short review

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Imaging and therapy targeting PSMA receptors for enhanced vision and precise treatment

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Summary In Europe, it is estimated that more than 65,000 men die each year from the consequences of advanced and metastatic prostate cancer (PCa). Currently, approximately 3.2 million European men are living with PCa. While the majority of PCa patients have favorable outcomes, the 5-year relative survival rate for those with metastatic PCa is only 32%. Recent advances in the diagnosis of PCa have been boosted by the introduction of the prostate-specific membrane antigen (PSMA), which might identify patients with the most aggressive form of the disease. Molecular imaging with positron emission tomography (PET) targeting PSMA receptors (PSMA-PET) has utterly revolutionized the diagnosis and staging of PCa; however, its application is still under debate. On the one hand, there has been little progress in recent years in surpassing the limitations of androgen deprivation therapy (ADT), the backbone of metastatic PCa treatment. Adding additional systemic therapy became standard in the last few decades. Current ADT is only transiently effective, and patients eventually progress during ADT treatment, a condition known as castration-resistant PCa (CRPC). On the other hand, radioligand therapy (RLT) targeting these PSMA receptors, most commonly used in the studies [^{177}Lu]lutetium-PSMA-617, has been available for this cancer stage for nearly a decade and has been recently incorporated into the European Association of Urology (EAU) guidelines as a robust treatment option for patients with metastatic CRPC.

Keywords Prostate-specific membrane antigen · Prostate cancer · Tumor staging · PSMA imaging · PSMA PET-CT · Theranostics

Background

PSMA is the abbreviation for prostate-specific membrane antigen, which is also known as glutamate carboxypeptidase type II. The protein is a type II membrane protein consisting of a total of 750 amino acids, located on chromosome 11 and was first discovered in the late 1980s. The PSMA protein is expressed in inflammatory, benign and malignant prostate tissue. However, in prostate cancer (PCa) and especially in the aggressive types with high Gleason score (GS), a score defines the pathological grading of the malignant prostate cell, or in metastatic and hormone-refractory PCa, PSMA levels are elevated up to thousand-fold the normal value [1]. Therefore, since its discovery, it has become an attractive target for a wide range of diagnostic imaging modalities and therapies in PCa. Today, molecular theranostics targeting this peptide are increasingly used clinically for diagnosis and treatment to improve treatment management and care of patients with PCa.

Current utility of PSMA-PET examination in patients with PCa

Molecular imaging with positron emission tomography (PET) that targets PSMA receptors (PSMA-PET) has completely reshaped the diagnosis and staging of PCa and is widely considered the most sensitive investigation currently available for men with PCa [2, 3]. At present, several PSMA ligands labeled either

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with [18F]fluorine or [68Ga]gallium are available for diagnostic purposes in various cohorts of patients with PCa. In general, the diagnostic performance of [18F]- and [68Ga]-based PSMA-PET examinations is quite comparable, and both tracers yield almost similar comprehensive diagnostic information. However, nonspecific uptake of the PSMA tracer in benign lesions such as ganglia, benign bone lesions, and lymph nodes are more frequently seen with [18F]-based PSMA PET imaging than with [68Ga]-based PET examination, especially with [18F]-PSMA-1007 [4]. Still, the most commonly used tracer clinically and investigated in studies is [68Ga]Ga-PSMA-11, which has even been approved by the US Food and Drug Administration (FDA) since 2020, and more recently by the European Medicines Agency (EMA).

One of the main clinical indications for PSMA-PET examinations, which is also mentioned in the recent guidelines of the European Association of Urology (EAU), is the primary staging of patients with high-risk PCa. These are patients who, at the time of tumor diagnosis, have an initial PSA level of ≥ 20 ng/ml or a pathologic International Society of Uropathology (ISUP) grade of 3 to 5; this classification groups the PCa depending on the GS, or a clinical stage of T3 or higher, i.e., the tumor has crossed the prostate capsule. In this regard, outcomes of prior studies have revealed that performing a PSMA-PET scan for tumor staging may alter the planned therapeutic approach in these patients due to higher sensitivity for detecting metastases [5] and may be a suitable substitute for conventional imaging with higher accuracy than the combined results of computed tomography (CT) and bone scans [6]. Moreover, PSMA-PET examination is associated with a higher percentage of treatment changes and fewer equivocal results than traditional imaging modalities. In addition, radiation exposure to patients is significantly lower with PSMA-PET-CT examination applying a low-dose CT scan protocol than conventional imaging using both a diagnostic CT scan protocol with intravenous contrast and bone scan [7]. However, results of PSMA PET examination with subsequent exact localization of the disease and upstaging in high-risk PCa patients to metastatic patients need to be interpreted with caution, as there is still lack of outcome data on the impact of treatment changes after PSMA-PET on long-term overall survival in these patients.

Another indication of PSMA PET examination is patients with biochemically recurrent PCa. In this context, the current EAU guidelines advise a PSMA PET scan in every case of proven biochemical recurrence in patients in whom the results of the scan might influence the subsequent treatment decisions. Indeed, the detection rate of PSMA-PET increases with higher PSA levels and higher GS and its sensitivity can reach over 40%, even with a PSA level of less than 0.2 ng/ml [8].

Furthermore, the presence of PSMA-positive lesions in PSMA-PET scan is prerequisite for the eligibility of the PSMA-targeted radioligand therapy (RLT) in patients with metastatic castration resistant prostate cancer (mCRPC) [9]. An additional essential role of PSMA-PET examination is to accurately assess lesions of patients with oligometastatic PCa who have been treated with radiotherapy (RT). Some clinical phase II studies have found PSMA-PET-guided RT to be an appropriate treatment option for patients with oligometastatic PCa or oligometastatic CRPC to delay additional systemic therapies even with androgen deprivation therapies (ADT) [10, 11]. Metastases treated with PSMA-PET-based single fraction radiosurgery can achieve excellent local control of the disease with minimal radiation toxicity [12].

Radionuclide therapy targeting PSMA receptors

PSMA-RLT has been successfully available for nearly a decade. PSMA is usually labeled with a beta emitter such as [177Lu]lutetium ([177Lu]), which allows targeted irradiation and thus damage to the prostate tumor cells. However, the anti-tumor efficacy of [177Lu]Lu-PSMA may decrease over time, and it may eventually lead to the use of [225Ac]actinium-PSMA with alpha radiation that is capable of damaging tumor cells even if they are beta radiation resistant [13].

[177Lu]Lu-PSMA therapy was first offered nearly a decade ago as the last treatment option for mCRPC patients after all other available standard therapies had failed. Since then, many studies have retrospectively demonstrated the broad anti-tumor efficacy as well as the good tolerability and beneficial clinical outcomes of this therapy using various therapeutic protocols [14, 15]. In October 2019, we also published the results of the Vienna therapy regime using a homogenous protocol among all treated mCRPC patients comprised of 3 cycles of 7.4 MBq every 4 weeks [16]. The results could identify 79% of patients who responded to therapy with 58 and 35% having a PSA drop of > 50 and > 80%, respectively, 1 month after the last treatment cycle.

Subsequently, the results of the prospective Vision and TheraP trials were published in 2021 [17, 18]. The Vision study, sponsored by Novartis Pharmaceuticals AG, demonstrated a 38% lower risk of death and a 60% lower risk of radiographic disease progression or death in mCRPC patients who received [177Lu]Lu-PSMA-617 therapy and standard of care therapy compared with mCRPC patients in the control arm who treated with standard of care alone. On the other hand, the TheraP trial, a multicenter, unblinded, randomized phase II study involved several centers in Australia, demonstrated significantly higher PSA response with fewer serious adverse events among mCRPC patients assigned to receive [177Lu]Lu-PSMA-617 therapy than in patients randomized for chemotherapy with cabazitaxel at the same stage of disease.

On March 23, 2022, following the results of the Vision trial, the FDA approved [^{177}Lu]Lu-PSMA-617 Pluvicto® (Novartis AG, Basel, Switzerland) for the treatment of adult men with PSMA-positive mCRPC previously treated with androgen receptor pathway inhibitors (ARPI) and taxane-based chemotherapy. Also, the new 2023 EAU guidelines strongly recommend the use of [^{177}Lu]Lu-PSMA-617 therapy in patients with mCRPC. The current eligibility criteria for this therapy according to these guidelines are: mCRPC patients with one or more metastatic lesions that strongly express PSMA (exceeding uptake in the liver) on diagnostic PSMA-PET scan who have been previously treated with at least one ARPI and at least one taxane-based chemotherapy.

Furthermore, after these promising results of the Vision study, additional phase III studies have been initiated to prove the effectiveness of [^{177}Lu]Lu-PSMA-617 therapy in mCRPC patients with other disease states, for example, the PSMAddition study (NCT04720157) and PSMAfore study (NCT04689828). Both are multicenter studies that also involve three clinical centers from Austria.

Meanwhile, there are dozens of national and international registered randomized or single-arm trials of PSMA-RLT such as NALuPROST (NCT04297410) and LuTectomy (NCT04430192) that offer PSMA-RLT as neoadjuvant therapy for patients with newly diagnosed hormone-sensitive high-risk PCa. Other trials are for patients with different advanced stages of PCa such as UpFrontPSMA (NCT04343885) and LuCAB (NCT05340374) trials that offer PSMA-RLT in combination with taxane-based chemotherapies, LuPARP (NCT03874884) combined PSMA-RLT with the PARP inhibitor olaparib, and the EVOLUTION trial combined PSMA-RLT with immunotherapies such as ipilimumab and nivolumab. Although the results of most of these studies have not yet been published, it is expected that they may provide insights into the relevance of PSMA-RLT for the treatment of patients with different stages of PCa.

Future perspectives of PSMA

PSMA-PET procedures for initial staging are known to perform better in terms of higher sensitivity and accuracy compared to standard staging. Currently, the clinical impact of this scan is under investigation in several trials, for example, in Australia the results of ANZCTR study (trial no. 12617000005358) with the aim to evaluate the prognostic value of PSMA-PET scan regarding disease-free status are awaited. Several studies are also ongoing in patients with biochemical recurrence of PCa to evaluate the efficacy and clinical impact of PSMA-PET staging. After the first results of PSMA-PET-guided metastases-directed therapy were published and seemed to be promising for delaying ADT, effectiveness of early androgen receptor targeted agents (ARTA) therapy has been under investigation based on PSMA-PET findings after treatment with curative intent.

Furthermore, the role of PSMA-PET in metastatic pretreated PCa is actually closely connected to the planning of radionucleotide therapy. After the first positive results of the Vision trial in later-line mCRPC, by the end of 2022, Novartis announced that [^{177}Lu]Lu-PSMA-617 therapy was also effective in the first-line mCRPC setting in the PSMAfore trial; final data are still awaited. In addition, similar to the positive outcome of the pilot study with ID: NCT03828838 on metastatic hormone-sensitive prostate cancer (mHSPC) [19], the results of the Bullseye study (NCT04443062) are expected to demonstrate the efficacy of PSMA-RLT in oligometastatic hormone-sensitive PCa with ≤ 5 metastases. Also, currently under investigation are immunotherapy/chemotherapy/ARTA combination therapies of [^{177}Lu]Lu-PSMA-617 in mCRPC, for example, in NCT03874884, NCT03805594, NCT04419402, NCT05340374 and NCT05150236 trials, as therapy intensification is currently under intense investigation in all disease states in PCa.

Conclusion

Prostate-specific membrane antigen (PSMA) is an interesting theranostics targeted molecule for diagnosis and therapy of different cohorts of patients with prostate cancer (PCa). PSMA positron emission tomography (PET) is a highly sensitive examination that can change treatment decisions in the primary staging of PCa and is capable of detecting metastases in biochemical recurrence, even at very low PSA levels. PSMA radioligand therapy is perhaps promising not only for patients with metastatic castration resistant PCa, but also for patients with an earlier stage of PCa.

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Conflict of interest S. Rasul and S. Korn declare that they have no competing interests.

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