australia: LuTectomy (NCT04430192)[55] and UpFrontPSMA (NCT04343885).[56] LuTectomy is a single-arm study investigating the dosimetry, safety, and potential benefit of Lu-PSMA prior to prostatectomy, and UpFrontPSMA is a randomized phase 2 study comparing sequential Lu-PSMA and docetaxel versus docetaxel alone in metastatic hormone-naïve prostate cancer.

One major challenge across all these studies is the unknown long-term safety profile of Lu-PSMA, which remains uncertain. The outcomes may also be influenced by the heterogeneous treatment approaches for patients treated after Lu-PSMA therapy within the study. Moreover, the study populations may be diverse in terms of disease burden, comorbidities, and treatment tolerability. Given the specific binding of PSMA ligands to the kidneys, long-term nephrotoxicity is a major concern. A recent retrospective study by Steinhelfer et al.[57] analyzed data from 106 patients who were treated with at least four cycles of Lu-PSMA and had glomerular filtration rate (GFR) data available at least 12 months after starting the therapy. A moderate decrease in estimated GFR (eGFR) was reported in 45% of the patients. Long term results of PSMAddition will shed light into this question.

Conclusion

PSMA-targeted diagnostics and therapy have transformed the management of prostate cancer patients at various stages of the disease. Moreover, the incorporation of PSMA-targeted therapy into a multimodal and patient-centered approach, in conjunction with existing treatments such as surgery, ADT, chemotherapy, and radiation therapy, offers a synergistic effect, potentially enhancing long-term prognosis and disease control.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

HA reports receiving honoraria from Advanced Accelerator Applications (AAA/Novartis) and Bayer Healthcare for delivering oral presentations at various conferences.

KR reports honoraria from Advanced Accelerator Applications (AAA/Novartis), Bayer Healthcare, and SIRTEX and a consultancy/advisory role with ABX GmbH, ABX-CRO, Bayer, AAA, Pharmtrace, Jahnsen Cielag, Amgen, and AstraZeneca.

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CRediT authorship contribution statement

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