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PSMA PET and radionuclide therapy in prostate cancer

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Abstract

Prostate cancer (Pca) is the most common malignancy in men and a major cause of cancer death. Accurate imaging plays an important role in diagnosis, staging, restaging, detection of biochemical recurrence, and for therapy of PCa patients. Since no effective treatment is available for advanced PCa, there is an urgent need to develop new and more effective therapeutic strategies. In order to optimize treatment outcome, especially in high risk PCa patients, therapy of PCa is moving rapidly towards personalization. Medical imaging, including positron emission tomography (PET)/computed tomography (CT), plays an important role in personalized medicine in oncology. In the recent years, much focus has been on prostate specific membrane antigen (PSMA) as a promising target for imaging and therapy with radionuclides, since it is upregulated in most PCa. In the prostate, one potential role for PSMA PET imaging is to help guiding focal therapy. Several studies have shown great potential of PSMA PET/CT for initial staging, lymph node staging, and detection of recurrence of PCa, even at very low PSA values after primary therapy. Furthermore, studies have shown that PSMA PET/CT has a higher detection rate than choline PET/CT. Radiolabeled PSMA ligands for therapy show promise in several studies with metastatic PCa, and is an area of active investigation. The “Image and treat” strategy, with radiolabeled PSMA ligands, has the potential to improve the treatment outcome of PCa patients, and is paving the way for precision medicine in PCa. The aim of this review is to give an overview of recent advancement in PSMA PET and radionuclide therapy of PCa.

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Keywords

Prostate cancer; prostate specific membrane antigen; PSMA; PET/CT; radioimmunotherapy; personalized medicine; precision medicine

Introduction

Prostate cancer (PCa) is the most common cancer diagnosed in men worldwide, leading to substantial morbidity and mortality [1]. Despite significant advances in PCa therapy in the past decades, many men, particularly those with high-risk disease, will have PSA recurrence, develop symptomatic local or distant disease, or die from their PCa. It is well-known that PCa is a heterogeneous disease, that even can be heterogeneous in the prostate of the same patient. In order to optimize treatment outcome, especially in high risk PCa patients, therapy of PCa is moving rapidly towards personalization [2]. Medical imaging has always played an important role in personalized medicine, which aim to deliver the right treatment to the right patients at the right time [3]. Accurate imaging plays an important role in diagnosis, staging, restaging, detection of biochemical recurrence, and for therapy of PCa patients [3,4]. In the recent years, much focus has been on prostate-specific membrane antigen (PSMA) as a target for imaging and therapy in PCa [5–11]. PSMA is highly expressed in all PCa, and the expression increases with tumor aggressiveness, metastatic disease and recurrence [9,11,12]. However, despite its name, PSMA is also expressed in neovasculature of other tumors incl. bladder, pancreas, lung and kidney cancers. Furthermore, PSMA is expressed in normal healthy tissue such as the salivary glands lacrimal glands, proximal renal tubules, epididymis, ovary, the luminal side of the ileum-jejunum system, and astrocytes and the central nervous system [7,13]. Normal prostatic tissue express only small amount in the apical epithelium of secretory ducts [12]. Several studies show promising results of PSMA positron emission tomography(PET)/computed tomography (CT) for evaluation of high risk PCa patients and for detection of recurrence after primary therapy, and shows great promise for improving the management of patients with PCa [6,14]. Moreover, PSMA can also serve as a target for therapeutic applications. Currently, several PSMA ligands are being investigated for their potential in theranostic applications in PCa, and studies indicate that radiolabeled PSMA ligands are effective as theranostic and therapeutic options in PCa [14]. Targeting PSMA with PET imaging and radionuclide therapy is a step towards personalized medicine in PCa [9]. The aim of the review is to give an overview of recent advances in PSMA PET and radionuclide therapy of PCa.

PSMA PET ligands

PSMA is a type II transmembrane protein which has a small intracellular and transmembrane portion and a relatively large extracellular portion [15]. This extracellular domain is the target for most PSMA PET ligands. PSMA is a product of the FOLH1 (Folate hydrolase 1) gene and although its role in the progression of PCa is unknown, it is increasingly expressed in more aggressive tumors[16]. PSMA is found in the normal prostate, however, in normal prostate cells it tends to be within the cytoplasm and located on the apical side of the epithelium surrounding the ducts and thus is unavailable for binding

[17]. Cytoplasmic PSMA is a truncated form of the antigen and is known as PSM' and does not have folate hydrolase activity and therefore is not a target for PSMA PET ligands [18]. Neoplastic transformation of prostate cells results in the translocation of PSMA from the apical to the luminal surface of the prostatic duct where it becomes accessible on the outside of the cell for binding to ligands. There are two binding pockets of PSMA, a glutamate sensing pocket and a non pharmacophore binding pocket which together contain two Zn ions. Most PSMA PET ligands bind to one or both of these binding pockets [14].

The first PSMA directed radiolabeled ligands were antibodies. 7E11 or capromab, is a chimeric antibody that is the only approved commercial PSMA imaging agent (ProstaScint, Jazz Pharmaceuticals, USA). This agent has been used commercially for almost 20 years [19]. A chelate is conjugated to the antibody in order to bind ^{111}In , thus making capromab, a SPECT agent. In theory this agent could also be labeled with ^{89}Zr , however, there has been little interest in doing so because of the limitations of this antibody. Although it is the only approved agent it has numerous disadvantages. For instance, 7E11 only binds the internal domain of PSMA so that only cells with damaged cell membranes (e.g. dying cells) take up the agent. Also, the agent is excreted into the bowel and bladder and therefore, it can be difficult to interpret scans in the retroperitoneum. It is often combined with a $^{99\text{m}}\text{Tc}$ -labeled red blood cell study to identify vessels and distinguish vessels from tumor. Imaging is also very delayed, requiring 4–6 days before there is sufficient clearance of background tissue to get adequate diagnostic imaging. Because 7E11 is chimeric autoantibodies can develop against it, limiting its use in some cases. These challenges have led to the limited clinical use of 7E11 as a clinical agent. Nevertheless, it remains the only PSMA directed imaging agent currently commercially available.

More recently, the antibody, J591 was developed as an extracellular antibody imaging agent for PSMA. J591 is a humanized monoclonal antibody and thus, in theory should have less immunogenicity than 7E11. Developed at Cornell by Neil Bander, the agent has not yet been commercialized although many applications have been developed for it and it has been extensively tested in clinical trials [20]. J591 is typically chelated with the chelate DOTA which enables it to be labeled with ^{111}In and $^{99\text{m}}\text{Tc}$ (although the latter is too short lived to be useful). Recently J591 was labeled with ^{89}Zr and ^{64}Cu to make it a PET imaging agent by conjugating other chelates to the antibody [14]. When DOTA is used as the chelate J591 can also be used for targeted radionuclide therapy with ^{90}Y and ^{177}Lu . Promising results have been reported with this radioimmunotherapeutic agent [20].

The natural limitations of macromolecular antibodies include their slow clearance and the necessity to scan on a different day than the injection resulting in at least two trips for the patient and delayed results. Meanwhile, there has been a rapid development of high affinity small molecules, including peptides and peptidomimetics, that could be used as imaging or theranostic agents. There has been intense interest in the development of small molecular weight PSMA inhibitors that bind to the antigen with high affinity but also clear rapidly from background creating a pragmatic imaging window of 1–2 hours after injection. The leading example of this has been ^{68}Ga -DOTATATE which has been highly successful in somatostatin receptor (SSR) expressing tumors such as neuroendocrine tumors. In the case of PSMA as a target, three classes of PSMA inhibitors have been developed including those

that are phosphorous based, thiol based and urea based. Initial work in this field focused on the development of phosphonate and phosphate inhibitors including 2-phosphonomethyl pentanedioic acid or 2-PMPA [21]. Although this ligand was promising, it did not prove to have as high uptake as the urea based compounds and has largely been abandoned. Kozikowski was the first to recognize the importance of urea based PSMA inhibitors and developed the first synthetic and testing methods [22]. This class of PSMA inhibitors have exceptional affinity for PSMA resulting in high uptakes even within 1–2 hours of injection and have come to dominate the field. There are two basic radiolabeling approaches for urea based PET PSMA ligands, those designed to chelate ^{68}Ga and those that directly conjugate ^{18}F . In theory, ^{18}F , with its longer half life and the ability to be produced in large amounts in a cyclotron is more commercially viable. Moreover, the energy of emitted gamma rays is lower with ^{18}F resulting in images with higher resolution [11]. In contrast, ^{68}Ga must be obtained from a generator that is purchased at each site and then “milked” as needed. This requires a large upfront expenditure for a medical center and makes its use in smaller medical facilities not feasible. Moreover, only 1–3 doses can be obtained from a generator per day, limiting the number of potential scans (unless additional generators are also purchased). Thus, if a medical center wishes to perform more than 1–3 PSMA scans per day they must either invest in more generators or limit the number of scans they perform per day. Such an approach also requires a local radiopharmacy capable of sterile handling of radiolabeling process. The half life of ^{68}Ga is only 68 minutes vs. 110 minutes for ^{18}F making it more difficult to deliver from a central source and requiring a dedicated pharmacist or chemist if the agent is to be used locally. Nonetheless, in facilities that can manage a ^{68}Ga generator, the chemistry is quite simple and the chelate required for ^{68}Ga conjugation can also be used with therapeutic radioisotopes such as ^{177}Lu and Y-90, making the agent inherently more flexible. It is unclear which direction will ultimately become more popular and the answer may vary according to country, health care system and regulatory climate. The ^{18}F based urea compounds were initially developed at Johns Hopkins University by Martin Pomper, Ron Mease and colleagues [11]. The first generation agent was known as *N*-[*N*-(*S*)-1,3-dicarboxypropyl] carbamoyl]-4-[^{18}F]fluorobenzyl-L-cysteine (^{18}F -DCFBC). ^{18}F -DCFBC was evaluated in a small clinical trial at Johns Hopkins and demonstrated normal uptake in the bladder, kidneys, and liver [23]. A fair amount of background signal was observed in the blood pool likely due to protein binding *in vivo*. This created potentially unfavorable tumor to background ratios which have the effect of reducing sensitivity. Nonetheless, early results with ^{18}F -DCFBC showed that it was highly sensitive for local recurrence, nodal and bony metastases. For instance, ^{18}F -DCFBC was more sensitive for PCa bone metastases than conventional bone scan in patients prior to androgen deprivation therapy [23]. While it was very promising as a first generation agent, a second generation agent with superior affinity, faster clearance and much less background was developed and named ^{18}F -DCFPyl [24]. Data from the first study that compared ^{18}F -DCFPyl with the ^{68}Ga agent, ^{68}Ga -PSMA-HBED (discussed below) indicated a higher sensitivity for ^{18}F -DCFPyl of more than 21% [25]. ^{18}F -DCFPyl has been licensed by Progenics and is under development currently as a commercial ^{18}F based urea PSMA PET agent. In theory, this agent could be delivered to PET centers as a ready-to-inject formulation much as ^{18}F -FDG is currently delivered.

Among the ^{68}Ga based urea PSMA PET agents, the most widely used is Glu NH CO NH Lys (Ahx) HBED-CC (^{68}Ga -PSMA-HBED-CC). This agent has been extensively tested predominantly in Germany but is now being used in Australia, Denmark and India. It was first synthesized by Eder et al who recognized that HBED was a superior chelate due to its better thermodynamic stability compared to DOTA which is the most commonly used chelator [26]. The name derives from N,N'-bis[2-hydroxy-5-(carboxyethyl)-benzyl]ethylenediamine-N,N'-diacetic acid (HBED-CC) which acts as a highly thermodynamically stable chelate for ^{68}Ga [27]. ^{68}Ga -PSMA HBED-CC demonstrates rapid cellular internalization and high accumulation within tumors. Non target uptake is seen in the salivary glands, lacrimal glands, liver, spleen, small bowel and urinary tract [14]. The agent is readily labeled at room temperature with a fast reaction and excellent stability, making it easy to use in Nuclear Radiopharmacies as opposed to complex PET laboratories needed for ^{18}F labeling. Interestingly, it is also possible to fluorinate this compound. ^{68}Ga -PSMA HBED-CC has been used in hundreds of patients worldwide and has produced excellent imaging results. While HBED-CC is excellent at chelating ^{68}Ga it is less useful in conjugating therapeutic radioisotopes so that the general utility of this agent is reduced. This relates to the high selectivity of the complexing agent HBED-CC for ^{68}Ga , but not for therapeutic isotopes such as ^{177}Lu or ^{90}Y [27]. Thus, ^{68}Ga -PSMA HBED-CC has been widely used for PSMA PET imaging, mainly in Europe.

Another widely used PSMA ligand is ^{68}Ga -PSMA DKFZ 617 that addresses the limitation of ^{68}Ga -PSMA HBED-CC with regard to limited binding of therapeutic radioisotopes. "DKFZ" refers to Deutsches Krebsforschungszentrum, the German Cancer Research Center in Heidelberg, Germany where it was developed [28]. This agent consists of 3 parts: the glutamate-urea-lysine which binds to PSMA, the chelator, DOTA and a linker. DOTA is capable of binding several isotopes including ^{68}Ga , ^{177}Lu and ^{90}Y . The molecule's binding affinity is remarkably sensitive to small changes in the linker, and changes in the linker also influences the pharmacokinetic properties of the agent [29]. Thus, PSMA DKFZ 617 is a true theranostic inhibitor capable of both imaging and therapy using different radioisotopes. Interestingly, in Europe PSMA DKFZ-617 is available commercially from ABX Advanced Biochemical Compounds although it is not formally approved for human use, it can be used under the direction of a physician for patients with cancer who require imaging and/or therapy [28]. ^{177}Lu has been widely used with PSMA-DKFZ 617 because it is predominantly a beta emitter with lower amounts of gamma radiation which reduces the need for radiation protection, lowers bone marrow toxicity and reduces the need for isolation and hospitalization [28,30]. Thus, PSMA DKFZ 617 utilizes the well known chelate, DOTA to bind a variety of PET emitters including therapeutic radiometals.

A related agent with similar properties is ^{68}Ga -PSMA DOTAGA FFK (Sub-Kue) for imaging and therapy (I&T) which is generally known as ^{68}Ga -PSMA I&T [31]. In this agent DOTAGA is substituted for DOTA as the chelate. Since the two chelates are similar in their ability to bind radiometals, this agent is also used for both imaging and theranostic purposes. This agent demonstrates high PSMA affinity and enhanced internalization efficiency compared to other PSMA PET agents. This agent can be produced in a fully automated GMP procedure.

Thus, there are a variety of approaches to PET PSMA ligands that are available. All of them demonstrate good sensitivity for metastatic PCa. Certainly, some differences will emerge among them. Thus, there are two major unknowns surrounding PET PSMA probes: Which of the available probes are the best performing? Which will be available commercially? The answer to these two questions may not be the same. The current literature is replete with small to moderate sized studies from single institutions using one of the above agents. There is a real dearth of information comparing different agents. Moreover, the quality of these early studies are unlikely to provide sufficient levels of proof for regulators to approve these agents. Therefore, carefully performed, multi-institutional trials comparing different agents will need to be performed. The question of commercialization is also difficult. ^{68}Ga and ^{18}F based PSMA ligands have completely different business models and assumptions. Meanwhile, most health care systems around the world are trying to pare down services and place high demands on new, expensive diagnostic agents. These factors will conspire to slow the rate of widespread adoption of PSMA based PET imaging.

PSMA PET for detection of primary tumor

The current standard of care world wide for the diagnosis of PCa is the 12 core systematic biopsy performed under transrectal ultrasound (TRUS). This approach has been widely criticized for overdetecting indolent lesions and under-detecting aggressive lesions. Thus, over the past 5 years there is a growing interest in the use of magnetic resonance imaging (MRI) and MR-TRUS fusion biopsy. Studies using MR-TRUS fusion biopsy have shown higher rates of intermediate and high risk cancer detection and lower rates of indolent or low grade cancer, at least, in part, overcoming the limitations of the 12 core systematic biopsy [32]. Although the use of MRI has been criticized as being too expensive, there is increasing emphasis on rapid, streamlined MRIs that can be performed more cost effectively. Therefore, given its cost and limited availability, PSMA PET imaging will likely have little impact on the majority of patients who are diagnosed with PCa. However, for some patients with high risk primary disease, PSMA PET imaging will be very useful. Because PSMA expression increases with increasing aggressiveness of the primary, PSMA PET imaging will not be useful in the majority of low-intermediate grade tumors. Thus, it is very unlikely to contribute in cases where the PSA continues to rise but MR guided biopsies are negative. Also, because PSMA PET will be insensitive to low grade cancers it is unlikely to contribute to active surveillance and probably would not be cost justified. On the other hand, more aggressive primary tumors are more likely to be positive on PSMA imaging (figures 1 and 2). Therefore, this study could be used to determine which patients justify intervention.

Moreover, in patients with large, high risk prostate cancers, accurate staging is important to correctly select proper clinical management. Today, patients are staged with conventional bone scans and CT scans. Both are relatively insensitive for early metastases. PSMA PET will have a role in detecting early bone lesions and especially nodal disease unsuspected by conventional imaging. The presence of positive nodes or bone metastases greatly alters the clinical management of patients. Even in the case where just nodes are involved, the PSMA PET scan could be useful in directing surgeons to remove involved node groups, thus, enabling a more targeted lymph node resection.

One potential role for PSMA PET imaging in primary diagnosis is to help guide focal therapy. Although MRI is excellent at identifying the center of a PCa, it is less good at defining the margins. For biopsy purposes, the ability to hit the tumor is all that matters. However, for treating tumors, all the tumor must be ablated. PSMA PET imaging could be very useful in defining the true extent of the PCa once it has been detected by MRI-TRUS fusion biopsy. Then, once ablation, by radiofrequency, laser, cryotherapy, electroporation or any other number of treatment modalities is complete, the patient could be monitored for recurrence with PSMA PET imaging along with serial PSA testing [33]. This approach would overcome the inherent limitations of using MRI in patients who have undergone focal therapy, in whom significant anatomic alterations have occurred. Interpretation of such scans can be difficult. In contrast, PSMA PET imaging would be relatively unaffected by post treatment artifacts as the uptake of the agent would be driven by the presence of residual cancer. Thus, PSMA PET imaging could play an important role in the focal therapy of PCa, a treatment that is likely to become more common with time. Recently, simultaneous ^{86}Ga -PSMA PET/MRI was compared with mpMRI and PET alone, and was found superior for localization of primary PCa. However, further prospective studies are necessary and warranted to evaluate the role of simultaneous PSMA PET/MRI in PCa [34].

PSMA PET in primary staging

Metastases from PCa are most common seen in LNs and bones in the early phase of metastatic disease, followed by liver and lung metastase in the later phase [35]. When PCa is confined to the prostate gland, it has an excellent chance for cure. However, the presence of LN metastases represent a significant adverse prognostic factor [36]. The 5-year survival rate depends on the total number of metastatic LNs ranging from a 5-year survival of 75–80 % in patients with a single metastatic LN to only 20–30 % in patients with more than five metastatic LNs [37]. Accurate LN staging is critical for treatment planning and therapy monitoring. Detection and exact location of LN metastasis before primary treatment, as well as in recurrent PCa, is important for the choice of the suitable treatment strategy and thus for patient prognosis. Lymph node involvement in PCa is commonly treated initially with androgen deprivation therapy and radiation therapy to the pelvis. Lymph node status (N staging) need be assessed only when potentially curative treatment is planned. Patients with stage T2, PSA <10 ng/ml, a Gleason score ≤ 6 , and <50% positive biopsy cores have a <10% likelihood of having LN metastases and can be spared LN evaluation [38]. Currently, surgical pelvic lymph node dissection (PLND) with histopathological examination is the standard of care and the most commonly used method of LN staging [38,39]. However, PLND can be challenging and with risk of complications like lymphocele, infection, deep venous thrombosis, bleeding, and urinary retention that may result in prolonged hospital stays [40]. Thus, there is a need for non-invasive imaging modalities for accurate N-staging in PCa.

For conventional imaging modalities like contrast-enhanced CT and MRI, the definition of suspicious LN's is based mostly on size criteria. The most commonly used threshold for enlarged LNs is 10 mm in short axis diameter, but recommended thresholds vary from 8 mm to 15 mm [39]. However, almost 80% of metastatic LNs in PCa are smaller than the threshold size of 8 mm and, therefore, cannot be detected using morphological imaging [41].

Thus, using size criteria alone often leads to incorrect staging with CT and MRI with understaging the disease, because small LNs may harbor microscopic disease. In a large review on the diagnostic performance of CT and MRI using RECIST criteria for detection of LN metastases in PCa, the pooled sensitivity and specificity for CT were 0.42 (95 % CI 0.26–0.56) and 0.82 (95 % CI 0.80–0.83), respectively, compared to 0.39 (95 % CI 0.22–0.56) and 0.82 (95 % CI 0.79–0.83) for MRI [41]. Thus, both CT and MRI have low sensitivities in LN staging in PCa. The use of DWI in MRI may improve the detection rate of LN metastases, but overlap between malignant and benign lesion have been reported [42].

In order to improve the the detection rate of LN metastases in PCa several PET isotopes have been tested in clinical studies, including ^{18}F -choline, ^{11}C -choline, ^{11}C -acetate, ^{18}F -fluciclovine (FACBC), with choline being the most common used isotope. However, a meta-analysis of choline PET for detection of LN metastases, including 10 studies with a total number of 441 patients, demonstrated only moderate pooled sensitivity of 49%, but with a specificity of 95% for [43]. Similar results with relative low sensitivities and high specificities for detection of LN metastases have been found in other choline PET/CT studies [44–46]. It has been demonstrated that 98 % of LN metastases of PCa show very high expression of PSMA [47]. Recently, Herleman et al, prospectively evaluated the accuracy of ^{68}Ga -PSMA PET/CT for LN staging prior to PLND with histology in 20 patients with PCa prior to radical prostatectomy, and in 14 patients prior to secondary LND [48]. Accuracy of PET and CT were analyzed separately for staging. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for detection of LN metastases were 84%, 82%, 84%, and 82% for PET criteria, and 65%, 76%, 75%, and 67% for CT criteria. PET was more accurate for LN compared with CT both at pLND (88% vs 75%) and sLND (77% vs 65%). Similar results were obtained in a study by Maurer et al. where, 130 patients with intermediate to high risk PCa were staged with ^{68}Ga -PSMA PET/MRI or PET/CT before radical prostatectomy and template PLND [49]. Histopathological findings of resected tissue were statistically correlated with the results of ^{68}Ga -PSMA-PET. Lymphnode metastases were found in 41 of 130 patients (31.5%). On patient based analysis the sensitivity, specificity and accuracy of ^{68}Ga -PSMA-PET were 65.9%, 98.9% and 88.5%, and those of morphological imaging were 43.9%, 85.4% and 72.3%, respectively. Of 734 dissected LN templates 117(15.9%) showed metastases. On template based analysis the sensitivity, specificity and accuracy of ^{68}Ga -PSMA-PET were 68.3%, 99.1% and 95.2%, and those of morphological imaging were 27.3%, 97.1% and 87.6%, respectively. However, lower detection rate of LN metastases was reported by Budäus et al, in a study with 30 patients [50]. Overall sensitivity, specificity, positive predictive value, and negative predictive value of ^{68}Ga -PSMA PET/CT for detection of LN metastases were 33.3%, 100%, 100%, and 69.2%, respectively. Per-side analyses revealed corresponding values of 27.3%, 100%, 100%, and 52.9%. There may be several explanations for the lower detection rate reported in this study by Budäus; especially PET/CT scans were combined from five different centers using two different PET ligands without participation of PET/CT specialists [48,50,51]. Recently, a retrospective study (n=26) reported similar accuracy of ^{68}Ga -PSMA PET/MRI to PET/CT for detection of LN and bone metastases in PCa [52]. In the study, a linear correlation of PET/MRI SUVs and PET/CT SUVs in LN and bone metastases was demonstrated. In PCa patients with biochemical recurrence after

primary treatment, high accuracy of PSMA PET/CT have also been reported for detection of LN metastases [52–56]. In a case report, ^{68}Ga -PSMA radio-guided surgery using a gamma probe intra-operatively was able to detect LN metastases precisely. Figure 3 shows primary staging with ^{68}Ga -PSMA PET/CT in a patient with high risk PCa.

Early detection or exclusion of bone metastases is of high clinical importance, both in management of patients with newly diagnosed high-risk PCa in order to guide optimal therapy, and later in the disease course, since the detection of bone metastases in advanced hormone refractory disease may indicate change of treatment strategy. For detection of bone metastases, $^{99\text{m}}\text{Tc}$ -MDP bone scan (BS) is widely used in high risk PCa patients and in biochemical recurrence. Although the $^{99\text{m}}\text{Tc}$ -MDP bone scan is a sensitive test for osteoblastic lesions and provides information on the entire skeleton, it has a low specificity, and many benign bone lesions may show increased radiotracer uptake, leading to false positive results. Adding single-photon emission (SPECT)/CT increases the specificity of conventional BS [57]. More recently, ^{18}F -fluoride PET/CT has been found to have improved sensitivity and specificity for sites of osseous metastatic involvement. Studies have demonstrated improved accuracy of ^{18}F -Fluoride PET/CT over MDP SPECT/CT in PCa [57–59]. Increased fluoride uptake in malignant bone lesions reflects the increase in regional blood flow and bone turnover characterizing on bone metastases. ^{18}F -Fluoride is however, not tumor specific and, therefore, prone to a high false positive rate [60,61]. Differentiation between malignant and benign lesions is obtained by further validation on CT or MRI. It is well known that bone metastases may have lower PSMA expression, than primary tumor and lymph node metastases [47], but studies have indicated that PSMA PET may be useful for detection of bone metastases in PCa patients [52,55,56,62–64] (figure 4). Studies indicate that PSMA PET/CT has a higher detection rate than conventional BS [64], choline PET/CT [65], and fluoride PET/CT [66]. In the study by Afshar-Oromieh et al, PSMA PET/CT detected more PC bone lesions when compared to choline, even at low PSA levels, and the tumor to background ratio was clearly ($>10\%$) higher on PSMA PET as compared to choline PET in most of the PC lesions [65]. However, the role of PSMA PET/CT in bone metastases needs to be evaluated further in large prospective trials.

PSMA PET in recurrence

During follow-up after primary treatment of PCa, monitoring of PSA serum levels (trigger PSA) and PSA kinetics, PSA doubling time PSA_{dt} and PSA velocity (PSA_{vel}) have been demonstrated to be sensitive markers of early recognition of recurrence of the disease after both radical prostatectomy (RP) and external beam radiotherapy (EBRT) [67]. After RP two consecutive serum levels of >0.2 ng/mL are considered as relapse, and after EBRT, PSA >2.0 ng/mL + nadir after radiotherapy define recurrence [68–70]. In patients demonstrating PSA relapse, the subsequent evaluation is of critical importance, since the treatment strategy depends on the patients having local recurrence, distant metastases or a combination of both. Local recurrence is seen in 30–50% of the patients within 10 years after RP. In patients with T1–T2 disease after EBRT, 30–40% will have recurrence within 10 years [71]. However, serum PSA can not discriminate between local relapse or sites of metastases which is essential for further treatment strategy. Diagnostic imaging is often used to differentiate between local and distant metastases. However, in PCa with biochemical failure after

therapy, current imaging techniques have a low detection rate at the PSA levels at which targeted salvage therapy is effective. Conventional imaging like CT has limited value for detection of recurrence in the prostatic bed after RP with a sensitivity of only 36% [72]. For detection of LN metastases the sensitivity and specificity of CT are 42% and 82%, respectively [41]. CT is primarily able to detect large tumors, typically greater than 2 cm, and can be useful in evaluation of visceral organs and bone metastases [72]. In biochemical recurrence after primary treatment, mpMRI has a higher detection rate of local recurrence than CT, and is especially used to diagnose small local cancer recurrence in a range of PSA serum values between 0.2 and 1 ng/mL [73]. In a meta-analysis, the pooled sensitivity and specificity on patient level of MRI for detection of local recurrence of PCa after RP were 82% and 87%, respectively [74]. DCE-MRI had higher pooled sensitivity and specificity as compared to T2WI. In patients treated with EBRT, the pooled sensitivity and specificity for MRI were 82% and 74%, respectively [74].

Several studies have demonstrated promising results with PSMA PET/CT in PCa patients with biochemical recurrence [54,56,63,65,75–81]. In a large retrospective study (n=319) by Afshar-Oromieh et al, PSMA PET/CT was performed in 319 patients with biochemical recurrence after primary therapy [63]. Median PSA was 4.59 ng/ml (range 0.01 – 41395). In 82% of the patients at least one lesion was detected. Of the lesions, 13 were defined as local relapses after prostatectomy, 328 as LN metastases, 129 as soft tissue metastases, 359 as bone metastases, and 72 as residual cancer within the prostate gland. Forty-two patients with pathological radiotracer uptake in PSMA PET/CT were further investigated by biopsy or surgery. In this analysis, 1 local relapse in 1 patient and 29 lymph nodes in 3 other patients were false-negative. All other tissues/lesions were true-positive (n=98) or true-negative (n=318), and no false positive lesions were detected. A lesion based analysis of sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) revealed values of 76.6 %, 100 %, 91.4 % and 100 %. A patient based analysis revealed a higher sensitivity of 88.1 %. In the study, tumor detection was positive associated with log PSA level and ADT, but not with Gleason Score and PSA_{adt}. In another large study, by Eiber et al, PSMA PET/CT in 248 patients with biochemical recurrence were analyzed retrospectively [75]. Median PSA level was 1.99 ng/ml (range, 0.2–59.4 ng/ml). In the study, detection rates were correlated with PSA level and PSA kinetics. The detection rates were 96.8%, 93.0%, 72.7%, and 57.9% for PSA levels of ≥ 2 , 1 to <2 , 0.5 to <1 , and 0.2 to <0.5 ng/ml, respectively, whereas detection rates increased with a higher PSA velocity (81.8%, 82.4%, 92.1%, and 100% in <1 , 1 to <2 , 2 to <5 , and ≥ 5 ng/ml/y, respectively). No significant association could be found for PSA_{adt}. In higher Gleason score (7 vs. 8), detection efficacy was significantly increased, but no significant difference in detection rate was shown regarding ADT. Both studies [63,75], reported positive findings at low PSA levels below 0.5 ng/mL, which may have implications for the treatment strategy. These results are higher than reported for choline PET/CT with reported median detection rate of 20% (range 7–31), 46% (range 43–56) and 80% (range 72–81) for PSA <1 ng/mL, 1–2 ng/mL, and >2 ng/mL, respectively [82–86]. The median detection rates of PSMA PET/CT reported in the restaging setting for PSA <0.5 ng/mL, 0.5–2 ng/mL and >2 ng/mL are 49% (range 48–50), 68% (range 67–69), and 90% (range 88–92), respectively [63,81,82]. In a retrospective study, Hijazi et al, evaluated the PLND in oligometastatic PCa patients after PSMA PET/

CT. The objective was to exclude metastases before local treatment (salvage pLND). Diagnostic accuracies per nodal lesion among the 213 removed LNs: sensitivity, 94%; specificity, 99%; positive predictive value (PPV), 89%, and negative predictive value (NPV), 99.5%. Figure 5 & 6 illustrate ^{68}Ga -PSMA PET/CT in PCa patients with rising PSA after primary therapy (RP).

Until now, Choline PET/CT has been the best validated PET agent for detection of recurrent PCa in patients with rising PSA after primary treatment [82,87]. However, choline PET/CT is less effective in patients with a low PSA level [82,88]. Therefore, studies have compared the detection rate of PSMA PET/CT and choline PET/CT in biochemical recurrence [54,65,77,81]. Recently, Morigini et al, prospectively compared PSMA PET/CT and choline PET/CT sequentially in 38 PCa patients with PSA relapse. Of the patients enrolled in the study, 34 (89%) had undergone RP, 4 (11%) radiation treatment, and 12 (32%) salvage radiation therapy after primary RP. Mean PSA level was 1.74. PET/CT scans were positive in 26 patients (68%) and negative in with both tracers in 12 patients (32%). Of the 26 positive scans 14 (54%) were positive with PSMA alone, 11 (42%) with both tracers, and only 1 (4%) with choline alone. At low PSA values (<5 ng/mL) the detection rate of PSMA and choline were 50% and 12.5%, respectively. At PSA 0.5–2.0 ng/mL, the values for PSMA and choline were 69% and 31%, respectively, and for PSA above 2 ng/mL the detection rates were 86% and 57%, respectively. On a lesion based analysis, PSMA detected more lesions than choline (59 vs 29, $P<0.001$), and the tumor to background ratio was significantly higher for PSMA than for choline. The results of the PET/CT scans had impact on the clinical management in 63% of the patients (24/38), with 54% (13/24) being due to PSMA PET/CT alone. The key finding in the study was that in patients with PSA relapse PSMA PET/CT demonstrated a significantly higher detection rate than choline PET/CT, and this finding was most evident for patients with low PSA levels (<0.5 ng/mL), with 50% of such patients have a positive PSMA PET/CT. Bluemel et al, investigated the value of PSMA PET/CT in PCa patients with biochemical recurrence and with a negative choline PET/CT [77]. In the study, 139 consecutive patients first underwent a ^{18}F -choline PET/CT, and if negative an additional PSMA PET/CT was offered. In 32 patients the PSMA PET/CT was performed, and findings were correlated to PSA levels. Overall detection rate for choline PET/CT alone was 74.4% (93/125), and for the sequential strategy 85.6% (107/125). PSMA PET/CT detected recurrence in 43.8% (14/32) of the choline negative patients. Pfister et al, also reported PSMA PET/CT to be superior to choline PET/CT for detection of recurrent PCa [54]. In the study, 38 patients had ^{18}F -choline PET/CT and 28 patients had ^{68}Ga -PSMA PET/CT before salvage lymphadenectomy. PET/CT results were compared with histology of removed LNs and suspicious lesions. In ^{18}F -choline and ^{68}Ga -PSMA patients, a total of 378 and 308 LNs and local lesions were removed, respectively. For choline and PSMA, the respective sensitivity (95 % confidence interval) was 71.2 % (64.5–79.6 %) and 86.9 % (75.8–94.2 %), specificity was 86.9 % (82.3–90.6 %) and 93.1 % (89.2–95.9 %), PPV was 67.3 % (57.7–75.9 %) and 75.7 % (64.0–98.5 %), NPV was 88.8 % (84.4–92.3 %) and 96.6 % (93.5–98.5 %), and accuracy was 82.5 % (78.3–86.8 %) and 91.9 % (88.7 %–95.1 %). A higher detection rate of PSMA PET/CT as compared to choline PET/CT, especially at low PSA levels, was also reported in a study (n=38) by Afshar et al [65]. Thus, several studies have demonstrated that PSMA PET/CT is superior as compared to choline

PET/CT for detection of recurrence in PCa patients [54,65,77,81]. Important is that PSMA PET/CT has higher detection rate than choline at low PSA levels (<0.5 ng/mL) which may have clinical implications for patients with rising PSA after therapy with curative intent (RP or radiation therapy) [89]

PSMA as a target for radionuclide therapy

Since no effective treatment is available for advanced prostate cancer, there is an urgent need to develop new therapeutic strategies. Endoradiotherapy using peptides or antibodies as targeting moieties combines the favorable targeting properties of these ligands with the biologic effects of high linear energy transfer (LET) radiation as is seen with alpha and beta particles [10]. Other advantages of endoradiotherapy are that smaller amounts of drug can be used as compared to conventional therapy, and the drugs can be labelled not only with therapeutic nuclides but also with diagnostic ones for imaging. Thus it is possible to perform imaging and dosimetry of the compound prior to therapy. Furthermore, the therapeutic effect is not only restricted to the target cell, but the radiation emitted is also cytotoxic to nearby cells. This effect is called the “bystander” or cross fire effect, which may be important in tumors with heterogeneous antigen or receptor expression, or insufficient vascularization [10]. In radioimmunotherapy (RIT), a radiolabeled antibody delivers a therapeutic radiation dose, most frequently to tumors, while sparing normal organs [5]. RIT can be delivered in a single dose or multiple fractions. Yet, only two RIT drugs have been Food and Drug Administration (FDA) approved for clinical RIT use in refractory low-grade B-cell non-Hodgkin lymphoma: Bexxar (^{131}I -tositumomab) but not sold since 2014, and Zevalin (^{90}Y -ibritumomab) [90]. Various tumor antigens have been proposed as target for RIT in PCa, including PSMA, kallikrein-related peptidases (fPSA, hK2), gastrin-releasing peptide receptor (GRP-R), mucins (mucin 1), LIV-1, gangliosides (L6), HER2, prostate stem cell antigen (PSCA), and the secreted and biomarkers free prostate-specific antigen [8,90,91]. Among these, PSMA is the most promising target for RIT in PCa [90]. PSMA is an excellent target for radionuclide imaging and therapy for several reasons. PSMA is (1) mainly expressed in PCa and in tumor associated neovasculature, (2) highly expressed at all stages of the disease, (3) upregulated in androgen-insensitive or metastatic disease, (4) expressed on the cell surface as an integral membrane protein, and not secreted or released into the circulation, and (5) internalized after antibody binding (receptor mediated endocytosis) [10]. While PSMA is expressed in some normal tissues (especially small intestine, proximal renal tubule cells, and salivary glands), this expression is low compared with tumor. In the recent years, several promising studies using PSMA RIT in PCa have been published, and PSMA is considered as the most promising target for RIT in PCa [5,90]. However, yet there is no FDA approved RIT compounds for treatment of advanced PCa. Among the clinically tested PSMA agent for imaging, ^{68}Ga -PSMA HBED-CC and ^{18}F -DCFPyL seems to be the most promising in PCa. Unfortunately, so far, both ^{68}Ga -PSMA HBED-CC and ^{18}F -DCFPyL are restricted to diagnostic purposes. However, the two compounds DKFZ-617 and PSMA I&T combines both imaging and therapy, since both agents can be labeled with ^{68}Ga for diagnostic purposes, and ^{177}Lu (or ^{90}Y) for radionuclide therapy in PCa patients [6]. Furthermore, MIP-1095 may be labeled with both ^{134}I for imaging and ^{131}I for therapy in PCa patients [92].

The physical and chemical characteristics of available radionuclides must be considered in choosing the radionuclide to be used in RIT. Several radionuclides have been proposed for RIT in PCa, with the beta-particle emitters ^{177}Lu , ^{90}Y and ^{131}I , being the most common used [5,90]. The relatively low energy beta particles of ^{131}I are ideal, but in vivo dehalogenation of radioiodinated molecules is a major disadvantage for internalizing antibody and peptide molecules [20]. Both ^{90}Y and ^{177}Lu are well suited to internalizing antigens like PSMA compared with ^{131}I , due to superior tumor retention [93]. Based upon the the physical properties of each radionuclide, there may be more optimal tumor types and clinical manifestations for each radionuclide [94]. ^{90}Y and ^{177}Lu are radionuclides that decay by beta-emission. ^{90}Y is a pure beta emitter, while ^{177}Lu emits both a beta particle and a gamma photon enabling imaging to be performed using a treatment dose. Furthermore, ^{177}Lu has a low energy beta particle with only 0.2–0.3 mm range and delivers much lower radiation dose to bone marrow compared with ^{90}Y . In addition, because of a longer physical half-life of 6.7 days (compared with ^{90}Y), the tumor residence times are higher [20]. Thus, higher activities of ^{177}Lu labeled agents can be administered with comparatively less myelosuppression, since RIT with lower energy beta emission with shorter range in tissue, would results in less radiation to surrounding tissue. The beta particles emitted from ^{90}Y is more energetic than those of ^{177}Lu (Max: 2.3 MeV vs Max:0.5 MeV). In general lower energy favors more effective energy transfer and radiobiologic effect for micrometastases, while higher energy beta emission, like ^{90}Y , may be more effective for RIT of larger tumors [5]. However, large tumors may also receive radiation dose from lower energy beta emitting radionuclides like ^{177}Lu , if there is sufficient intra-tumoral distribution of the radionuclide. In order to increase the response to RIT various strategies have been used including (1) fractionated dose regimen (multidose) therapy, (2) combinations of RIT with radiosensitizing chemotherapy, (3) pretargeting RIT (pRIT) strategies, and (4) RIT with personalized cocktail of radiolabeled antibodies or radionuclides [90].

PCa is an ideal solid tumor for RIT, since PCa is a radiosensitive tumor with typical metastatic spread to LNs and bones, that have high exposure to circulating antibodies. The most used antibody for PSMA RIT in advanced PCa is the humanized IgG monoclonal antibody J591, but other compounds have also been used [7,90,92,95–110]. In a dual center phase II study reported by Tagawa et al, 47 PCa patients received ^{177}Lu -J591. All included patients had progressed after hormonal therapies. A total of 10.6% experienced 50% decline in PSA, 36.2% experienced 30% decline, and 59.6% experienced any PSA decline following their single treatment. Sites of PCa metastases were targeted in 44 of 47 (93.6%) as determined by planar imaging. All experienced reversible hematologic toxicity, with grade 4 thrombocytopenia occurring in 46.8% (29.8% received platelet transfusions) without significant hemorrhage. No serious non-hematologic toxicity occurred. Those with poor PSMA imaging were less likely to respond. The authors concluded, that a single dose of ^{177}Lu -J591 was well tolerated with reversible myelosuppression. Accurate tumor targeting and PSA responses were seen with evidence of dose response. Recently, ^{177}Lu -PSMA-617 RIT has been performed in PCa patients. Kabasakal et al investigated the absorbed dose of ^{177}Lu -PSMA-617 in different organs of seven patients with progressive PCa after a single diagnostic dose (mean activity 192.6 MBq) [111]. The aim of the study was to estimate the pretreatment radiation doses in patients before radiotherapy using a

tracer amount of ^{177}Lu -labeled PSMA ligand. The calculated radiation-absorbed doses for each organ showed substantial variation, and the highest radiation estimated doses were calculated for parotid glands and kidneys. Calculated radiation-absorbed doses per MBq were 1.17 ± 0.31 mGy for parotid glands and 0.88 ± 0.40 mGy for kidneys. The radiation dose given to the bone marrow was significantly lower than those of kidney and parotid glands. It was concluded that, the dose-limiting organ seems to be the parotid glands rather than kidney and bone marrow. Recently, Ahmadzadehfar et al, respectively investigated the side effects and response rate of ^{177}Lu -PSMA-617 therapy in 24 hormone and chemotherapy refractory PCa patients [106]. Median PSA was 522 ng/mL (range 17–2360). Twenty-two of the 24 patients received two cycles of therapy. Eight weeks after the first cycle of therapy 79.1% of the patients had a decline in PSA level. Eight weeks after the second cycle of therapy 68.2% had a decline in PSA relative to the baseline value. Anemia (grade 3) was observed only in 3 patients but there were no relevant nephro- or hemotoxicity (grade 3 or 4) in the other patients. A positive response to therapy in terms of decline in PSA was reported to happen in about 70% of patients. Also recently, Rahbar et al evaluate tumor response, adverse effects, and survival in 28 PCa patients that received therapy with ^{177}Lu -PSMA-617 [112]. A total of 50 therapies were performed in 28 patients with metastatic PCa and exhausted conventional therapy. In the study, PSA decline was seen in 59% and 75% of patients after 1 and 2 therapies, respectively. Moreover, a PSA decline of 50% or greater occurred in 32% and 50%. Therapies were well tolerated in all patients, renal and hematologic parameters changed in significantly, and permanent xerostomia or other safety-related toxicity did not occur. The estimated median survival was 29.4 weeks, significantly longer than survival in the historical best supportive care group [112]. In a multicenter retrospective study by Rahr et al, 82 patients with castration resistant PCa received a single dose of ^{177}Lu -PSMA-617 therapy [108]. Data was collected at baseline and 8 weeks after therapy. Bone, LN, liver and lung metastases were present in 99%, 65%, 17% and 11% of the patients, respectively. Complete dataset of 74 patients were available for analysis. 47 (64%) of the patients showed a PSA-decline, of these 23 (31%) had a PSA decline > 50%, 35(47%) had a stable disease with a PSA decline from < 50% to an increase < 25%, and 17(23%) showed a progressive disease with PSA increase > 50%. Also in this study, treatments with ^{177}Lu -PSMA were well tolerated with no significant changes in hematology or kidney function.

In a recent study by Zehnmann et al, MIP-1095 was labeled with ^{134}I for imaging in 16 PCa patients and with ^{131}I for radio nuclide therapy in 28 PCa patients [92]. Dosimetry estimates showed higher absorbed dose were in salivary glands and kidneys. PSA values decreased > 50% in 60.7% of the treated patients, and in men with bone pain, 84.6% showed complete or moderate reduction in pain. Hematological toxicities were mild, and no adverse effects on renal function were observed.

Conclusion

Much focus has been on PSMA as a promising target for imaging and therapy with radionuclides, since it is upregulated in most PCa. In the prostate, one potential role for PSMA PET imaging is to help guiding focal therapy, and in the recent years, several studies have shown great potential of PSMA PET/CT for initial staging, LN staging, and detection

of recurrence of PCa, even at very low PSA values after primary therapy. Furthermore, studies indicate that PSMA PET/CT has a higher detection rate than choline PET/CT. Radiolabeled PSMA ligands for therapy show promise in several studies with metastatic PCa, and is an area of active investigation. Thus, this PSMA “Image and treat” strategy with radiolabeled PSMA ligands, has the potential to improve the treatment outcome of PCa patients. PSMA as a target for imaging and therapy is paving the way for personalized medicine in PCa.

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Figure 1.

54-year old man (serum PSA =10.85 ng/ml). Axial T2W MRI shows a hypointense lesion in the midline peripheral zone (arrow) (A), which has restricted diffusion on ADC maps (B) and $b=2000\text{s/mm}^2$ DW MRI (C) (arrow). The lesion has increased vascularity in comparison with the remainder of the prostate on the DCE MRI (arrow) (D). ^{18}F -DCFBC PET image (E) shows specific uptake within the midline peripheral zone lesion (arrow). TRUS/MRI fusion guided biopsy of this lesion revealed Gleason 4+4 prostate adenocarcinoma.

Figure 2. 72-year old man (serum PSA = 26 ng/ml). Axial T2W MRI shows a hypointense lesion in the left peripheral zone (arrow) (A), which has restricted diffusion on ADC maps (B) and $b=2000\text{s/mm}^2$ DW MRI (C) (arrow). The lesion has increased vascularity in comparison with the remainder of the prostate on the DCE MRI (arrow) (D). ¹⁸F-DCFBC PET image (E) shows no specific uptake within the lesion.

Figure 3.

68-year old man with newly diagnosed high risk prostate cancer (T3, Gleason 10, PSA 14.6 ng/ml). ^{68}Ga -PSMA PET/CT showed the primary prostate cancer with increased PSMA activity in the left side of the prostate on the MIP image (A) and the axial fused PET/CT image (B). Axial fused PET/CT images showed high PSMA activity in a 5 mm lymph node metastase(C). Two sclerotic bone metastases with high PSMA activity were seen on the MIP (A) and on the axial fused PET/CT images in the left ilium (D) and in corpus of TH9 in the spine (E).

Figure 4.

74-year old man (serum PSA = 618.7 ng/ml) with castrate resistant prostate cancer. Axial CT scan shows a subtle lymph node posterior to inferior vena cava in the retroperitoneum (red arrow, A). Axial CT image at bone window in the same level shows a blastic (green arrow) and a ground-glass (blue arrow) bony lesion in the vertebral body (B). Axial ^{18}F -DCFBC PET image shows specific uptake within the lymph node (SUV=5) (red arrow) and in the ground-glass bony lesion (SUV=7.5) (blue arrow), whereas the uptake in the osteoblastic bony lesion is milder and heterogeneous (SUV=3.4) (green arrow) (

Figure 5.

61-year old man with known prostate cancer (T1, Gleason 6, PSA 4) were followed with repeated serum PSA and TRUS biopsies in active surveillance. After 6 years the PSA increased to 13 ng/ml within 6 months. A bone MDP SPECT/CT showed no signs of bone metastases, and MRI of the prostate showed PIRADS 5 lesions in 2 sites. Two months later the patient underwent laparoscopic radical prostatectomy with pelvic lymph node dissection. Histology of the removed lymph nodes showed no signs of metastases. However, control PSA 6 weeks after the operation showed PSA of 107 ng/ml, and the patient was referred to ^{68}Ga -PSMA PET/CT. The PSMA PET/CT showed multiple bone metastases on the MIP (A) and on the fused axial PET/CT images (B&D). Some of the lesions were sclerotic on CT (C), but most of the bone lesions were with only discrete changes or were not seen on CT (E). No signs of recurrence in the prostatic bed or lymph node metastases were detected with PSMA PET/CT.

Figure 6.

59-year old man with known high risk prostate cancer (T3, Gleason 9) treated with radical prostatectomy. Three years later PSA was rising to 1.6. ^{68}Ga PSMA PET/CT showed no signs of recurrence in the prostatic bed or bone metastases. However, several small lymph node metastases were detected on PSMA PET/CT. A 5 mm lymph node metastase is seen on MIP and axial fused image (white arrow, A&B), and very small lymph node metastases (< 5 mm) are seen on the axial fused PET/CT images (red arrows, B&D) and on corresponding axial CT images (red arrows, C&E)