Overview of selected completed prospective studies on PSMA-targeted radioligand therapy with [177Lu]Lu-PSMA-617 in metastatic castration-resistant prostate cancer

Übersicht über ausgewählte abgeschlossene prospektive Studien zur PSMA-gerichteten Radioligandentherapie mit [177Lu]Lu-PSMA-617 beim metastasierten kastrationsresistenten Prostatakarzinom

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Keywords

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ABSTRACT

Background Theranostics in nuclear oncology combines diagnostic and therapeutic procedures using radiotracers to target tumor cells. Prostate-specific membrane antigen (PSMA) is a key target in metastatic prostate cancer, and the radioligand [177Lu]Lu-PSMA-617, which binds to PSMA, has shown promising results in treating metastatic castration-resistant prostate cancer (mCRPC), leading to its approval by the European Medicines Agency in 2022.

Method In this narrative review, the current evidence of [177Lu]Lu-PSMA-617 in mCRPC was discussed in the context of selected studies and the joint EANM/SNMMI guidelines for Lutetium-177-labeled PSMA-targeted radioligand therapy.

Results The use of [177Lu]Lu-PSMA-617 for post-chemotherapy mCRPC is supported by substantial evidence from the phase II TheraP and the phase III VISION trials, demonstrating its safety and efficacy. The theranostic approach identifies patients likely to benefit from [177Lu]Lu-PSMA-617, which is effective only in tumors with sufficient PSMA expression, as detected by PSMA-ligand PET/CT, which is also used for response assessment.

Conclusion The success of [177Lu]Lu-PSMA-617 in post-chemotherapy mCRPC patients has led to further ongoing studies evaluating its use earlier in the treatment sequence, prior to chemotherapy. To ensure beneficial treatment outcome, adequate patient selection and evaluation of imaging-based response through PSMA-ligand PET/CT is necessary.

Key Points

- Indications for [177Lu]Lu-PSMA-617 are based on the TheraP and VISION clinical trials.
- Adequate patient selection using PSMA-ligand PET/CT is essential for beneficial outcomes.
- Response evaluation is based on imaging, PSA levels, and the patient's clinical condition.

Citation Format

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ZUSAMMENFASSUNG

Hintergrund Theranostik in der nuklearen Onkologie kombiniert diagnostische und therapeutische Verfahren unter Verwendung von Radiotracern, um Tumorzellen gezielt anzugreifen. Das prostata-spezifische Membranantigen (PSMA) ist eine wichtige Zielstruktur des metastasierten Prostatakrebs, und der Radioligand [177Lu]Lu-PSMA-617, das an PSMA bindet, hat vielversprechende Ergebnisse bei der Behandlung von me-

tastasiertem kastrationsresistentem Prostatakrebs (mCRPC) gezeigt, was zur Zulassung durch die Europäische Arzneimittel-Agentur im Jahr 2022 führte.

Methode In diesem narrativen Review wurde die aktuelle Evidenz von [177Lu]Lu-PSMA-617 bei mCRPC im Kontext ausgewählter Studien und der gemeinsamen EANM/SNMMI-Leitlinien zur Lutetium-177-markierten PSMA-gerichteten Radioligandentherapie diskutiert.

Ergebnisse Die Anwendung von [177Lu]Lu-PSMA-617 bei mCRPC nach Chemotherapie wird durch umfangreiche Evidenz aus der Phase-II-TheraP- und der Phase-III-VISION-Studie unterstützt, die seine Sicherheit und Wirksamkeit belegen konnten. Der theranostische Ansatz identifiziert Patienten, die wahrscheinlich von [177Lu]Lu-PSMA-617 profitieren. Dieses ist nur bei Tumoren mit ausreichender PSMA-Expression wirksam, wie durch PSMA-Liganden PET/CT nachgewiesen wird, die auch für die Beurteilung des Ansprechens verwendet wird.

Schlussfolgerung Der Erfolg von [177Lu]Lu-PSMA-617 bei Patienten mit mCRPC nach Chemotherapie hat zu weiteren laufenden Studien geführt, die den Einsatz dieses Therapeutikums früher im Behandlungsverlauf, noch vor der Chemotherapie, evaluieren. Um einen Behandlungserfolg zu erreichen, sind eine adäquate Patientenauswahl und die Bewertung des bildgebungsbasierten Ansprechens durch PSMA-Liganden PET/CT erforderlich.

Kernaussagen

- Die Indikationen für [177Lu]Lu-PSMA-617 basieren auf den klinischen Studien TheraP und VISION.
- Eine angemessene Patientenauswahl mittels PSMA-Liganden PET/CT ist entscheidend für vorteilhafte Behandlungsergebnisse.
- Die Bewertung des Ansprechens basiert auf Bildgebung, PSA-Werten und dem klinischen Patientenzustand.

Introduction

In the field of nuclear oncology, theranostics represents an integrated clinical approach that combines diagnostic and therapeutic procedures. It uses radiotracers to identify and target tumor cells, thereby guiding tailored treatments. Prostate-specific membrane antigen (PSMA), a type II transmembrane glycoprotein, is an established target in prostate cancer cells [1]. PSMA is overexpressed in approximately 90 % of metastatic prostate cancers, particularly in metastatic castration-resistant prostate cancer (mCRPC), highlighting its potential for targeted treatment [2, 3]. CRPC occurs when prostate-specific antigen (PSA) levels continue to rise or new lesions appear on imaging despite hormone treatments effectively lowering testosterone levels [4]. In 2015, a study group from the German Cancer Research Center in Heidelberg reported promising results for attaching the radionuclide Lutetium-177 (^{177}Lu) to a small molecule inhibitor of PSMA, leading to the development of [^{177}Lu]Lu-PSMA-617 [5]. ^{177}Lu is a primarily beta-emitting radionuclide with a half-life of 6.65 days and a mean tissue penetration range of 0.7 mm. After binding to PSMA, the complex is internalized and partially trapped in endosomes, delivering radiation that destroys targeted and neighboring cells [6]. Compassionate use programs in Germany soon adopted [^{177}Lu]Lu-PSMA-617 for patients with mCRPC who had exhausted alternative treatments, noting its treatment response and low toxicity [7, 8, 9, 10, 11, 12]. In 2018, the first prospective phase II trial (LuPSMA trial) confirmed the treatment's response and its safety [13]. Subsequently, the prospective phase II TheraP trial showed that [^{177}Lu]Lu-PSMA-617 had a better treatment response and lower toxicity compared to cabazitaxel, a second-line chemotherapy drug commonly used to treat mCRPC in patients who have undergone most other metastatic prostate cancer treatments [14, 15]. In 2021, the prospective phase III VISION trial demonstrated improvements in progression-free survival (PFS) and overall survival (OS) with [^{177}Lu]Lu-PSMA-617 plus standard of care (SOC) compared to the SOC alone [16]. This evidence led to the approval of [^{177}Lu]Lu-PSMA-617 (Pluvicto) by the European Medicines Agency (EMA) in December 2022 for treating PSMA-positive mCRPC [17]. This article reviews the evidence for this treatment in PSMA-positive mCRPC, focusing on selected completed prospective studies and the role of molecular imaging.

Materials and Methods

This review discusses the evidence for [^{177}Lu]Lu-PSMA-617, considered the primary ^{177}Lu-labeled PSMA ligand due to its approval, in mCRPC, based on completed prospective studies and EANM/SNMMI guidelines for ^{177}Lu-labeled PSMA-targeted radioligand therapy (PSMA-RLT) [18], without the intention of providing a systematic review. Furthermore, new developments in the field were added based on a literature review conducted in PubMed in May 2024 by A.K. and M.S. The PubMed search used the following terms to identify literature on the use of [^{177}Lu]Lu-PSMA-617 in patients with prostate cancer: "prostate cancer" OR "prostatic neoplasms", AND (^{177}Lu OR lutetium-177 OR Lu OR lutetium OR "Lutetium"), AND (PSMA OR PSMA-617 OR "prostate-specific membrane antigen" OR "vipivotide tetraxetan").

Evidence for [^{177}Lu]Lu-PSMA-617 in mCRPC from selected prospective studies

The current indications of RLT with [^{177}Lu]Lu-PSMA-617 for mCRPC are based on substantial evidence from two pivotal clinical trials, the phase II TheraP trial and the phase III VISION trial (▶ **Table 1**) [14, 16]. In the TheraP trial, [^{177}Lu]Lu-PSMA-617 was compared with cabazitaxel in patients who had progressed after treatment with a novel anti-androgen and the first-line chemotherapy drug docetaxel [14]. The results demonstrated an advantage for [^{177}Lu]Lu-PSMA-617, with higher PSA response rates (PSA decline ≥ 50 % from baseline in 66 % vs. 37 % for cabazitaxel) and fewer severe adverse events, supporting the use of [^{177}Lu]Lu-PSMA-617 as

▶ **Table 1** Selected baseline patient characteristics and treatment outcomes from the phase II TheraP [14] and the phase III VISION trials [16].

	Phase II TheraP trial [14]		**Phase III VISION trial [16]**	
PET-based inclusion criteria	1. [^{68}Ga]Ga-PSMA-11 PET with at least SUVmax 20 at a site of disease 2. SUVmax greater than 10 at all other sites of measurable (diameter of ≥ 10 mm) metastatic disease		[^{68}Ga]Ga-PSMA-11 PET with visual uptake greater than liver parenchyma in metastatic lesions of any size in any organ system	
PET-based exclusion criteria	[^{18}F]FDG–positive/PSMA-negative disease (PSMA-negative defined as an SUVmax < 10)		[^{68}Ga]Ga-PSMA-11 uptake with visual uptake equal to or lower than the liver parenchyma in: 1. lymph nodes with SAD ≥ 2.5 cm 2. solid-organ lesions with SAD ≥ 1 cm 3. bone lesions with a soft tissue component ≥ 1 cm SAD	
Study arms	[^{177}Lu]Lu-PSMA-617	Cabazitaxel	[^{177}Lu]Lu-PSMA-617 + SOC	SOC alone
Included patients, n	99	101	551	280
Age, median (years)	72.1	71.8	70.0	71.5
Metastatic sites, %				
Lymph node	52.5	46.5	49.7	50.4
Bone	90.9	89.1	91.5	91.4
Visceral metastases	7.11	12.91	11.4[1]	13.6[1]
Previous treatments, %				
Novel anti-androgen drug	92	90	100	100
Docetaxel	100	100	96.9	97.5
Cabazitaxel	0	0	37.9	38.2
Imaging-based PFS, median (months)	Not assessed		8.7	3.4
HR (95 % CI), *p*-value			0.4 (0.29–0.57), < 0.001	
OS, median (months)	19.1[2]	19.6[2]	15.3	11.3
HR (95 % CI), *p*-value	0.77		0.62 (0.52–0.74), < 0.001	

HR: hazard ratio, OS: overall survival, PFS: progression-free survival, SUVmax: maximum standard uptake value. [1] Only liver metastases, not all visceral metastases. [2] Restricted mean survival time from a follow-up analysis of the TheraP cohort [19].

an alternative to cabazitaxel [14, 18]. A follow-up analysis of the TheraP trial cohort over a median of 35.7 months showed similar restricted mean survival times: 19.1 months for [^{177}Lu]Lu-PSMA-617 and 19.6 months for cabazitaxel [19]. Notably, after completing the study treatment, 20 % of participants initially assigned to cabazitaxel and 32 % assigned to [^{177}Lu]Lu-PSMA-617 received the alternative regimen. This follow-up analysis suggests that while [^{177}Lu]Lu-PSMA-617 offers benefits in treatment response and toxicity, its impact on OS is comparable to cabazitaxel. The VISION trial supports the use of [^{177}Lu]Lu-PSMA-617 for patients with PSMA-positive mCRPC who have previously been treated with at least one novel anti-androgen (e. g., enzalutamide or abiraterone) and with at least one chemotherapy regimen (e. g., docetaxel or cabazitaxel). In the VISION trial, patients treated with [^{177}Lu]Lu-PSMA-617 plus SOC demonstrated a median imaging-based PFS of 8.7 months compared to 3.4 months with SOC alone, while the median OS increased from 11.3 to 15.3 months [16]. The reported efficacy of [^{177}Lu]Lu-PSMA-617 in post-chemotherapy mCRPC patients raises questions about its potential use earlier in the treatment sequence. Recently, results from the phase 3 PSMAfore trial (NCT04689828), which is investigating the use of [^{177}Lu]Lu-PSMA-617 in chemotherapy-naïve mCRPC patients (prior to chemotherapy with e. g., docetaxel or cabazitaxel), have been reported [20]. Preliminary trial results show that [^{177}Lu]Lu-PSMA-617 extends imaging-based PFS by 6.4 months compared to switching to a novel anti-androgen therapy, suggesting its potential as an alternative for PSMA-positive mCRPC patients. However, no significant difference in median OS was observed: 19.25 months in the [^{177}Lu]Lu-PSMA-617 group versus 19.71 months in the anti-androgen group. Notably, 84.2 % of the latter crossed over to [^{177}Lu]Lu-PSMA-617 after progression, which may have reduced observable OS differences [20].

The Role of Molecular Imaging in Selecting Patients for PSMA-RLT

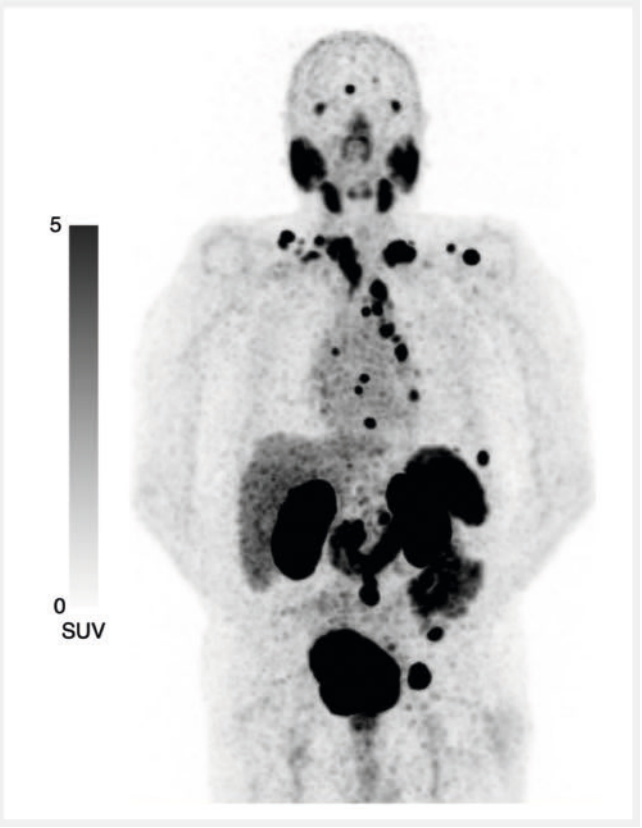
A key advantage of the theranostic approach is visualizing biological targets and identifying patients likely to benefit from treatment based on radioligand uptake in pre-treatment diagnostic

imaging. ^{177}Lu-labeled PSMA-RLT is effective only in tumors with sufficient PSMA expression, as demonstrated by the TheraP and the VISION trials using [^{68}Ga]Ga-PSMA-11 [14, 16]. The TheraP trial required at least one tumor lesion with a maximum standard uptake value (SUVmax) over 20, and all measurable lesions (diameter ≥ 10 mm) with an SUVmax above 10 [14]. It also excluded patients with [^{18}F]FDG–positive/PSMA-negative disease (PSMA-negative defined as an SUVmax < 10) (▶ **Table 1**) [14].

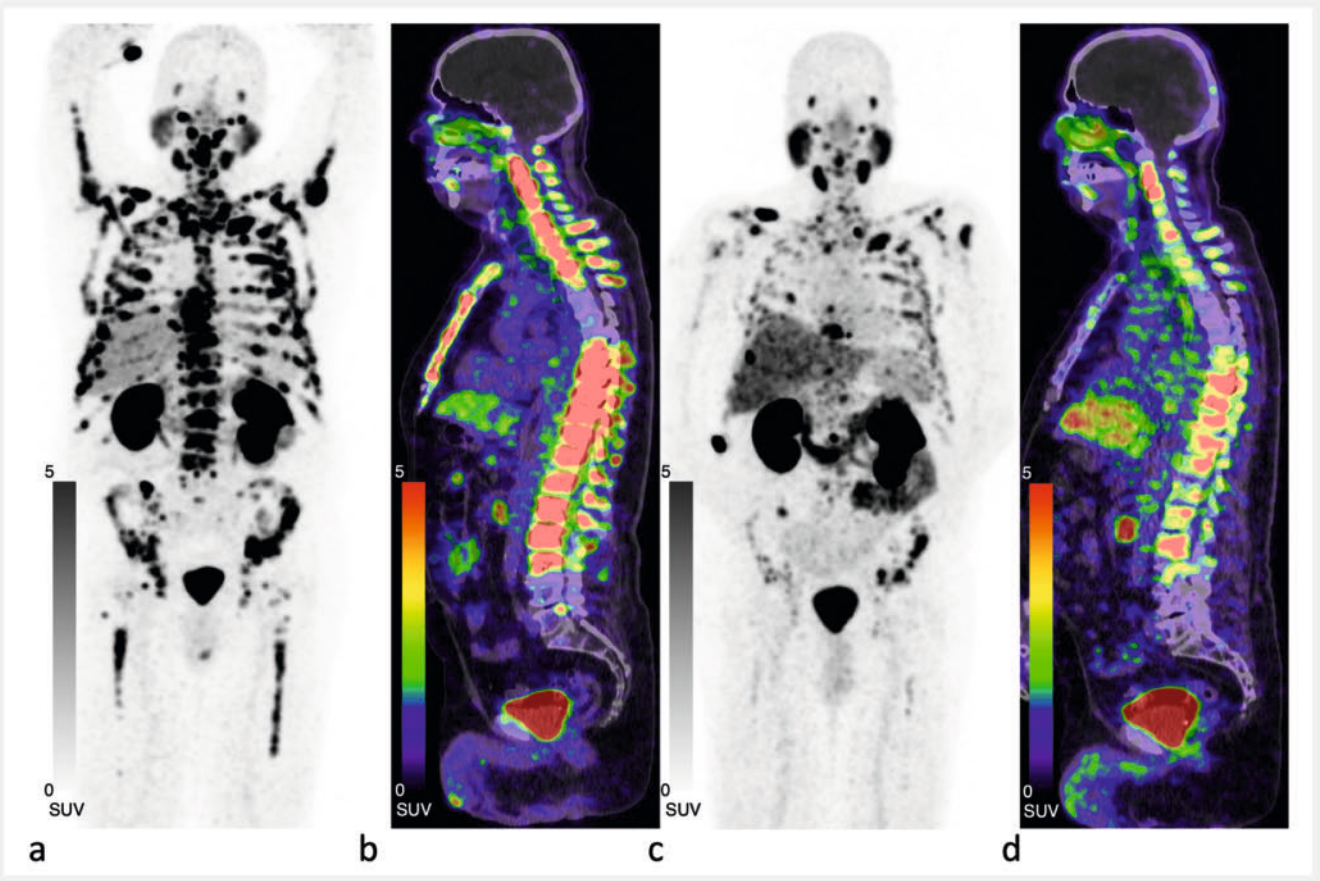
In contrast, the VISION trial assessed PSMA positivity by visual PSMA-ligand uptake to be greater than the liver in one or more metastatic lesions of any size in any organ system [16]. The protocol defined PSMA-negative lesions as measurable lesions with PSMA-ligand uptake equal to or lower than that of the liver parenchyma (▶ **Table 1**) [16]. Compared to VISION's PET criteria, TheraP's stricter criteria led to a higher rate of imaging screen failures (28 % vs. 13 %) [14, 16]. While TheraP's stringent criteria limited eligibility, they resulted in superior PSA response rates (66 % vs. 46 %) compared to the VISION trial, which did not require [^{18}F]FDG-PET evaluations [14, 16]. Supporting this, a retrospective analysis showed that patients meeting TheraP PET criteria (at least one tumor lesion with an SUVmax over 20) had a median OS of 15.0 months and a PSA response rate of 54.5 %, compared to 10.0 months and 20 % in those who did not meet the criteria [21]. Limited clinical benefits were observed for patients not meeting VISION PET criteria, with a retrospective analysis reporting a median OS of 9.6 months and a PSA response of 21 %, compared to 15.0 months and 46 % in VISION trial patients [16, 22]. In addition, a retrospective analysis of 89 patients assessed for [^{177}Lu]Lu-PSMA-617 found only three instances of [^{18}F]FDG–positive/PSMA-negative diseases not detected by PSMA-ligand PET-only analysis similar to the VISION trial [23]. This observation, combined with the inclusion of patients with small PSMA-negative tumors and the demonstration of an OS advantage in the largest cohort of mCRPC patients, makes the VISION PET criteria (visual PSMA-ligand uptake greater than the liver) currently preferable for selecting patients for ^{177}Lu-labeled PSMA-RLT (▶ **Fig. 1**) [18, 24]. However, the decision to proceed with PSMA-RLT should be made by a multidisciplinary tumor board, as determining eligibility for treatment requires a comprehensive evaluation beyond just PET-based criteria. Patients with borderline eligibility may still benefit from PSMA-RLT, especially if they have exhausted all other therapeutic options.

Moreover, further evidence supports the importance of PSMA-ligand uptake in predicting treatment outcomes. A retrospective analysis found that low average PSMA expression predicts poorer OS in patients treated with [^{177}Lu]Lu-PSMA-617, while the absence of low PSMA-expressing metastases is associated with the best OS [25]. In line with this, substudies of the TheraP and the VISION trials showed that higher PSMA-ligand uptake correlates with better responses to [^{177}Lu]Lu-PSMA-617 [26, 27]. In the TheraP trial, men with a whole-body mean SUV (SUVmean) ≥ 10 had significantly better odds of a PSA response to [^{177}Lu]Lu-PSMA-617 compared to cabazitaxel (odds ratio (OR), 12.19 vs. 2.22) [26]. Conversely, patients with the lowest mean SUVmean (<6.9) tend to have higher PSA response rates with cabazitaxel (OR, 0.53) [26]. In accordance with this, a VISION trial substudy found that a higher baseline whole-body SUVmean was associated with better OS (hazard ratio, 0.88), with patients in the highest SUVmean quartile having an OS of 21.4 months compared to 12.6–14.6 months in the lower quartiles [27]. A potential explanation for the interaction between PSMA-ligand uptake and treatment outcome may be the correlation between PSMA expression in PET imaging and absorbed doses during ^{177}Lu-labeled PSMA-RLT. Patients with lower uptake in pre-therapeutic PET imaging reportedly experienced limited treatment response due to lower absorbed doses of ^{177}Lu [28]. These findings emphasize the importance of adequate patient selection based on PSMA-ligand uptake in PET scans to optimize outcomes with ^{177}Lu-labeled PSMA-RLT, particularly when considering alternative treatments for those with lower PSMA-ligand uptake.

Additionally, in cases of suspected PSMA-ligand-negative disease, particularly liver disease not visible on non-contrast CT as part of a PSMA-ligand PET/CT scan, a contrast-enhanced CT or MRI examination should be performed [18]. This is important, as liver metastases are a strong negative prognosticator of OS after treatment with ^{177}Lu-labeled PSMA-RLT [29]. Moreover, in cases of poorly differentiated disease or suspected viable PSMA-negative lesions (e. g., active non-sclerotic PSMA-negative bone metas-



▶ **Fig. 1** Maximum intensity projection (MIP) of a [68Ga]Ga-PSMA-I&T PET in a mCRPC patient prior to treatment with [177Lu]Lu-PSMA-617. The scan shows lymph node and bone metastases with visual PSMA-ligand uptake greater than that of the liver, while no measurable lesions with PSMA-ligand uptake equal to or below liver level were detectable, making the patient suitable for treatment with [177Lu]Lu-PSMA-617 according to the PET-based eligibility criteria from the phase III VISION trial [16].



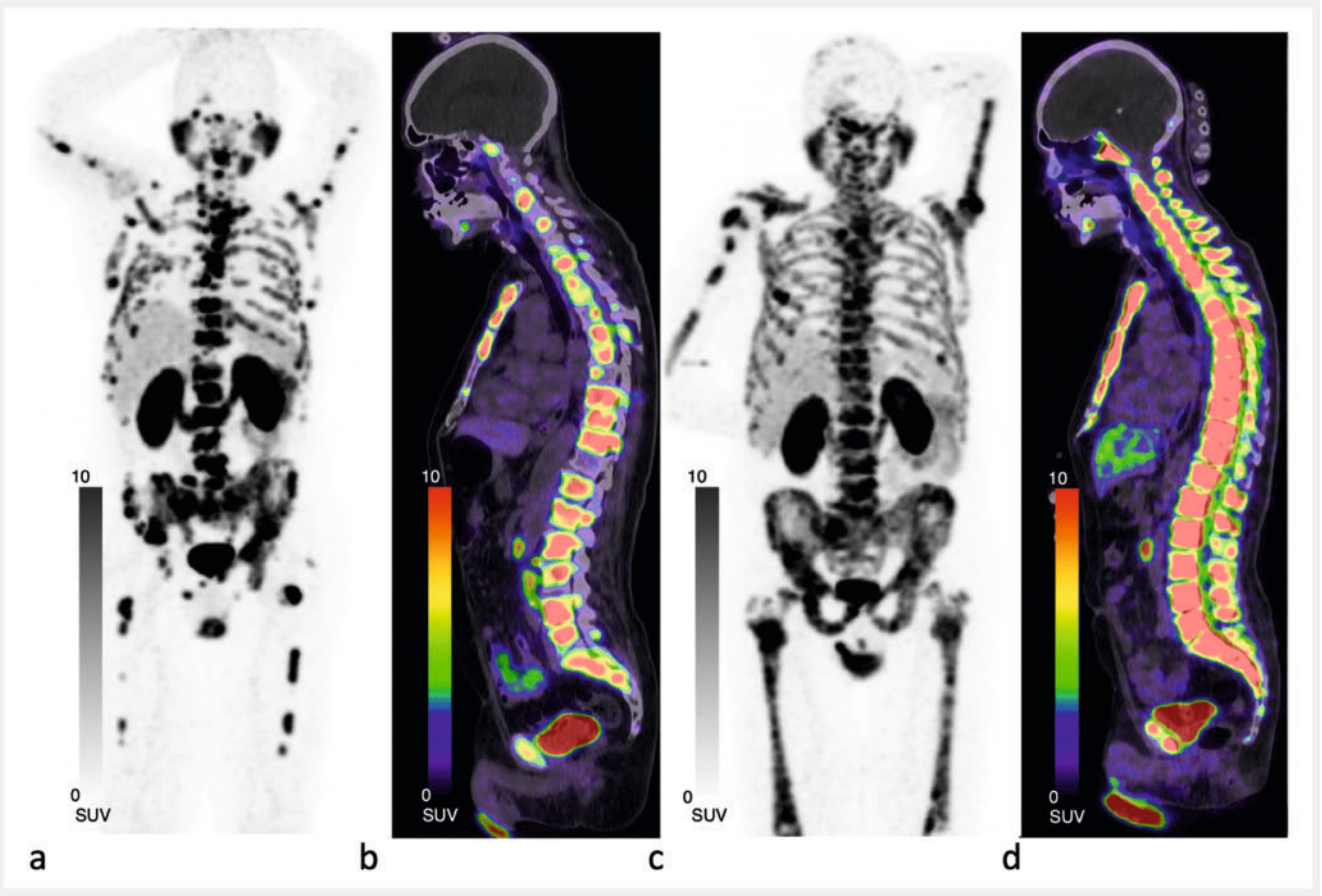
▶ **Fig. 2** Maximum intensity projections (MIP) and PET/CT fusion images of a [68Ga]Ga-PSMA-I&T PET scan of an mCRPC patient with disseminated bone metastases before treatment (**a** and **b**) and after two cycles of [177Lu]Lu-PSMA-617 (**c** and **d**), demonstrating partial remission. Concordantly, after two therapy cycles, the patient showed a PSA response (PSA decline of 68.4 % from baseline), according to the Prostate Cancer Clinical Trials Working Group 3 (PCWG 3) criteria [37].

tases), an additional [^{18}F]FDG PET can be helpful [18]. PSMA-negative/[^{18}F]FDG-positive lesions, indicating high glycolytic activity, can occur in up to 30 % of mCRPC patients eligible for PSMA-RLT [14, 30]. These aggressive, nonresponding lesions are associated with a shorter OS after PSMA-RLT compared to PSMA-positive//[^{18}F]FDG-positive or PSMA-positive//[^{18}F]FDG-negative lesions [31]. In line with this, patients with high volumes of [^{18}F]FDG-positive disease (metabolic tumor volume ≥ 200 mL) showed lower PSA response rates compared to those with lower volumes (38 % vs. 56 %) [26].

Furthermore, there are various PSMA ligands for PET imaging (e. g., [^{68}Ga]Ga-PSMA-11, [^{68}Ga]Ga-PSMA-I&T, [^{18}F]F-DCFPyL, and [^{18}F]F-rhPSMA-7.3), with different in-vivo characteristics [32]. Analyses have shown that for [^{68}Ga]Ga-PSMA-11 and [^{18}F]F-DCFPyL, normal tissue biodistribution patterns, including the liver, are similar, allowing liver-based PET selection criteria, as used in the VISION trial, to be applied to both [33]. However, adapting established PET selection criteria for other PSMA-ligands is rarely discussed in the literature. While differences may be minor, future analyses with different PSMA-ligands are needed to evaluate their impact on patient selection for ^{177}Lu-labeled PSMA-RLT.

The Role of Molecular Imaging for Response Assessment

The optimal imaging tool for response assessment is PSMA-ligand PET combined with contrast-enhanced CT of the chest, abdomen, and pelvis to detect PSMA-negative lesions, especially in the liver [18]. Restaging should be performed every 12 weeks (after every two therapy cycles) and at the end of treatment to evaluate the imaging-based response [18]. If PSMA-ligand PET is unavailable, posttreatment PSMA-ligand SPECT or scintigraphy can yield promising results for response assessment [18]. This is due to ^{177}Lu's ability to emit gamma radiation, which can be imaged with gamma cameras. Published data indicates that changes in post-treatment gamma imaging sufficiently correlate with treatment response and PFS, suggesting that gamma imaging could be a useful tool [34, 35]. However, the VISION trial used contrast-enhanced CT and bone scans for response assessment, with contrast-enhanced CT being considered a minimum standard for treatment monitoring [16, 24]. The use of alternative radiotracers for SPECT imaging, such as [^{99m}Tc]Tc-MIP-1404, is currently being investigated for baseline imaging prior to therapy but has not yet been evaluated for response assessment during PSMA-RLT, to the best of our knowledge [36]. Further developments in this area



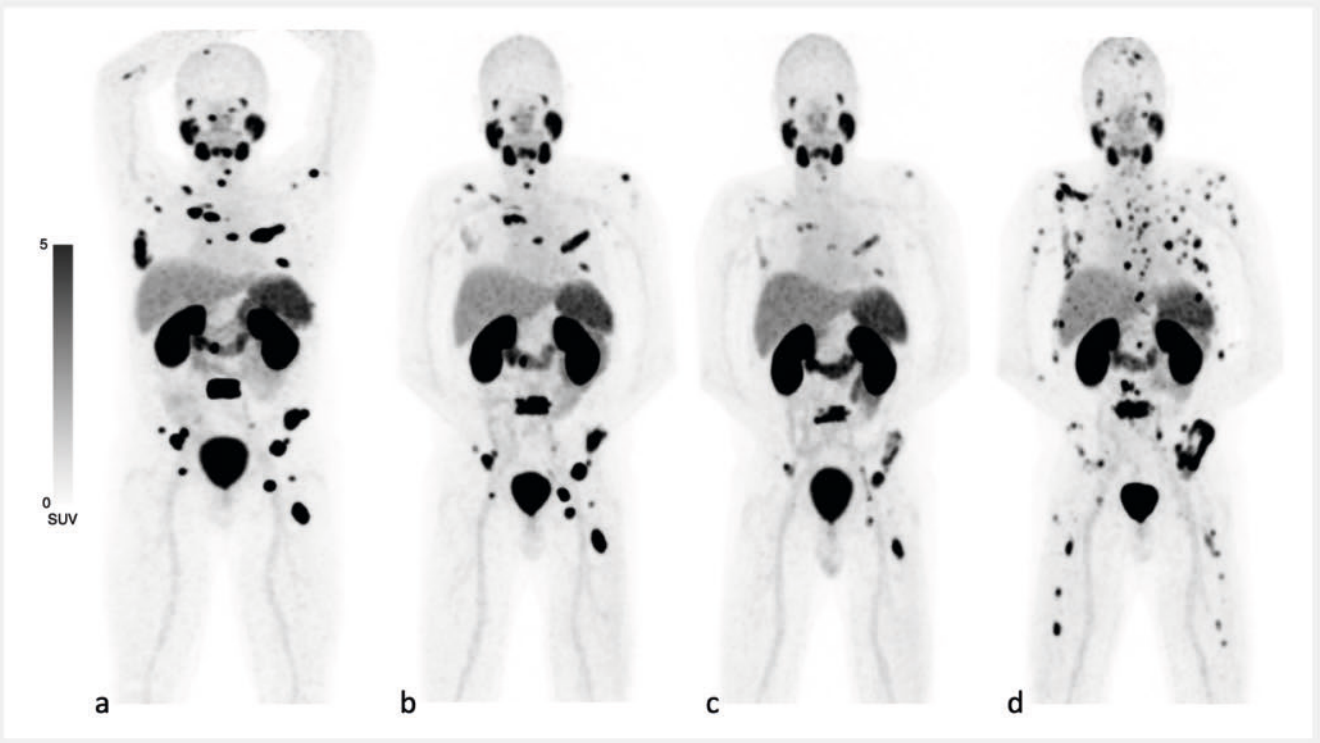
▶ **Fig. 3** Maximum intensity projections (MIP) and PET/CT fusion images of a [68Ga]Ga-PSMA-I&T PET scan of an mCRPC patient with lymph node and disseminated bone metastases before treatment (**a** and **b**) and lymph node and bone metastases with diffuse bone marrow infiltration after two cycles of [177Lu]Lu-PSMA-617 (**c** and **d**), demonstrating progressive disease. Correspondingly, after two treatment cycles, the patient showed PSA progression (PSA increase of 49 % from baseline), according to PCWG 3 criteria [37].

could make the evaluation and monitoring of PSMA-RLT accessible to a broader range of institutions that may not have PET/CT facilities. Exemplary response patterns in mCRPC patients treated with [^{177}Lu]Lu-PSMA-617 are shown in ▶ **Fig. 2**, ▶ **Fig. 3**, ▶ **Fig. 4**.

Response assessment ideally requires concretely defined criteria for consistent application in clinical practice. For this purpose, a new framework for response evaluation criteria in PSMA-ligand PET (RECIP 1.0) was established based on data from ^{177}Lu-labeled PSMA-RLT [38]. Using semi-automatic segmentation software for whole-body tumor burden assessment, RECIP 1.0 classifies responses as: complete response (no PSMA-ligand uptake on interim PET), partial response (≥ 30 % decline in total tumor volume without new lesions), progressive disease (≥ 20 % increase in total tumor volume and new lesions), and stable disease (all other scenarios) (▶ **Fig. 5**) [38]. A retrospective analysis showed its higher prognostic value and inter-reader reliability compared to established criteria like RECIST 1.1 in mCRPC patients [39]. However, assessing whole-body tumor volume is not standard in clinical practice and is currently not required for the evaluation of treatment response. Furthermore, there is no clear definition of progression that marks treatment failure for ^{177}Lu-labeled PSMA-RLT. Imaging-based progression, PSA progression, and clinical decline should all be considered [18, 37]. A careful, multidisciplinary review is needed to integrate these factors and avoid discontinuing therapy too soon for patients who may still benefit.

Performing ^{177}Lu-labeled PSMA-RLT

^{177}Lu-labeled PSMA-RLT is typically administered in nuclear medicine departments with specialized facilities that meet radiation protection requirements for unsealed radiation sources. In Germany, after administration, patients must stay on a radioisotope ward for at least 48 hours to reduce the risk posed to others by external radiation (gamma emission of ^{177}Lu) or exposure to excreted radioactivity, ensuring that individuals of the public cannot be exposed to more than 1 mSv per year [40, 41]. These facilities must include dedicated treatment rooms and procedures for patient isolation and managing contaminated materials until residual radioactivity decays to safe levels. Nuclear medicine physicians, certified in the therapy with open radioactive substances ("Fachkunde in der Therapie mit offenen radioaktiven Stoffen"), are responsible for the appropriate use of ^{177}Lu-labeled PSMA-RLT [41]. They discuss the technical and clinical aspects of the treatment with the patient, manage aftercare and follow-up, and



▶ **Fig. 4** Maximum intensity projections (MIP) of a [68Ga]Ga-PSMA-I&T PET scan of an mCRPC patient with disseminated bone metastases before treatment **a**, and after two **b**, four **c**, and six **d** cycles of [177Lu]Lu-PSMA-617. The patient demonstrated partial remission up to the 2nd interim PSMA-ligand PET/CT after four treatment cycles **c**. At final staging after the 6th treatment cycle **d**, the patient presented with multiple new bone metastases, indicating progressive disease. Correspondingly, the patient showed the best PSA response (PSA decline of 81.1 % from baseline) at the time of the 6th treatment cycle, but at the time of the final PSMA-ligand PET/CT after the 6th treatment cycle, a PSA progression (PSA increase of 90.6 % from nadir) was detectable, according to PCWG 3 criteria [37].

collaborate closely with referring and managing physicians. German legislation also requires the involvement of a medical physics expert in treatments with radioactive substances where the level of involvement depends on the standardization of the treatment [40, 41]. Based on the approval by EMA the current clinical practice involves administering [^{177}Lu]Lu-PSMA-617 with a fixed activity of approximately 7.4 GBq intravenously every six weeks for up to six cycles in stable mCRPC patients [18].

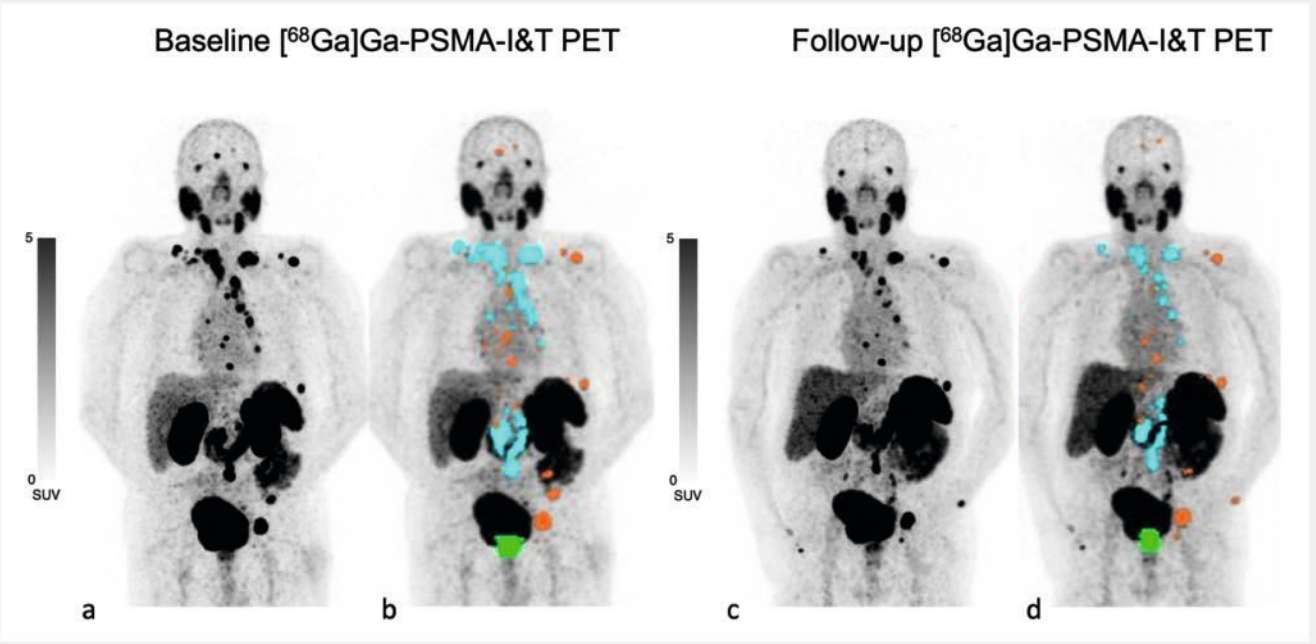
Adverse events related to ^{177}Lu-labeled PSMA-RLT

In addition to metastatic prostate cancer, there are organs that may be exposed to radiation from ^{177}Lu-labeled PSMA-RLT, which are therefore considered organs at risk (OAR; e. g., salivary glands, red bone marrow, kidney). Some of the treatment-related adverse events reported for ^{177}Lu-labeled PSMA-RLT are due to the radiation exposure of these OAR. The VISION trial reported that the most common treatment-related adverse events in patients receiving [^{177}Lu]Lu-PSMA-617, were fatigue (43.1 %), dry mouth (38.8 %), and nausea (35.3 %), mostly mild to moderate [16]. In addition, a considerable proportion of patients may experience moderate or severe decreases in kidney function, as measured by eGFR, in the long term after initiating ^{177}Lu-labeled PSMA-RLT [42]. The most common severe adverse events in the VISION trial include anemia (12.9 %), thrombocytopenia (7.9 %), and lymphocytopenia (7.8 %), though these were generally uncommon [16]. Consistent with these findings, the TheraP trial reported an increase of ≥ 10 % in dry mouth and thrombocytopenia with [^{177}Lu]Lu-PSMA-617 compared to cabazitaxel [14]. However, there were significantly fewer severe adverse events in the [^{177}Lu]Lu-PSMA-617 group compared to the cabazitaxel group (33 % vs. 53 %), highlighting its safety [14]. The practicing physician and other referring and managing physicians must be aware of potential adverse events and their adequate management [18].

Dosimetry

The European Council Directive 013/59/EURATOM, Article 56, mandates treatment verification [43], and for standardized treatments qualitative verification at a suitable time point with optional safety dosimetry for the above-mentioned OAR [18, 44]. For these reasons, the recommendation by the German Society of Nuclear Medicine from 2016, prior to EMA approval of [^{177}Lu]Lu-PSMA-617, includes a safety dosimetry protocol [45].

Supporting this approach, a dosimetry substudy of the VISION trial reported a good safety profile and acceptable cumulative absorbed doses for the kidneys, salivary glands, and red bone marrow [46], while dosimetry results from other studies have been reviewed in [47]. Internal dosimetry for RLT is generally performed



▶ **Fig. 5** Maximum intensity projections (MIP) of a [68Ga]Ga-PSMA-I&T PET scan of an mCRPC patient before treatment **a** with the corresponding semiautomatic tumor segmentation **b**, and after two cycles of [177Lu]Lu-PSMA-617 (**c** and **d**). The semiautomatic quantitative assessment of tumor burden, including the primary tumor (green) as well as lymph node (blue) and bone metastases (orange), resulted in a total tumor volume of 265.1 ml before treatment **b** and of 137.7 ml after two treatment cycles **d**, with no detectable appearance of new lesions. This corresponds to a partial remission (≥ 30 % reduction in total tumor volume) according to the RECIP 1.0 criteria by Gafita et al. [38]. The semiautomatic tumor segmentation was performed using aPROMISE software version 2.3.0, with manual adjustments made as necessary.

based on the MIRD (Medical Internal Radiation Dose) formalism [48] using serial post-treatment imaging preferably with 3 D quantitative SPECT.

Due to inter-patient variability and to avoid compromising individual patient safety, some level of dosimetry is advantageous for standardized treatment regimens such as for [177Lu]Lu-PSMA-617 [18]. This can involve performing dosimetry for therapy cycle 1 and extrapolating the dose for subsequent cycles based on the injected activity [46] or using simplified single time point imaging protocols in later cycles [49, 50].

Furthermore, several studies have demonstrated positive correlations between baseline imaging parameters, absorbed radiation doses, and treatment response [28]. Therefore, patient-specific, dosimetry-guided treatment regimens that use higher activities or additional treatment cycles could be beneficial. Such regimens can increase therapy efficacy while maintaining safety by keeping absorbed doses to organs at risk below predefined limits.

Conclusion

The current indications of [177Lu]Lu-PSMA-617 are supported by the phase II TheraP and the phase III VISION trials, which have demonstrated its efficacy and safety. For optimal patient outcomes, it is crucial to ensure adequate patient selection using PSMA-ligand PET/CT. Furthermore, the evaluation of treatment response should include imaging studies, PSA level assessments, and the patient's clinical condition. These factors collectively contribute to achieving the best possible therapeutic results with 177Lu-labeled PSMA-RLT.

Conflict of Interest

Markus Sauer reports fees from ABX (consultant), Janssen (speaker) and Novartis (speaker) outside the submitted work. No other potential conflict of interest relevant to this article was reported.

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