PSMA hybrid imaging in prostate cancer – current applications and perspectives

PSMA-Hybridbildgebung in der Diagnostik des Prostatakarzinoms – aktuelle Anwendungen und Perspektiven

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Key words

prostate, PET-CT, metastases, PET, staging

received 24.11.2022
accepted 28.04.2023
published online 22.06.2023

Bibliography

Fortschr Röntgenstr 2023; 195: 1001–1008
DOI 10.1055/a-2088-9543
ISSN 1438-9029

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ABSTRACT

Background Prostate cancer (PCa) is the most common malignancy in men and the second most common tumor-associated cause of death in the male population in Germany. Prostate-specific membrane antigen (PSMA)-targeted hybrid imaging using positron emission tomography (PET) in combination with CT or MRI represents a comparably new method that gained increasing importance in the diagnostic process of PCa in recent years.

Method Current applications of PSMA hybrid imaging were summarized according to the German and European guidelines on PCa. New developments were elaborated based on a literature review of PubMed conducted in 10/22.

Results PSMA-PET/CT demonstrated higher detection rates for metastases in high-risk PCa and recurrent PCa after primary therapy than established imaging methods (CT, MRI, and bone scan). Despite promising results from prospective trials in both scenarios and substantial influence on clinical decision making, data regarding the influence of PSMA-PET on PCa-specific and overall survival are still lacking. Hence, PSMA PET/CT is recommended with a "weak" strength rating in most situations. However, its importance in new treatment options like metastasis-directed therapy or PSMA-radioligand therapy expands the scope of PSMA-PET in the clinical routine.

Conclusion PSMA-targeting hybrid imaging represents the most sensitive diagnostic test in several stages of PCa and allows the development of new treatment strategies. Prospective studies are needed to evaluate the influence of PSMA-PET on patient survival.

Key Points

- PSMA-PET/CT is superior to conventional imaging in the primary staging of high-risk prostate cancer.
- PSMA hybrid imaging can detect metastases in patients with biochemical recurrence at low PSA values.
- Clinical decision making is frequently influenced by results of PSMA-PET/CT.

Citation Format

- Koehler D, Berliner C, Shenas F et al. PSMA hybrid imaging in prostate cancer – current applications and perspectives. Fortschr Röntgenstr 2023; 195: 1001–1008

ZUSAMMENFASSUNG

Hintergrund Das Prostatakarzinom (PCa) ist das häufigste Malignom des Mannes und die zweithäufigste krebsbedingte Todesursache der männlichen Bevölkerung in Deutschland. Die Bildgebung des prostataspezifischen Membranantigens (PSMA) mittels Hybridverfahren wie der Positronen-Emissions-Tomografie (PET) in Kombination mit der CT oder MRT stellt eine vergleichsweise neue Methode dar, die in den letzten Jahren zunehmend an Bedeutung in der Diagnostik des PCa gewonnen hat.

Methode Aktuelle Anwendungen der PSMA-Hybridbildgebung wurden basierend auf den deutschen und europäischen Leitlinien zum Thema Prostatakarzinom erörtert und um neue

Entwicklungen basierend auf einer Literaturrecherche in PubMed aus 10/22 ergänzt.

Ergebnisse Die PSMA-PET/CT weist sowohl im Primärstaging von Hochrisikoprostatakarzinomen als auch beim Rezidiv nach Primärtherapie höhere Detektionsraten von Metastasen als die etablierten Methoden (CT, MRT und Skelettszintigrafie) auf. Trotz vielversprechender Ergebnisse prospektiver Studien in beiden Szenarien und dem deutlichen Einfluss der PSMA-PET auf Therapieentscheidungen liegen aktuell noch keine Analysen bezüglich ihres Einflusses auf das PCa-spezifische Überleben und das Gesamtüberleben vor. Daher wird in den meisten Situationen eine „kann"-Empfehlung für die PSMA-PET/CT ausgesprochen. Neue Behandlungsstrategien wie die metastasengerichtete Therapie oder die PSMA-Radioligandentherapie erweitern jedoch bereits jetzt schon den Einsatzbereich der PSMA-PET und verankern sie weiter im klinischen Alltag.

Schlussfolgerung Die PSMA-Hybridbildgebung stellt in verschiedenen Stadien des PCa die sensitivste Staging-Methode dar und ermöglicht damit die Entwicklung neuer Behandlungskonzepte. Prospektive Analysen sind jedoch notwendig, um ihren Einfluss auf das Patientenüberleben zu evaluieren.

Introduction

Prostate cancer (PCa) is the most common malignant tumor in men [1]. The associated mortality rate has decreased progressively in the last decades and is lower than in many other malignancies [2]. In spite of this positive development, PCa remains the second most common cancer-related cause of death in men in Germany [1]. To further improve patient survival and quality of life, it is important to determine the disease process as precisely as possible. The prostate-specific membrane antigen (PSMA) has become increasingly important in this regard in recent years. PSMA (synonym: glutamate carboxypeptidase II) is a transmembrane protein discovered for the first time on prostate cancer cells in 1987 [3]. Its function in the prostate and PCa is not yet fully understood. However, current knowledge indicates a role in the absorption of folic acid, which can mean an advantage in DNA synthesis [4]. PSMA is a particularly useful target structure for molecular imaging and treatment since its expression is usually significantly higher in PCa than in normal prostate tissue and its production corresponds to the tumor grade (Gleason score) [5, 6] However, in addition to the prostate, other tissues like the salivary glands, the small intestine, the kidneys, and parts of the nervous system produce PSMA [7, 8] (▶ **Fig. 1a, b**). It is also seen in the endothelial cells of newly formed blood vessels of other solid tumors and can be expressed in reactive processes [8, 9] (▶ **Fig. 1c, d**). This nonspecific uptake can result in a diagnostic dilemma in cases with an otherwise curative treatment concept. Therefore, to ensure correct interpretation of PSMA imaging, e. g. via positron emission tomography (PET), use of a hybrid method by combining with further cross-sectional imaging (CT or MRI) is indispensable for the evaluation of morphological characteristics [10, 11].

Low-molecular PSMA inhibitors are primarily used to visualize PSMA. They are characterized by good binding with subsequent internalization and favorable excretion dynamics [12]. The first of these substances to be used in the clinical routine was [^{68}Ga]Ga-HBED-CC (corresponding to [^{68}Ga]Ga-PSMA-11) [13]. In recent years, additional PSMA ligands have become established [12, 14]. These differ, for example, with regard to their routes of excretion, i. e., renal excretion vs. hepatic excretion (▶ **Fig. 2**). In the case of renal excretion, the activity of the radiopharmaceutical in the urinary tract can result in false-positive findings or masking of nearby tumor manifestations. To minimize the influence of urinary excretion, various approaches have been used in PET acquisition protocols. Images acquired very early within the first minutes after application can visualize PSMA-positive lesions before urinary activity becomes a relevant factor [15]. The administration of diuretics and the use of an additional late phase are further possibilities for minimizing the influence of artifacts due to urinary activity [16]. In contrast, newer radioligands have lower activity in the urinary tract after the recommended uptake times [14, 17]. As a result, PSMA-positive lesions near the bladder or ureter (local recurrence or locoregional lymph node metastases) are easier to identify [18]. However, in the case of ^{18}F-labeled radioligands, which include [^{18}F]PSMA-1007 with primary hepatic excretion, nonspecific uptake in non-malignant structures like the ganglia, lymph nodes, and bones is more common and can result in false-positive findings [19]. However, regardless of the various advantages and disadvantages of the available ligands, current analyses have not shown any significant difference in detection rates between the substances regardless of their radionuclides or their route of excretion [19, 20].

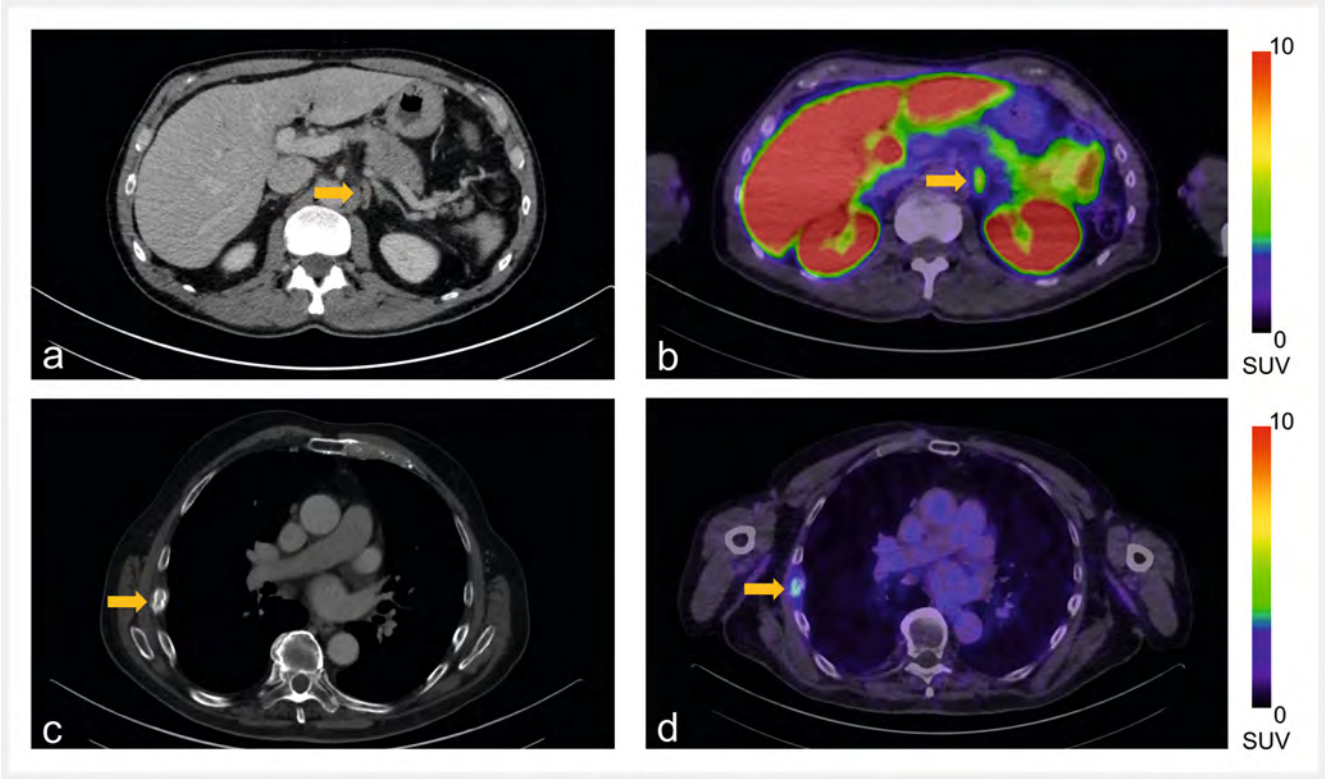
There are numerous indications for PSMA hybrid imaging, and these are constantly evolving in parallel with new therapeutic possibilities. The goal of this review is to present the current areas of application of PSMA-PET and new developments.

Materials and Methods

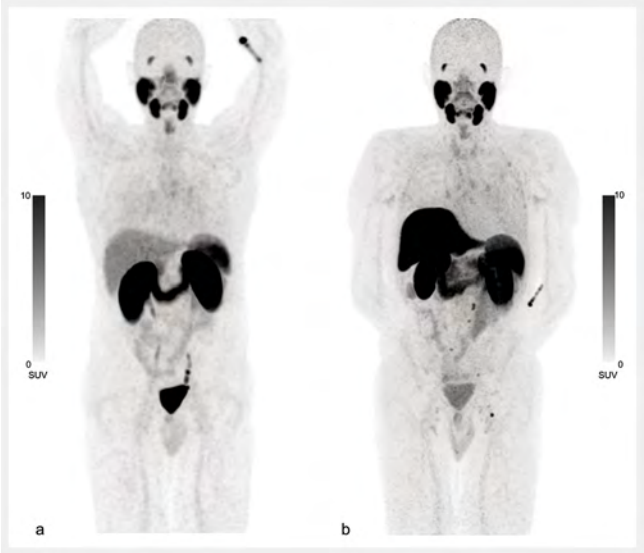
The current applications of PSMA hybrid imaging are based on the recommendations of the German S3 guidelines on prostate cancer from 2021 [21] and the prostate cancer guidelines of the European Association of Urology (EAU) last updated in 2022 [22]. New developments in the field based on a PubMed literature search in 10/2022 are also taken into consideration.

Primary staging after initial diagnosis of prostate cancer

Upon initial detection of prostate cancer, patients with a higher risk profile (Gleason score ≥ 8 or clinical assessment of the primary tumor as cT3 / cT4) should undergo MRI or CT of the pelvic organs in accordance with the guidelines and additionally undergo skeletal scintigraphy for staging in the case of a PSA value > 10 ng/ml or



▶ **Fig. 1** Contrast enhanced CT of the abdomen **a** and fusion image of a [^{18}F]PSMA-1007 PET/CT **b** showing moderate PSMA expression of a celiac ganglion (arrow). Contrast-enhanced CT of the thorax **c** and fusion image of a [^{68}Ga]Ga-PSMA-I&T PET/CT **d** showing low PSMA expression of a fractured rib (arrow).



▶ **Fig. 2** Maximum intensity projections (MIP) of a [^{68}Ga]Ga-PSMA-I&T PET **a** and a [^{18}F]PSMA-1007 PET **b** of the same patient after 11 months. **a** shows the predominantly renal excretion of [^{68}Ga]Ga-PSMA-I&T with high activity in the urinary bladder and low uptake in the liver. **b** demonstrates the predominantly hepatic excretion of [^{18}F]PSMA-1007 with low activity in the urinary bladder and high uptake in the liver.

bone pain [21]. Similarly, the EAU guidelines recommend this combination of morphological imaging and scintigraphy in high-risk prostate cancer (Gleason score ≥ 8 or PSA value > 20 ng/ or ≥ cT2c primary tumor) [22]. In contrast to this approach, PSMA hybrid imaging makes it possible to evaluate the primary tumor, the lymphatic vessels, the skeletal system, and the visceral organs (particularly in combination with contrast-enhanced CT/MRI) in one examination. Based on the authors' experience in the clinical routine, we would like to point out the disadvantages of separate imaging/skeletal scintigraphy, which are often performed at different locations and times. There is consequently a risk of the separate examinations not being viewed together, resulting in unclear assessments. Disadvantages regarding the availability of the hybrid imaging method compared to conventional imaging must be mentioned. Nonetheless, as a result of the increasing evidence in the literature regarding the benefits of PSMA hybrid imaging, the current S3 guidelines include information on the diagnostic superiority of PSMA-PET/CT for detecting metastases. However, use of the method is currently only a "can recommendation" for patients with high-risk cancer [21]. A leading reason for the inclusion of the PSMA-PET/CT in the guidelines was the randomized controlled proPSMA study. In this trial, PSMA-PET/CT demonstrated a significantly higher sensitivity (85 % vs. 38 %) and specificity (98 % vs. 91 %) in high-risk patients for the detection of metastases than the combination of CT and skeletal scintigraphy [23]. Superiority of PSMA hybrid imaging compared to conventional methods in the primary staging of high-risk patients was

also seen in the PROSTAGE study [24]. However, if only the diagnostic performance in the detection of lymph node metastases compared to histology is taken into consideration, a lower sensitivity (approx. 40 %) with a consistantly high specificities (95–98 %) were seen in the following prospective studies [25, 26]. An important reason for this is the limited resolution of PSMA-PET/CT resulting in low detection rates of micrometastases in small lymph nodes. However, the method still has a solid positive predictive value (54–87 %) [25, 26].

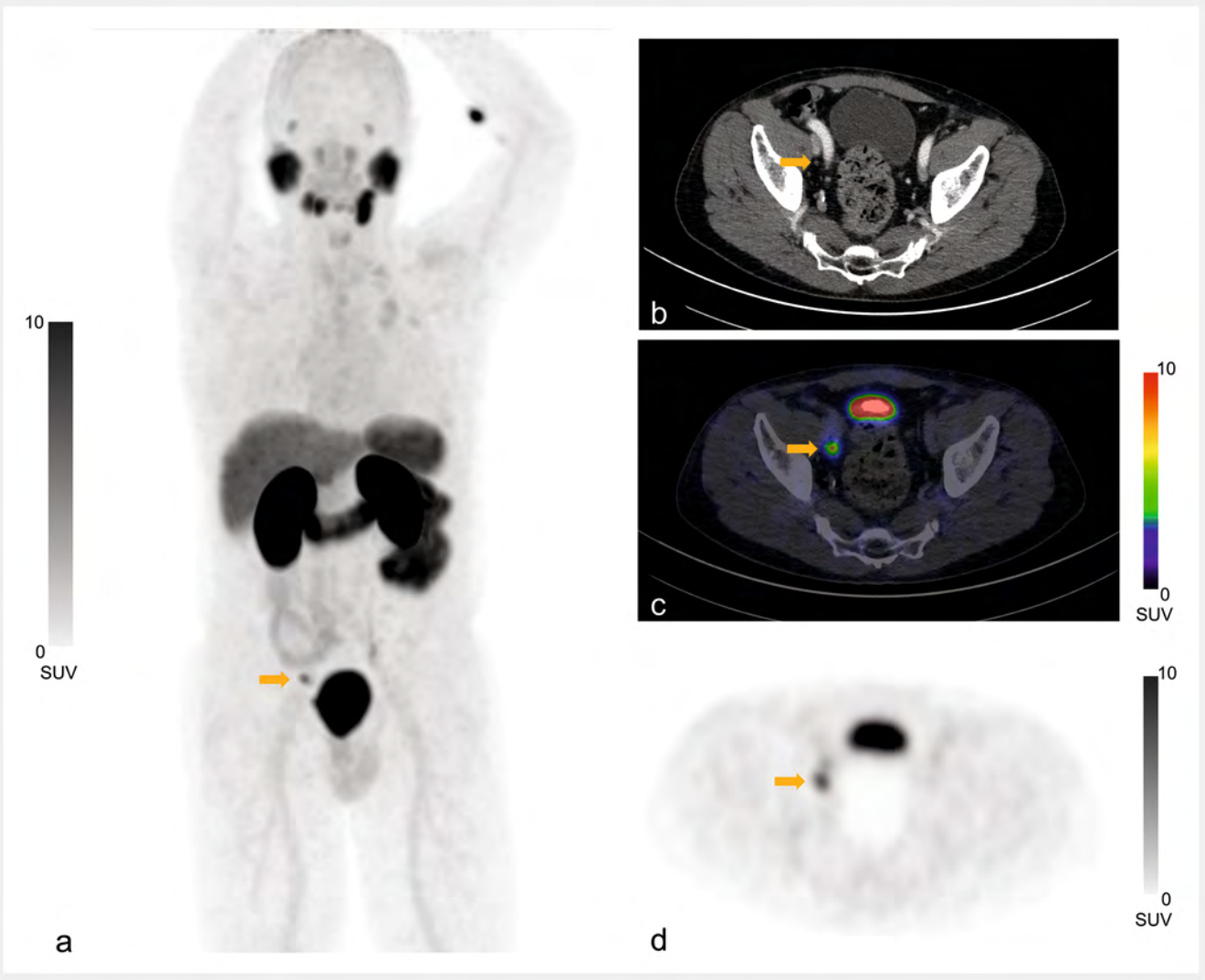
In summary, the strength of PSMA hybrid imaging is not the exclusion of metastases but rather the detection of metastases outside the standard treatment field so that treatment concepts can be optimized. Its influence on clinical end points like PCa-specific survival is not yet known. In addition, there is currently insufficient evidence regarding its value in cancers with a low risk profile, e. g., for active surveillance.

Biochemical recurrence of prostate cancer

In spite of the generally good prognosis of prostate cancer compared to many other malignancies [2], a significant number of patients experience a recurrence [27, 28]. Biochemical recurrence (BCR) is defined as an increase in PSA to > 0.2 ng/ml after radical prostatectomy or > 2 ng/ml above the nadir after primary radiation in at least two measurements [21] and is the currently most common indication for PSMA-PET. In the case of BCR, PSMA-PET/CT is generally considered a “can recommendation” [21]. The EAU also strongly recommends PSMA-PET/CT after primary radiation [22]. Both guidelines emphasize the need for a therapeutic consequence of hybrid imaging [21, 22]. Locally limited tumor manifestations (local recurrence and/or locoregional lymph node metastases) as well as transition to a systemic disease with distant metastases should be considered as causes of a new increase in PSA value. To differentiate between these entities, clinical parameters like the initial Gleason score, the time from primary therapy to BCR, and the PSA doubling time are currently taken into consideration [21]. The use of skeletal scintigraphy to diagnose recurrence is extremely limited since it can usually only detect metastases in the case of highly elevated PSA values or a rapid increase in PSA [29]. It should therefore only be used in symptomatic patients or at a PSA > 10 ng/ml [21]. Retrospective studies showed a significantly higher sensitivity and specificity of PSMA-PET/CT compared to skeletal scintigraphy in the detection of metastases [30]. Moreover, PSMA hybrid imaging is not limited to the diagnosis of bone metastases and can identify correlates of a BCR already in the early course of the disease. According to a large meta-analysis, PSMA-PET/CT yielded a positive result in 45 % of cases at a PSA increase to 0.2–0.49 ng/ml. Increasing PSA values resulted in improved detection rates so that a pathological correlate of BCR could be detected in 95 % of cases with a PSA > 2.0 ng/ml [31] (▶ **Fig. 3**). Newer prospective studies confirmed these high detection rates at low PSA values [32, 33], which can be relevant for further treatment decisions. According to the guidelines, patients with BCR after prostatectomy should be offered salvage radiotherapy as early as possible (PSA < 0.5 ng/ml) [21]. Prospective studies were able to show that treatment decisions in the case of BCR were influenced by information from PSMA hybrid imaging in > 30 % of cases [33–35]. It is important to mention that a negative examination should not delay salvage therapy [21, 22]. Similar to primary staging, patients who will not benefit from the usual treatment concepts can be identified with PSMA hybrid imaging. The risk of performing misguided treatments like salvage radiation in the case of undetected metastases outside the pelvis or systemic treatment in the case of locoregional disease can be minimized by precise imaging. If the increasing number of urological and oncological treatment options in the case of recurrence (e. g., watchful waiting, salvage radiotherapy, surgical treatment of metastases, or hormone therapy/chemotherapy) is taken into consideration, imaging can make a significant contribution to the individual treatment decision. This is reflected particularly in current treatment strategies for oligometastases. Metastasis-directed therapy treats metastases in a targeted manner with radiation or surgical methods and may delay the need for systemic treatment. A retrospective study by Steuber et al. showed that metastasis-directed therapy extends cancer-specific survival compared to androgen deprivation therapy (ADT) [36]. With the higher accuracy of PSMA-targeted hybrid imaging, it can be assumed that treatment results will further improve. A post-hoc analysis of the prospective ORIOLE study showed a significant extension of progression-free survival when all PSMA-positive lesions were consolidated by using targeted radiation [37]. The association between PSMA imaging and intervention is even stronger in radioguided surgery (RGS). For this purpose, patients with PSMA-positive metastases preoperatively receive γ-emitting radioligands like [^{99m}Tc]Tc-PSMA-I&S in order to identify these lesions intraoperatively using a γ-probe. While no lymph node metastases could be detected in salvage lymph node dissection without PSMA labeling in up to 20 % of cases, it was possible to lower the number of negative results to approx. 6 % via PSMA-RGS [38]. Initial results regarding clinical end points of metastasis-directed therapy are promising. However, prospective studies regarding final evaluation of these techniques are still needed.

Imaging and therapy with PSMA radioligands “theranostics”

As an alternative to the mentioned radionuclides to date, PSMA inhibitors coupled with α- or β-emitters have also been developed for therapeutic purposes. The ability of a PSMA ligand to be used both in treatment and diagnosis is the basis of “theranostics”. The substances most commonly used for this purpose are PSMA-617 [39] and PSMA-I&T [40] labeled with lutetium-177 (^{177}Lu), a β$^-$-emitter with a half-life of approx. 6.6 days. [^{177}Lu]Lu-PSMA-617 (Pluvicto) was approved by the European Medicines Agency at the end of 2022 as a drug for treating metastasized castration-resistant prostate cancer (mCRPC) [41]. PSMA radioligand therapy (PSMA-RLT) can be indicated in mCRPC patients with disease progression based on the recommendation of an interdisciplinary tumor board after all treatment alternatives according to the guidelines have been exhausted [21]. The basis for PSMA-RLT is the presence of PSMA-positive lesions on pretherapeutic hybrid imaging, a sufficient bone marrow reserve, and adequate kidney

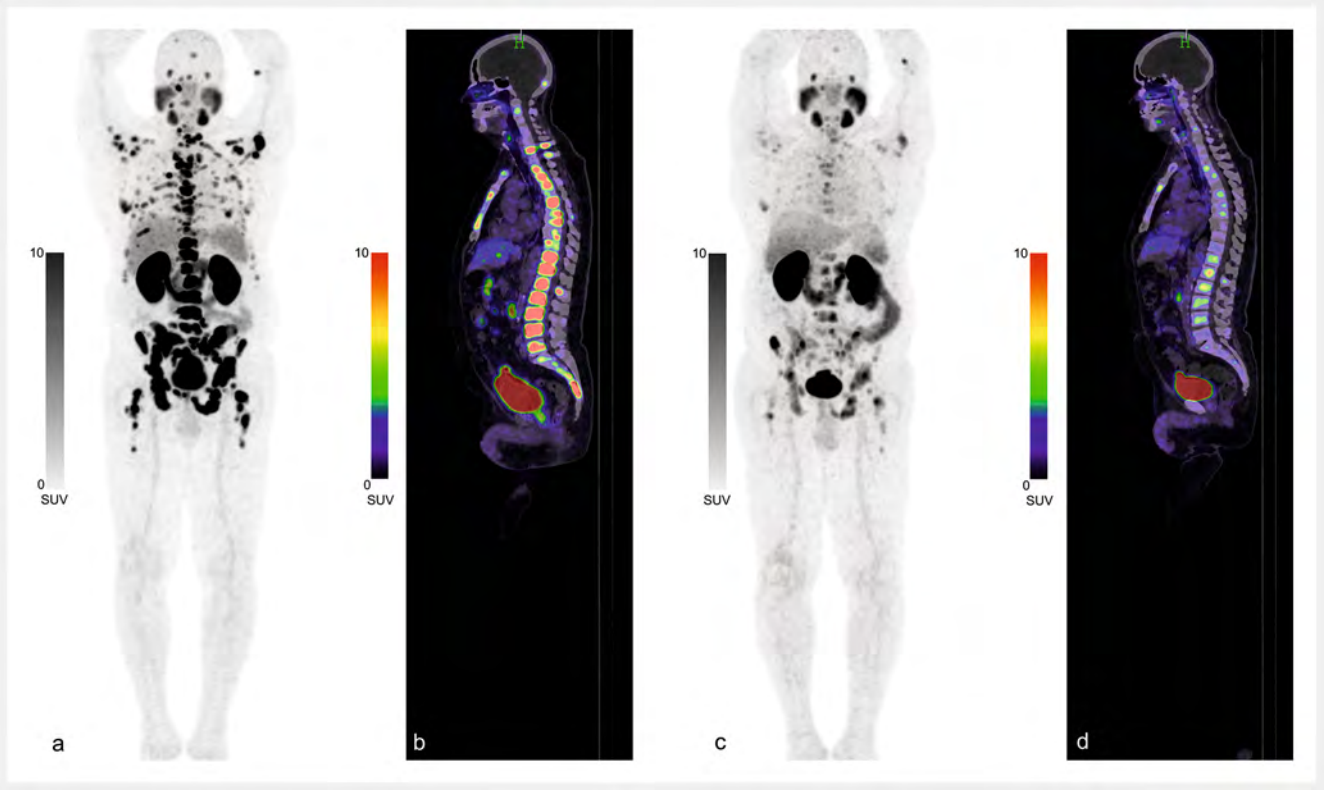


▶ **Fig. 3** [^{68}Ga]Ga-PSMA-I&T PET/CT of a patient with biochemical recurrence (PSA = 0.88 ng/ml) of prostate cancer 12 years after prostatectomy. Intense PSMA expression of a 6 mm lymph node (arrow) next to the external iliac vessels on the right. The corresponding histopathological evaluation confirmed prostate cancer metastasis. Visualization of the lesion on the maximum intensity projection (MIP) **a**, contrast-enhanced CT **b**, PET/CT fusion image **c**, and axial PET **d**.

and liver function [42]. Current data increasingly supports PSMA-RLT. In the prospective VISION trial, patient survival could be extended significantly by multiple months in the comparison of [^{177}Lu]Lu-PSMA-617 therapy to a control group with only best supportive care [43]. In relation to systemic chemotherapy with cabazitaxel, PSMA-RLT also yielded a better clinical and laboratory response with low toxicity [44]. PSMA-RLT is a palliative treatment concept with comparably few side effects that can delay disease progression (▶ **Fig. 4**).

Factors influencing the detection rate of PSMA-PET

PSMA expression in PCa cells is influenced by multiple factors. As mentioned above, there is an immunohistochemical correlation between the Gleason score and the expression of PSMA [5, 6]. Nonetheless, PET-negative findings can occur in relevant cancers (Gleason score ≥ 7). One possible reason for this is a heterogeneous PSMA expression with too many PSMA-negative cells [45, 46]. Although the amount of PSMA-negative PCa cells decreases with an increasing Gleason score, relevant PSMA-negative areas are also seen in some higher-grade tumors [45, 46]. A possible cut-off at which an increased probability of a negative PSMA-PET would be expected has not yet been defined. However, it must be assumed that a single factor like the PSMA expression pattern is usually not sufficient for a valid assessment. Multiple parameters are needed to detect PCa. The PSA level represents a further component. A positive correlation between PSA level and the detection rate of PSMA-PET, particularly in relation to BCR, has been seen in multiple studies [31]. The same is true for the PSA doubling time. Current prospective studies showed a higher rate of PET-positive findings in patients with a rapid increase in PSA [33, 35].



▶ **Fig. 4** [^{68}Ga]Ga-PSMA-I&T PET/CT of a patient with disseminated prostate cancer metastases to the bones with high PSMA expression. PET/CT before **a** and after **b** 2 cycles of [^{177}Lu]Lu-PSMA-617. Decrease of the PSA after therapy from 84 ng/ml to 23 ng/ml.

In addition to these influencing variables of the tumor, PSMA expression can be modulated iatrogenically by ADT. Androgen receptors play a central role in tumor development and tumor regulation in PCa. Androgens suppress PSMA transcription. Conversely, ADT upregulates PSMA expression [47]. However, the clinical picture is significantly more complex. Studies to date have shown both increases and decreases in PSMA expression on PET/CT during short-term ADT lasting a few days to weeks [48, 49]. Increased PSMA expression together with a decrease in tumor volume during treatment is a possible reason for this. In accordance with this theory, long-term ADT in castration-sensitive patients results in a decrease in positive lesions on PSMA-PET [50]. PSMA-positive lesions that are still visible in these cases could thus be a first indication of castration-resistant cell clones [50]. On the whole, the effect of ADT on PSMA expression is extremely complex and there are currently insufficient studies to be able to determine which changes can be expected during treatment. Therefore, a consensus statement by the EAU and the European Association of Nuclear Medicine (EANM) recommends using PSMA-PET either before the start of systemic therapy or at the earliest 3 months after the start of ADT in hormone-sensitive patients [51].

Summary

The establishment of PSMA radioligands marks a milestone in the diagnosis of prostate carcinoma. Their superior accuracy compared to previous methods has already had a significant effect on the development of new treatment methods and concepts. High-quality long-term studies of the effects of PSMA-PET on the prostate cancer-specific survival or the overall survival of patients are not yet available but are expected in the coming years.

Conflict of Interest

The authors declare that they have no conflict of interest.

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