HHS Public Access

Author manuscript

Curr Opin Oncol. Author manuscript; available in PMC 2017 July 18.

Published in final edited form as:

Curr Opin Oncol. 2016 May ; 28(3): 216–221. doi:10.1097/CCO.0000000000000277.

PSMA PET in prostate cancer – a step towards personalized medicine

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Abstract

Purpose of review—Increasing attention is being given to personalized medicine in oncology, where therapies are tailored to the particular characteristics of the individual cancer patient. In recent years, there has been greater focus on PSMA in prostate cancer (PCa) as a target for imaging and therapy with radionuclides. This review highlights the recent advancements in PSMA PET in PCa during the past year.

Recent findings—Several reports on PSMA PET/CT in PCa patients are demonstrating promising results, especially for detection of biochemical recurrence. ^{18}F-PSMA PET/CT may be superior to ^{68}Ga-PSMA PET/CT. The detection rate of PSMA PET is influenced by PSA level. PSMA PET/CT may have a higher detection rate than choline PET/CT. Only a few reports have been published on PSMA PET/MRI, and this modality remains to be elucidated further.

Conclusion—Molecular imaging with PSMA PET is paving the way for personalized medicine in PCa. However, large prospective clinical studies are needed to further evaluate the role of PSMA PET/CT and PET/MRI in the clinical workflow of PCa. PSMA is an excellent target for imaging and therapy with radionuclides, and the “image and treat” strategy has the potential to become a milestone in the management of PCa patients.

Keywords

Prostate cancer; PSMA; PET/CT; PET/MRI; personalized medicine

INTRODUCTION

Prostate cancer (PCa), the most common cancer in men, is the second leading cause of cancer deaths among men[1]. The clinical management of PCa is challenging due to the variable clinical and pathologic behavior of the disease. Thus, the treatment of PCa should be optimized and specific to each patient in order to improve their outcomes. Much attention

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No conflicts of interest

is being given to the development of precision medicine in oncology, where pharmaceutical therapies are tailored to the particular characteristics of the individual cancer patient. Precision medicine requires accurate characterization and location of the cancer. In recent years, there has been increasing focus on prostate-specific membrane antigen (PSMA) as a target for both imaging and therapy[2]. PSMA is a type II integral membrane glycoprotein (100–120 kDa), with an intracellular component, a transmembrane component, and a large extracellular domain[3,4]. PSMA is highly expressed by all PCa, and its expression increases with tumor aggressiveness, metastatic disease and disease recurrence[2,5]. Despite its name, PSMA is also expressed in several healthy tissues such as the salivary glands, proximal renal tubules, epididymis, ovary, the luminal side of the ileum-jejunum, and astrocytes in CNS, while normal prostatic tissue expresses little PSMA in the apical epithelium of secretory ducts[6–7,••8]. Furthermore, PSMA is expressed in the neovasculature of other tumors, including bladder, pancreas, lung, and kidney cancers, but not in normal vasculature[7,9]. Therefore, PSMA represents an excellent target for both imaging and therapy of PCa[2,••8]. During the last two decades, many efforts have been undertaken to develop high affinity PSMA ligands for both imaging and therapy [2,••8]. This “image and treat” strategy has the potential to become a milestone in the management of PCa patients[10–12]. The purpose of this review is to highlight the most important developments of PSMA PET imaging reported in the past year.

PSMA PET ligands

The first widely used PSMA imaging agent in PCa was ProstaScintTM (EUSA Pharma), an ^{111}In-labeled version of the monoclonal antibody 7E11 that targets PSMA. However, this PSMA agent targets only the internal domain of PSMA and therefore is only accessible to its antigen target in dying and dead cells where the membrane is permeable. Furthermore, the PSMA radiotracer is technically demanding to administer, with only moderate clinical diagnostic performance[4]. The recently developed antibody-based PSMA PET radiotracers primarily target the extracellular domain of the PSMA (hence also detecting viable cells) and include ^{64}Cu- and ^{89}Zr- labeled PSMA antibodies and antibody fragments and ^{64}Cu-labeled aptamers[3]. More recently, small molecule high affinity PSMA antagonists have been developed that are labeled with ^{68}Ga-, ^{18}F-, ^{11}C-, ^{64}Cu -, and ^{86}Y [3]. One of these ligands, ^{68}Ga (HBED-CC), also known as PSMA-11, has up to now been the most clinically used PSMA PET radiotracer in PCa patients. This agent has a strong binding affinity to PSMA, and is efficiently internalized into PCa cells[13,14]. A human biodistribution study (n=37) of ^{68}Ga (HBED-CC) PET/CT reported no adverse events[15]. Within healthy organs, kidneys and salivary glands show the highest radiotracer uptake, while lacrimal glands, liver, spleen and bowel show relatively moderate uptake[15]. Intense radiotracer uptake in the urinary bladder is due to excretion of the radiotracer through the kidneys. Excellent contrast on the images is seen 1 h post injection (p.i.) even at low PSA levels. Kabasakal et *al.* compared ^{68}Ga-PSMA PET images obtained at 5 min p.i and 60 min p.i. and found no difference in the number of lesions detected[16]. However, SUVmax for primary tumors, LN and bone metastases were significantly higher on late images, while on early images prostatic evaluation was easier because of lack of urinary tracer activity within the bladder. Thus, early imaging may be useful for the evaluation of lesions close to the bladder.

Biphasic imaging may help in discriminating benign from malignant lesions since ^{68}Ga-PSMA uptake increases over time in PC cells via internalization of the PSMA protein. Recently, modifications of PSMA-11 have resulted in a novel small molecule PSMA-ligand, PSMA-617, with a significantly higher binding affinity to PSMA and also highly efficient internalization into PCa cells[18]. Like ^{68}Ga (HBED-CC), kidneys and salivary glands show the highest ^{68}Ga-PSMA-617 uptake, whereas lacrimal glands, spleen, liver and bowel show relative moderate uptake[•19]. PSMA-617 can be labeled with ^{68}Ga, ^{111}In, ^{177}Lu, and ^{90}Y, and therefore may potentially be used for imaging as well as for therapy[•19]. In the past few years, ^{177}Lu-PSMA-617 has been used for treating metastatic PCa at several centers[20–22].

PSMA ligands may also be labeled with ^{18}F for PSMA PET imaging. Unlike generator-produced ^{68}Ga, a cyclotron is needed for production of ^{18}F -PSMA agents. However, like ^{18}F-FDG, ^{18}F-PSMA agents may be centrally produced and distributed to multiple institutions due to its longer half-life of 110 min. Moreover, ^{18}F imaging results in improved spatial resolution and more accurate quantitation due to shorter positron range and higher positron yield of ^{18}F versus ^{68}Ga[23]. N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]- 4-fluorobenzyl-L-cysteine (DCFBC) is a first generation low-molecular-weight, urea-based inhibitor of PSMA which binds to PCa cells with high PSMA expression in preclinical studies[24] The basic structure is the same as the ^{68}Ga-based agents with the exception that the latter have a chelate attached for binding the radiometal. The estimated ^{18}F-DCFBC mean effective radiation dose to patients is comparable to that of ^{18}F-FDG[24]. A new second-generation ^{18}F-PSMA–agent (^{18}F-DCFPyL) demonstrates higher affinity and faster clearance resulting in higher tumor to background ratio, which may produce better detection of lower-grade or smaller-sized PCa compared with ^{18}F-DCFBC[•25]. Dietlein et *al* compared ^{18}F-DCFPyl PET/CT and ^{68}Ga-PSMA(HBED-CC) PET/CT in patients with biochemically relapsed PCa (n=14)[••26]. All suspicious lesions identified by ^{68}Ga-PSMA-HBED-CC were also detected with ^{18}F-DCFPyL. In 3 patients, additional lesions were observed using ^{18}F-DCFPyL PET/CT. The mean SUV_{max} in the concordant ^{18}F-DCFPyL PSMA lesions was significantly higher as compared to ^{68}Ga-PSMA-HBED-CC (14.5 vs. 12.2, p=0.028, n=15). Thus, ^{18}F-DCFPyL represents a highly promising alternative to ^{68}Ga-PSMA-HBED-CC for PET imaging in PCa.

More recently, a different PSMA agent, EuK-Subkff-68Ga-DOTAGA (^{68}Ga-PSMA I&T), was developed, which also can be labeled with ^{177}Lu for therapy[•27]. A favorable dosimetry of ^{68}Ga-PSMA I&T has been reported, and organ doses (kidneys) are comparable to or lower than those from ^{18}F-FDG[28]. PSMA I&T may also be labeled with ^{111}In for SPECT imaging, and has been used for radio-guided surgery in a case report[29].

PSMA PET/CT in primary staging

Accurate staging of PCa is of high importance for treatment decisions and patient management[30]. Treatment strategies are dictated by the presence or absence of metastases. Prostate cancer most often spreads to lymph nodes (LNs) and bone, and highest PSMA expression has been demonstrated in adenocarcinoma of the prostate and LN metastases, while a lower expression of PSMA is seen in bone metastases[31,32]. In the prostate,

magnetic resonance imaging (MRI) is widely used for characterization of malignant tumors. Rowe et *al* prospectively compared ^{18}F- DCFBC PET/CT and MRI for detection and characterization of primary PCa in men (n=13) undergoing surgery with histology[••33]. MRI was more sensitive than ^{18}F-DCFBC PET for detection of malignancy in the prostate on a per-segment (sensitivities of 0.17 and 0.39 for PET and MRI, respectively) and per-dominant-lesion analysis (sensitivities of 0.46 and 0.92 for PET and MRI, respectively). However, ^{18}F-DCFBC PET was more specific than MR imaging by per-segment analysis (specificities of 0.96 for PET and 0.89 for MRI, for corresponding sensitivity). PSMA-PET may be used as PET/CT in combination with MRI or as hybrid PET/MR. Recently, the initial experience with ^{68}Ga-PSMA PET/MRI was reported as promising for tumor delineation in the prostate[34], and ^{68}Ga-PSMA PET may have a role for gross tumor volume delineation in radiation treatment planning of primary PCa[35]. PET/MRI has the potential to identify clinically significant PCa, to guide biopsies, and for planning of focal therapy, but further studies are needed to establish the role of PET/MRI in PCa. Given the cost of PET/CT, it is unlikely that PSMA PET/CT or PET/MRI will displace MRI as a method for detecting prostate cancer and guiding biopsies and focal therapies.

Lymph node metastases represent a significant adverse prognostic factor in PCa and can be associated with systemic metastases[36]. The gold standard for diagnosing LN metastases in locally advanced PCa is extended pelvic lymph node dissection (PLND)[30]. Hijazi et *al* evaluated PLND for nodal oligometastatic PCa detected by ^{68}Ga-PSMA PET/CT in 35 patients (23 biochemical recurrence; 12 primary staging)[37]. Malignant lesions were detected in 91.4 % (32/35). In the study, PLND was performed in 17 men with oligometastatic disease. Diagnostic accuracies per nodal lesion (213 removed nodes) were: sensitivity, 94%; specificity, 99%; positive predictive value (PPV), 89%; and negative predictive value (NPV), 99.5%. Similar high sensitivity (88.1%) of ^{68}Ga-PSMA PET/CT for LN metastases was demonstrated in another study[••38]. In contrast, lower detection rate for LN disease has also been reported[39]. Thus, prospective clinical trials in large cohorts are needed to evaluate the role of PSMA-PET/CT in primary N-staging of PCa. In a small pilot study, ^{68}Ga-PSMA(HBED-CC) was used for radio-guided surgery of metastatic LNs in PCa[40]. Recently, ^{68}Ga-PSMA PET/MRI and ^{68}Ga-PSMA PET/CT were retrospectively compared in 26 patients, who underwent ^{68}Ga-PSMA PET/CT$_{\text{low dose}}$ (1 h p.i.) followed by ^{68}Ga-PSMA PET/MRI (3 h p.i.)[•41]. The overall discordance in PET positive findings was low, and the agreement between PET/CT and PET/MRI was high. The SUVs of pathological lesions were influenced by the time of acquisition, as previously reported[42]. It was demonstrated that SUVs of LNs were significantly higher on PET/MRI 3 h p.i. than on PET/CT 1 h p.i.; however, there were no significant differences between the bone lesions SUVs[•41].

Conventional imaging modalities (CIM), like bone scan and CT, have limited sensitivity and specificity for detection of metastatic PCa. Rowe et *al* investigated prospectively ^{18}F-DCFBC for detection of metastatic disease in PCa[43]. ^{18}F-DCFBC PSMA PET/CT was able to detect a larger number of lesions (592 positive with 63 equivocal) than CIM (520 positive with 61 equivocal) overall, in both hormone-naïve (n=9) and castration-resistant cancer (n=8). DCFBC detection of LN, bone lesions and visceral lesions was superior to CIM. Fluoride PET/CT is a common agent for detection of bone metastases, and a recent

case report indicates that PSMA PET/CT may be superior to fluoride PET/CT in PCa, although this may be contingent on whether the patient is on androgen ablation therapy (ADT) [44]. Some PCa patients have suspicious lesions in the lungs, but SUV analysis of ^{68}Ga-PSMA PET cannot discriminate reliably between lung metastases and primary lung cancer as the neovasculature could be positive in the latter[45].

PSMA PET/CT in recurrence

One of the important clinical issues in the management of PCa is early detection of recurrent disease. An accurate diagnostic modality with high sensitivity and specificity is necessary to select the optimal treatment strategy, i.e., surgery, external radiation or systemic therapy. Recently, PSMA PET/CT has demonstrated promising results in patients with biochemical recurrence of PCa. Afshar-Oromieh et *al* retrospectively analyzed the diagnostic value of ^{68}Ga-PSMA PET/CT in a large cohort (n=319) of PCa patients with biochemical recurrence[••38]. A lesion-based analysis demonstrated sensitivity, specificity, NPV and PPV of 76.6 %, 100 %, 91.4 % and 100 %, respectively. On a patient-based analysis the sensitivity was 88.1 %. In the study, tumor detection was positively associated with log PSA level but not with PSA doubling time (PSAdt). However, not all lesions were histologically confirmed. The effect of PSA levels and kinetics on PSMA PET/CT detection rate have also been investigated in other studies[46,••47,••48]. In a study by Ceci et *al*, ^{68}Ga-PSMA PET/CT was positive in 74.2% of patients (52/70) with a mean PSA of 3.5 ng/mL[46]. A positive scan was demonstrated in 85 % of patients (17/20) with PSA <2 ng/ mL and PSAdt <6.5 months, and in 18.7% of patients (3/16) with PSA <2 ng/mL and PSAdt ≥6.5 months. In patients with PSA <2 ng/mL PSMA PET/CT was positive in 59% of patients (23/39), which is in agreement with the study by Afshar-Oromieh et *al* that reported a detection rate of 61.1 % in 90 patients with PSA <2 ng/mL[••38]. By contrast, PSAdt was associated with positive ^{68}Ga-PSMA PET/CT in the study by Ceci et al. In a retrospective study (n=248), Eiber el *al* demonstrated pathological scans in 89.5% (222/248) of the patients (median PSA 1.99 ng/mL) with biochemical recurrence[••47]. 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. Again, limited pathologic validation is available. Interestingly, the detection rate of 58% in patients with a PSA level <0.5ng/mL may have the most important clinical impact since European guidelines[30] define a PSA value <0.5ng/mL as the upper limit for salvage radiation therapy. Detection rates increased with a higher PSA velocity (81.8%, 82.4%, 92.1%, and 100% among patients with <1, 1 to <2, 2 to <5, and ≥5 ng/mL/y PSA velocities, respectively). However, no significant association could be found for PSAdt in this study.

PSMA expression may be inversely regulated by the androgen receptor. Preclinical studies have shown PSMA expression to be down regulated by androgen therapy and up regulated by ADT[49,50]. One study reported a strong and significant association between a positive PET result and ADT[••38]. In contrast, other studies reported no significant difference in detection efficacy regarding ADT[46,••47]. The effect of ADT on the PSMA PET results is not fully understood and needs to be elucidated further in clinical trials.

The pelvic LNs are a common site of recurrent PCa after surgery or radiation. However, modalities like CT and MRI are non-specific and are not considered reliable enough for routine N-staging[51,52]. Giesel et *al* retrospectively evaluated the volume and size of LNs identified by ^{68}Ga-PSMA PET/CT in 21 patients with biochemical relapse[53]. A total of 49 PET positive LNs were identified, and ^{68}Ga-PSMA PET/CT detected LN recurrence in two-thirds of patients who would have been missed using conventional morphological criteria. Sterzing et *al* retrospectively analyzed the impact of PSMA PET/CT on changes in staging and radiotherapy management in 57 PCa patients (15 primary staging, 42 recurrence after radical prostatectomy)[54]. PET/CT and CT were performed in all patients. The TNM staging was changed in 50.8% (29/57) after PSMA PET/CT, and resulted in a different radiotherapeutic management strategy compared to the plan based on conventional CT imaging. Another study also reported on the impact of PSMA PET/CT on the clinical management of biochemical recurrence[55].

The most commonly used clinical PET agent for patients with biochemical recurrence in the past 10 years has been choline, either labeled with ^{18}F or ^{11}C[56]. Morigi et *al* compared prospectively ^{18}F-choline PET/CT with ^{68}Ga-PSMA PET/CT in 38 patients with biochemical recurrence[••48]. When PSA was below 0.5 ng/mL, the detection rate was 50% for ^{68}Ga-PSMA versus 12.5% for ^{18}F-choline. When PSA was 0.5–2.0 ng/mL, the detection rate was 69% for ^{68}Ga-PSMA versus 31% for ^{18}F-choline, and when PSA was above 2.0, the detection rate was 86% for ^{68}Ga-PSMA versus 57% for ^{18}F-choline. On lesion-based analysis, ^{68}Ga-PSMA detected more lesions than ^{18}F-choline (59 vs. 29, $P<0.001$). Furthermore, the tumor-to-background ratio in positive scans was higher for ^{68}Ga-PSMA than for ^{18}F-choline, and may allow identification of even very small lesions. The major limitation of this study, as with many of the other PSMA studies, is that confirmation with histopathology was obtained in only 24 patients. The superior sensitivity of ^{68}Ga-PSMA PET/CT, as compared with ^{18}F-choline PET/CT, has also been reported in a recent retrospective study of 37 patients with biochemical recurrence[57]. In this study, PSMA PET/CT detected PCa lesions with improved contrast when compared to standard ^{18}F-choline PET/CT, especially at low PSA levels.

SUMMARY

Much focus has been on PSMA as a target for imaging and therapy with radionuclides in PCa. In the past year, several PSMA PET/CT studies are beginning to demonstrate promising results, and PSMA PET/CT is now in clinical use at an increasing number of institutions. Only a limited number of reports have been published on PSMA PET/MRI. Large prospective clinical studies are needed to further evaluate the role of PSMA PET/CT and PET/MRI in the clinical management of PCa. Furthermore, PSMA has the potential to be an excellent therapeutic target in PCa patients. Thus, molecular imaging with PSMA PET is paving the way for personalized medicine in PCa.

Acknowledgments

Peter Choyke receives support from the Intramural Program of the National Cancer Institute.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63:11–30. [PubMed: 23335087]
2. Bouchelouche K, Choyke PL, Capala J. Prostate specific membrane antigen- a target for imaging and therapy with radionuclides. Discov Med. 2010; 9:55–61. [PubMed: 20102687]
3. Mease RC, Foss CA, Pomper MG. PET imaging in prostate cancer: focus on prostate-specific membrane antigen. Curr Top Med Chem. 2013; 13:951–962. [PubMed: 23590171]
4. Jadvar H. PSMA PET in Prostate Cancer. J Nucl Med. 2015; 56:1131–1132. [PubMed: 25977465]
5. Wright GL Jr, Haley C, Beckett ML, Schellhammer PF. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol Oncol. 1995; 1:18–28. [PubMed: 21224086]
6. Tasch J, Gong M, Sadelain M, Heston WD. A unique folate hydrolase, prostate-specific membrane antigen (PSMA): a target for immunotherapy? Crit Rev Immunol. 2001; 21:249–261. [PubMed: 11642607]
7. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997; 3:81–85. [PubMed: 9815541]
8••. Kiess AP, Banerjee SR, Mease RC, Rowe SP, Rao A, Foss CA, Chen Y, Yang X, Cho SY, Nimmagadda S, et al. Prostate-specific membrane antigen as a target for cancer imaging and therapy. Q J Nucl Med Mol Imaging. 2015; 59:241–268. A detailed review on small-molecule PSMA inhibitors for imaging. [PubMed: 26213140]
9. Elsasser-Beile U, Buhler P, Wolf P. Targeted therapies for prostate cancer against the prostate specific membrane antigen. Curr Drug Targets. 2009; 10:118–125. [PubMed: 19199907]
10. Bouchelouche K, Capala J. 'Image and treat': an individualized approach to urological tumors. Curr Opin Oncol. 2010; 22:274–280. [PubMed: 20150811]
11. Bouchelouche K, Tagawa ST, Goldsmith SJ, Turkbey B, Capala J, Choyke P. PET/CT Imaging and Radioimmunotherapy of Prostate Cancer. Semin Nucl Med. 2011; 41:29–44. [PubMed: 21111858]
12. Pfestroff A, Luster M, Jilg CA, Olbert PJ, Ohlmann CH, Lassmann M, Maecke HR, Ezziddin S, Bodei L, Radionuclide Therapy Committee of the European Association of Nuclear M. Current status and future perspectives of PSMA-targeted therapy in Europe: opportunity knocks. Eur J Nucl Med Mol Imaging. 2015; 42:1971–1975. [PubMed: 26373947]
13. Eder M, Neels O, Muller M, Bauder-Wust U, Remde Y, Schafer M, Hennrich U, Eisenhut M, Afshar-Oromieh A, Haberkorn U, et al. Novel Preclinical and Radiopharmaceutical Aspects of [68Ga]Ga-PSMA-HBED-CC: A New PET Tracer for Imaging of Prostate Cancer. Pharmaceuticals (Basel). 2014; 7:779–796. [PubMed: 24983957]
14. Eder M, Schafer M, Bauder-Wust U, Hull WE, Wangler C, Mier W, Haberkorn U, Eisenhut M. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjug Chem. 2012; 23:688–697. [PubMed: 22369515]
15. Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, Holland-Letz T, Giesel FL, Kratochwil C, Haufe S, et al. PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging. 2013; 40:486–495. [PubMed: 23179945]
16. Kabasakal L, Demirci E, Ocak M, Akyel R, Nematyazar J, Aygun A, Halac M, Talat Z, Araman A. Evaluation of PSMA PET/CT imaging using a 68Ga-HBED-CC ligand in patients with prostate cancer and the value of early pelvic imaging. Nucl Med Commun. 2015; 36:582–587. [PubMed: 25738559]
17. Sahlmann CO, Meller B, Bouter C, Ritter CO, Strobel P, Lotz J, Trojan L, Meller J, Hijazi S. Biphasic Ga-PSMA-HBED-CC-PET/CT in patients with recurrent and high-risk prostate carcinoma. Eur J Nucl Med Mol Imaging. 2015 (in press).
18. Benesova M, Schafer M, Bauder-Wust U, Afshar-Oromieh A, Kratochwil C, Mier W, Haberkorn U, Kopka K, Eder M. Preclinical Evaluation of a Tailor-Made DOTA-Conjugated PSMA Inhibitor with Optimized Linker Moiety for Imaging and Endoradiotherapy of Prostate Cancer. J Nucl Med. 2015; 56:914–920. [PubMed: 25883127]

19•. Afshar-Oromieh A, Hetzheim H, Kratochwil C, Benesova M, Eder M, Neels OC, Eisenhut M, Kubler W, Holland-Letz T, Giesel FL, et al. The theranostic PSMA-ligand PSMA-617 in the diagnosis of prostate cancer by PET/CT: biodistribution in humans, radiation dosimetry and first evaluation of tumor lesions. J Nucl Med. 2015; 56:1697–705. A biodistribution and dosimetry study of PSMA-617 PET in patients with prostate cancer. [PubMed: 26294298]

20. Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benesova M, Mier W, Kopka K, Haberkorn U. [(1)(7)(7)Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015; 42:987–988. [PubMed: 25573634]

21. Kabasakal L, AbuQbeitah M, Aygun A, Yeyin N, Ocak M, Demirci E, Toklu T. Pre-therapeutic dosimetry of normal organs and tissues of Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2015; 42:1976–83. [PubMed: 26227531]

22. Ahmadzadehfar H, Rahbar K, Kurpig S, Bogemann M, Claesener M, Eppard E, Gartner F, Rogenhofer S, Schafers M, Essler M. Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. EJNMMI Res. 2015; 5:114. [PubMed: 26099227]

23. Sanchez-Crespo A. Comparison of Gallium-68 and Fluorine-18 imaging characteristics in positron emission tomography. Appl Radiat Isot. 2013; 76:55–62. [PubMed: 23063597]

24. Cho SY, Gage KL, Mease RC, Senthamizhchelvan S, Holt DP, Jeffrey-Kwanisai A, Endres CJ, Dannals RF, Sgouros G, Lodge M, et al. Biodistribution, tumor detection, and radiation dosimetry of 18F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. J Nucl Med. 2012; 53:1883–1891. [PubMed: 23203246]

25•. Szabo Z, Mena E, Rowe SP, Plyku D, Nidal R, Eisenberger MA, Antonarakis ES, Fan H, Dannals RF, Chen Y, et al. Initial Evaluation of [(18)F]DCFPyL for Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging of Prostate Cancer. Mol Imaging Biol. 2015; 17:565–574. A promising second generation ^{18}F-PSMA PET agent, 18F-DCFPyL. [PubMed: 25896814]

26••. Dietlein M, Kobe C, Kuhnert G, Stockter S, Fischer T, Schomacker K, Schmidt M, Dietlein F, Zlatopolskiy BD, Krapf P, et al. Comparison of [(18)F]DCFPyL and [(68)Ga]Ga-PSMA-HBED-CC for PSMA-PET Imaging in Patients with Relapsed Prostate Cancer. Mol Imaging Biol. 2015; 17:575–584. ^{18}F-DCFPyL PET may be superior to ^{68}Ga-PSMA-HBED-CC PET for detection of recurrence in protate cancer patients. [PubMed: 26013479]

27•. Weineisen M, Schottelius M, Simecek J, Baum RP, Yildiz A, Beykan S, Kulkarni HR, Lassmann M, Klette I, Eiber M, et al. 68Ga- and 177Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies. J Nucl Med. 2015; 56:1169–1176. PSMA I&T can be labeled with ^{68}Ga for PET imaging and ^{177}Lu for radionuclide therapy. [PubMed: 26089548]

28. Herrmann K, Bluemel C, Weineisen M, Schottelius M, Wester HJ, Czernin J, Eberlein U, Beykan S, Lapa C, Riedmiller H, et al. Biodistribution and radiation dosimetry for a probe targeting prostate-specific membrane antigen for imaging and therapy. J Nucl Med. 2015; 56:855–861. [PubMed: 25883128]

29. Schottelius M, Wirtz M, Eiber M, Maurer T, Wester HJ. [In]PSMA-I&T: expanding the spectrum of PSMA-I&T applications towards SPECT and radioguided surgery. EJNMMI Res. 2015; 5:68–72. [PubMed: 26608882]

30. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014; 65:467–479. [PubMed: 24321502]

31. Schmittgen TD, Teske S, Vessella RL, True LD, Zakrajsek BA. Expression of prostate specific membrane antigen and three alternatively spliced variants of PSMA in prostate cancer patients. Int J Cancer. 2003; 107:323–329. [PubMed: 12949815]

32. Sweat SD, Pacelli A, Murphy GP, Bostwick DG. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Urology. 1998; 52:637–640. [PubMed: 9763084]

33••. Rowe SP, Gage KL, Faraj SF, Macura KJ, Cornish TC, Gonzalez-Roibon N, Guner G, Munari E, Partin AW, Pavlovich CP, et al. (1)(8)F-DCFBC PET/CT for PSMA-Based Detection and

Characterization of Primary Prostate Cancer. J Nucl Med. 2015; 56:1003–1010. Comparison of MRI and 18F-DCFBC PETfor detection of malignancy in the prostate. [PubMed: 26069305]

34. Eiber M, Nekolla SG, Maurer T, Weirich G, Wester HJ, Schwaiger M. (68)Ga-PSMA PET/MR with multimodality image analysis for primary prostate cancer. Abdom Imaging. 2015; 40:1769–1771. [PubMed: 25412869]
35. Zamboglou C, Wieser G, Hennies S, Rempel I, Kirste S, Soschynski M, Rischke HC, Fechter T, Jilg CA, Langer M, et al. MRI versus Ga-PSMA PET/CT for gross tumour volume delineation in radiation treatment planning of primary prostate cancer. Eur J Nucl Med Mol Imaging. 2015 (in press).
36. Gakis G, Boorjian SA, Briganti A, Joniau S, Karazanashvili G, Karnes RJ, Mattei A, Shariat SF, Stenzl A, Wirth M, et al. The role of radical prostatectomy and lymph node dissection in lymph node-positive prostate cancer: a systematic review of the literature. Eur Urol. 2014; 66:191–199. [PubMed: 23735200]
37. Hijazi S, Meller B, Leitsmann C, Strauss A, Meller J, Ritter CO, Lotz J, Schildhaus HU, Trojan L, Sahlmann CO. Pelvic lymph node dissection for nodal oligometastatic prostate cancer detected by Ga-PSMA-positron emission tomography/computerized tomography. Prostate. 2015; 75:1934–40. [PubMed: 26356236]
38••. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, Eisenhut M, Boxler S, Hadaschik BA, Kratochwil C, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015; 42:197–209. A large retrospective study with ^{68}Ga-PSMA PET/CT demonstrating promising results for detection of biochemical recurrence of prostate cancer. [PubMed: 25411132]
39. Budaus L, Leyh-Bannurah SR, Salomon G, Michl U, Heinzer H, Huland H, Graefen M, Steuber T, Rosenbaum C. Initial Experience of Ga-PSMA PET/CT Imaging in High-risk Prostate Cancer Patients Prior to Radical Prostatectomy. Eur Urol. 2016; 69:393–6. [PubMed: 26116958]
40. Maurer T, Weirich G, Schottelius M, Weineisen M, Frisch B, Okur A, Kubler H, Thalgott M, Navab N, Schwaiger M, et al. Prostate-specific Membrane Antigen-radioguided Surgery for Metastatic Lymph Nodes in Prostate Cancer. Eur Urol. 2015; 68:530–534. [PubMed: 25957851]
41•. Freitag MT, Radtke JP, Hadaschik BA, Kopp-Schneider A, Eder M, Kopka K, Haberkorn U, Roethke M, Schlemmer HP, Afshar-Oromieh A. Comparison of hybrid Ga-PSMA PET/MRI and Ga-PSMA PET/CT in the evaluation of lymph node and bone metastases of prostate cancer. Eur J Nucl Med Mol Imaging. 2016; 43:70–83. The first study to compare ^{68}Ga-PSMA PET/CT and ^{68}Ga-PSMA PET/MRI. [PubMed: 26508290]
42. Afshar-Oromieh A, Haberkorn U, Schlemmer HP, Fenchel M, Eder M, Eisenhut M, Hadaschik BA, Kopp-Schneider A, Rothke M. Comparison of PET/CT and PET/MRI hybrid systems using a 68Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer: initial experience. Eur J Nucl Med Mol Imaging. 2014; 41:887–897. [PubMed: 24352789]
43. Rowe SP, Macura KJ, Ciarallo A, Mena E, Blackford A, Nadal R, Antonarakis E, Eisenberger M, Carducci M, Ross A, et al. Comparison of PSMA-based 18F-DCFBC PET/CT to Conventional Imaging Modalities for Detection of Hormone-Sensitive and Castration-Resistant Metastatic Prostate Cancer. J Nucl Med. 2016; 57:46–53. [PubMed: 26493203]
44. Rowe SP, Mana-Ay M, Javadi MS, Szabo Z, Leal JP, Pomper MG, Pienta KJ, Ross AE, Gorin MA. PSMA-Based Detection of Prostate Cancer Bone Lesions With F-DCFPyL PET/CT: A Sensitive Alternative to Tc-MDP Bone Scan and NaF PET/CT? Clin Genitourin Cancer. 2016; 14:115–8.
45. Pyka T, Weirich G, Einspieler I, Maurer T, Theisen J, Hatzichristodoulou G, Schwamborn K, Schwaiger M, Eiber M. [68Ga]PSMA-HBED PET for differential diagnosis of suspicious lung lesions in patients with prostate cancer. J Nucl Med. 2015 (in press).
46. Ceci F, Uprimny C, Nilica B, Geraldo L, Kendler D, Kroiss A, Bektic J, Horninger W, Lukas P, Decristoforo C, et al. (68)Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? Eur J Nucl Med Mol Imaging. 2015; 42:1284–1294. [PubMed: 25975367]
47••. Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, Graner FP, Kubler H, Haberhorn U, Eisenhut M, et al. Evaluation of Hybrid (6)(8)Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. J Nucl Med. 2015; 56:668–

674. The detection rate of PSMA PET/CT is influenced by PSA level and PSA velocity. [PubMed: 25791990]

48••. Morigi JJ, Stricker PD, van Leeuwen PJ, Tang R, Ho B, Nguyen Q, Hruby G, Fogarty G, Jagavkar R, Kneebone A, et al. Prospective Comparison of 18F-Fluoromethylcholine Versus 68Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. J Nucl Med. 2015; 56:1185–1190. PSMA PET/CT is superior to choline PET/CT for detection of recurrence of prostate cancer. [PubMed: 26112024]

49. Liu T, Wu LY, Fulton MD, Johnson JM, Berkman CE. Prolonged androgen deprivation leads to downregulation of androgen receptor and prostate-specific membrane antigen in prostate cancer cells. Int J Oncol. 2012; 41:2087–2092. [PubMed: 23041906]

50. Evans MJ, Smith-Jones PM, Wongvipat J, Navarro V, Kim S, Bander NH, Larson SM, Sawyers CL. Noninvasive measurement of androgen receptor signaling with a positron-emitting radiopharmaceutical that targets prostate-specific membrane antigen. Proc Natl Acad Sci U S A. 2011; 108:9578–9582. [PubMed: 21606347]

51. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol. 2014; 65:124–137. [PubMed: 24207135]

52. Hovels AM, Heesakkers RA, Adang EM, Jager GJ, Strum S, Hoogeveen YL, Severens JL, Barentsz JO. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clin Radiol. 2008; 63:387–395. [PubMed: 18325358]

53. Giesel FL, Fiedler H, Stefanova M, Sterzing F, Rius M, Kopka K, Moltz JH, Afshar-Oromieh A, Choyke PL, Haberkorn U, et al. PSMA PET/CT with Glu-urea-Lys-(Ahx)-[(68)Ga(HBED-CC)] versus 3D CT volumetric lymph node assessment in recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015; 42:1794–1800. [PubMed: 26162799]

54. Sterzing F, Kratochwil C, Fiedler H, Katayama S, Habl G, Kopka K, Afshar-Oromieh A, Debus J, Haberkorn U, Giesel FL. Ga-PSMA-11 PET/CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients. Eur J Nucl Med Mol Imaging. 2015

55. Demirkol MO, Acar O, Ucar B, Ramazanoglu SR, Saglican Y, Esen T. Prostate-specific membrane antigen-based imaging in prostate cancer: impact on clinical decision making process. Prostate. 2015; 75:748–757. [PubMed: 25598074]

56. Yu CY, Desai B, Ji L, Groshen S, Jadvar H. Comparative performance of PET tracers in biochemical recurrence of prostate cancer: a critical analysis of literature. Am J Nucl Med Mol Imaging. 2014; 4:580–601. [PubMed: 25250207]

57. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, Holland-Letz T, Hadaschik BA, Giesel FL, Debus J, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2014; 41:11–20. [PubMed: 24072344]

KEY POINTS

- ^{68}Ga PSMA PET/CT is demonstrating promising results in prostate cancer patients, especially for detection of biochemical recurrence after primary treatment.
- Second generation ^{18}F-PSMA PET/CT may be superior to ^{68}Ga-PSMA PET/CT.
- PSMA PET/CT may have a higher detection rate than choline PET/CT.
- The role of PSMA PET/MRI remains to be elucidated further, especially for guiding biopsies and delivery of focal therapy.
- “Image and treat” strategy is possible with PSMA ligands labeled with radioisotopes for imaging and therapy, and PSMA molecular imaging is paving the way for personalized medicine in prostate cancer.