PSMA Ligands for PET-Imaging of Prostate Cancer

Sarah M Schwarzenboeck1, Isabel Rauscher2, Christina Bluemel3, Wolfgang P Fendler4,5, Steven P Rowe6, Martin G Pomper6, Ali Asfhar-Oromieh7,8, Ken Herrmann4,9, Matthias Eiber2,4

1 Department of Nuclear Medicine, Rostock University Medical Centre, Rostock, Germany
2 Department of Nuclear Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
3 Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany
4 Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, USA
5 Department of Nuclear Medicine, Ludwig-Maximilians-University of Munich, Munich, Germany
6 The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
7 Department of Nuclear Medicine, Heidelberg University Hospital, Heidelberg, Germany
8 Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Centre, Heidelberg, Germany
9 Klinik für Nuklearmedizin, Universitätsklinikum Essen, Essen, Germany

Corresponding author:
Sarah M. Schwarzenböck
Department of Nuclear Medicine, Rostock University Medical Centre, Gertrudenplatz 1, 18147 Rostock, Germany.
Phone: +49 381 494 9101; fax: +49 381 494 9102;
e-mail: sarah.schwarzenboeck@med.uni-rostock.de

Key Words: prostate cancer, PET/CT, PSMA
Total Words: 7135
Running Title: PSMA PET-Imaging for Prostate Cancer
Abstract

Targeting the prostate-specific membrane antigen (PSMA) with $^{68}$Ga-labelled and $^{18}$F-labelled PET-agents has become increasingly important in recent years. Imaging of biochemically recurrent prostate cancer (PC) has been established as a widely accepted clinical indication for PSMA ligand PET/CT in many parts of the world due to the results of multiple, primarily retrospective, studies that indicate superior detection efficacy compared to standard of care imaging. For high-risk primary PC, evidence is growing that this modality significantly aids in the detection of otherwise occult nodal and bone metastases. For both clinical indications in recurrent as well as in primary prostate cancer, preliminary data demonstrate a substantial impact on clinical management. Emerging data imply that intraprostatic tumor localization, therapy stratification, and treatment monitoring of advanced disease in specific clinical situations might become future indications. Current criteria for image reporting of PSMA ligand PET are evolving given the expanding body of literature on physiologic and pathologic uptake patterns and pitfalls. This CME article intends to give an educational overview on the current status of PSMA ligand PET imaging including imaging procedure and interpretation, clinical indications, diagnostic potential, and impact on treatment planning.
Introduction
Prostate cancer (PC) is the most common cancer in men and the third most frequent cause of cancer-related death in men worldwide (1). After primary treatment, in approximately 30-40% of patients biochemical recurrence (BCR) occurs. After potential salvage treatment options patients are usually treated with androgen-deprivation therapy (ADT). Typically after 2–8 years of ADT, PSA begins to rise again indicating metastatic castration resistant prostate cancer (mCRPC), the lethal form of the disease.

In the primary setting, detection of extra-prostatic spread is crucial for further treatment planning as well as prognosis. However, cross-sectional imaging and bone scintigraphy, as recommended in many guidelines, have shown limitations in detecting sites of nodal or bone involvement in pre-operative patients (2-4). Further, in patients with high suspicion of PC, multi-parametric magnetic resonance imaging (mpMRI) helps to rule out clinically significant disease and to guide targeted biopsy (5), although mpMRI can miss aggressive PC lesions (6). In the BCR accurate restaging is crucial as local vs. systemic disease substantially influences further treatment management. Accurate diagnosis of the site(s) and extent of disease can be used in tailoring potential salvage treatments; however, standard of care imaging also has sensitivity and specificity limitations in this regard.

In contrast, positron emission tomography/computed tomography (PET/CT) combining functional and morphological information is increasingly being used within the last decade for PC imaging. \(^{18}\)F-FDG is the most widely used radiotracer in oncologic PET/CT imaging; however, only a minority of PC (i.e. only aggressive, poorly differentiated or undifferentiated PC) show a high glycolytic rate, limiting the use of \(^{18}\)F-FDG PET (7,8). In Europe, radiolabelled choline derivatives (\(^{18}\)F-fluorocholine or \(^{11}\)C-choline) were amongst the most commonly used PET tracers for PC imaging. They were most frequently used for restaging of PC and primary staging in selected cases (e.g. high risk PC). Detection and localization of primary PC is limited by
nonspecific uptake in benign intraprostatic pathologies (9). Recent metaanalyses reported a high specificity of 95%, but a poor sensitivity of 49% in primary nodal staging (10). Detection rates are positively associated with PSA-level, but low (<50%) in patients with early BCR (i.e. PSA-value <2 ng/ml) (11). Other PET radiopharmaceuticals such as $^{11}$C-Acetate have been investigated or even FDA approved, such as $^{18}$F-FACBC in parts demonstrating superiority compared to choline derivatives (12-15).

Given the limitations with the most widely investigated PET tracers, targeting the prostate-specific membrane antigen (PSMA) with molecular imaging agents has recently been increasingly investigated. PSMA is a transmembrane protein that is highly overexpressed (100-1000 fold) on almost all PC tumors (16-19). Only 5-10% of primary PC lesions have been shown to be PSMA-negative (20,21). PSMA expression levels increase with higher tumor stage and grade (16,18,22). Presently, the only FDA approved PSMA-agent is a radiolabelled anti-PSMA antibody (ProstaScint, capromab pendetide; EUSA Pharma, Langhorne, PA); however, this targets an intracellular epitope of PSMA (7E11) (19) which cannot be accessed in viable tumor cells and limits diagnostic performance (23).

In contrast, small molecule PSMA ligands bind to the active site in the extracellular domain of PSMA and are internalized and endosomally recycled, leading to enhanced tumor uptake and retention and high image quality (24-27). The most widely used $^{68}$Ga-labelled PSMA-ligands for PET-imaging are $^{68}$Ga-PSMA-11 (syn. $^{68}$Ga-PSMA-HBED-CC) and the theranostic agents $^{68}$Ga-PSMA-617 and $^{68}$Ga-PSMA-I&T (28,29). $^{18}$F-labelled agents include $^{18}$F-DCFBC (30,31), $^{18}$F-DCFPyL (32) and $^{18}$F-PSMA 1007 (33). They exploit the average lower positron range reducing blurring effects, longer half-life and the potential of centralized production and distribution of $^{18}$F compared to $^{68}$Ga. An (also tabular) overview of the most common PSMA ligands in clinical use was recently published (34).
This article intends to give an educational overview on the current status of PSMA ligand PET including imaging procedure and interpretation, clinical indications, diagnostic potential, and impact on treatment planning.

Main Clinical Indications of PSMA ligand PET/CT and Current Evidence in the Literature

1. Biochemical Recurrence

Approximately 30-40% of patients will fail primary treatment with a rising PSA indicating recurrent or metastatic disease. Depending on the localization and extent of disease and prior treatment, different salvage options are available. Salvage surgery or salvage radiotherapy (RT) are used for local and nodal recurrence, stereotactic RT for oligometastatic disease or systemic treatment in disseminated disease. Therefore, accurate restaging is crucial in recurrent PC patients. Currently, imaging of BCR is the most clinically accepted and validated indication for PSMA ligand PET/CT. As a prospective head-to-head comparison of $^{68}$Ga-PSMA ligands and choline derivatives is missing, several, mainly retrospective, studies investigating BCR patients showed a higher diagnostic efficacy for PSMA ligand to choline derivatives (35-37). SUV$_{max}$ and tumor-to-background ratios were superior for $^{68}$Ga-PSMA-11 compared to $^{18}$F-fluorocholine (35), and $^{68}$Ga-PSMA-11 showed a higher detection rate than $^{11}$C-choline for lymph nodes as well as bone metastases (37). Positive findings exclusively detected by $^{18}$F-fluorocholine PET/CT were rare (36). Three large retrospective studies (including 319 patients, 248 and 1,007 patients, respectively) reported detection rates for $^{68}$Ga-PSMA-11 PET/CT in BCR of 88% and almost 90% (38-40). In patients after curative treatment with a very low PSA level of <0.5 ng/mL the reported detection rate of PSMA ligand PET/CT ranged from 50 to 58% in different studies (36,38-40). A recent study including only patients after prior radiotherapy (median PSA of 5.8 ng/ml) presented detection rates of 33.3% for PSA <0.5 ng/mL, 71.4% for PSA 0.5 to <1 ng/mL.
and 93.3% for PSA 1 to <2 ng/mL. Local recurrence after radiotherapy was reported in 71% of the cohort and 40% had suspected lymph node metastasis (41). A first meta-regression analysis in a systematic review including 10 studies was recently published. It resulted in a predicted positivity rate of PSMA-ligand PET/CT of 42%, 58%, 76%, and 95% for PSA values of 0-0.2, 0.2-1, 1-2, and >2 ng/ml (42). However, the results of this analysis need to be interpreted with cautions as different 68Ga-PSMA-based PET-tracers were pooled and no systematic histologic verification was available. Figure 1 and 2 show examples of nodal and local recurrence detected by 68Ga-PSMA ligand PET/CT.

Studies evaluating 18F-labelled PSMA ligands suggest similar conclusions. In metastatic PC patients, the diagnostic performances of 18F-DCFBC and 18F-DCFPyL PET/CT were both superior compared to standard of care imaging for detecting suspicious lesions (32,43). In a head-to-head comparison in 14 patients with recurrent PC, staging with 18F-DCFPyL PET/CT was equivalent to 68Ga-PSMA-11 (44). A follow-up study from the same group using PSA-adjusted parallel biochemically recurrent PC patient cohorts (including a total of 191 patients) found that 18F-DCFPyL was non-inferior to 68Ga-PSMA-11 (45) and suggested an improved sensitivity of the 18F-labelled radiotracer in the PSA range of 0.5-3.5 ng/mL (with the caveat that different injected doses and acquisition parameters were utilized for the two PSMA-targeted agents). Further in-depth clinical studies with standardized acquisition protocols and histological validation are needed to establish the comparative performance of these two radiotracers.

2. Primary Staging

In high-risk PC patients diagnosis of local extent and extra-prostatic spread, i.e. sites and extent of nodal and distant metastases, is crucial influencing further treatment planning (standard nodal dissection vs. extended dissection; change of primary RT field). Growing evidence underscores the role of PSMA ligand PET/CT imaging in primary PC, especially for N-/M-staging in a high-
risk population. In detecting sites of nodal or bone involvement in pre-operative patients cross-sectional imaging has shown a limited pooled sensitivity and specificity of 42% and 82% for CT and 39% and 82% for MRI, respectively (3), as up to 80% of lymph node metastases in PC are harbored in normal sized lymph nodes (2). Several studies showed a clear superiority of PSMA ligand PET/CT compared to standard of care imaging (CT, MRI or bone scan) (21,46-49). For example, in a retrospective analysis of 130 patients with primary intermediate to high-risk PC using template based pelvic histopathology as reference, $^{68}$Ga-PSMA-11 PET performed significantly better than morphological imaging for N-staging both on a patient and a template basis ($p=0.002$ and $<0.001$, respectively). On template based analysis the sensitivity, specificity and accuracy were 68.3%, 99.1% and 95.2% for $^{68}$Ga-PSMA-11 PET and 27.3%, 97.1% and 87.6% for morphological imaging, respectively (21). Similar results on the diagnostic efficacy of PSMA ligand PET for the detection of nodal metastases were obtained in other studies (47,49). For bone metastases, Pyka et al. demonstrated that $^{68}$Ga-PSMA-11 PET significantly outperformed bone scan due both to its high sensitivity and high specificity on a patient and region basis ($p=0.006$ and $p<0.0001$, respectively). As a histologic gold standard is not feasible in most cases for bone lesions a best valuable comparator was defined based in this study on a consensus review of all available current and follow-up images (including bone scan/SPECT, PET, CT, MR) and clinical data (48).

In regards to intraprostatic tumor localization by $^{68}$Ga-PSMA-11 PET/CT, imaging findings were correlated with histopathology using segment or voxel-based approaches in several studies (50-52). These studies demonstrated relatively similar results with a significantly higher $^{68}$Ga-PSMA-11 uptake in positive segments compared to negative segments ($SUV_{\text{max}}^{11.8}$ vs. 4.9 and 11.0 vs. 2.7, respectively, $p < 0.001$ each) (50,51). Results from combining $^{68}$Ga-PSMA-11 and mpMRI on 53 preoperative intermediate/high risk patients indicated a potential for targeting biopsies. Hybrid $^{68}$Ga-PSMA-11 PET/MRI significantly outperformed
mpMRI and $^{68}$Ga-PSMA-11 PET in sensitivity and specificity for tumor localization on a sextant basis (76% and 97% for hybrid $^{68}$Ga-PSMA-11 PET/MRI, 58% and 82% for mpMRI and 64% and 94% for $^{68}$Ga-PSMA PET, respectively) (53).

Using $^{18}$F-labelled compounds in a first cohort of 13 patients, sensitivity of MRI in the detection of primary PC was superior to $^{18}$F-DCFBC PET/CT; however, $^{18}$F-DCFBC PET/CT demonstrated a higher specificity for clinically significant disease (31). The relatively low sensitivity of $^{18}$F-DCFBC in this context was likely at least partially attributable to its high blood pool activity and low tumor-to-background ratios in relation to other small molecule PSMA-targeted ligands, limitations potentially addressed by newer $^{18}$F-labeled agents such as $^{18}$F-DCFPyL and $^{18}$F-PSMA 1007. A first retrospective study using $^{18}$F-PSMA 1007 imply its high diagnostic potential by correctly detecting 18 out of 19 histopathologically validated lymph node metastases in 8 patients with primary PC (33).

3. Advanced Disease

Typically after 2–8 years of ADT the rise of PSA heralds the onset of mCRPC which is the lethal form of the disease and requires further systemic treatment (second ADT and taxane based chemotherapy). The role of choline PET/CT in monitoring of systemic treatment in mCRPC has been investigated in previously published studies and is still under debate (54,55). Sclerotic bone metastases are not regarded as “target lesions” using RECIST 1.1 and bone scintigraphy suffers from the well-known “flare phenomenon”. As preclinical data show that changes in PSMA-expression can indicate therapeutic success of taxane-based therapy (56), PSMA ligand PET/CT might overcome many of the limitations of standard of care imaging. However, ADT might represent a potential confounder due to temporal PSMA upregulation after initiation, followed by downregulation and finally gross overexpression in androgen resistant tumors as has been found in preliminary studies (57-60).
Monitoring systemic treatment in certain clinical scenarios could become a future indication for PSMA ligand imaging, however, evidence is currently still sparse (61). PSMA ligand PET/CT has an evolving role in PSMA-targeting treatments (e.g. radioligand therapy), evaluating target expression and therefore potentially predicting response (62-64). A rare, but potential limitation is absent or low PSMA-expression (e.g. in visceral metastases) in advanced disease which may be related to therapy-induced specific biological subtypes (e.g. neuroendocrine differentiated PC) (65,66). For further information on the use of PSMA-ligands for diagnosis as well as therapy see (67,68).

Impact on Treatment Planning

Treatment management of PC is highly associated with the site(s) and extent of disease (local/nodal vs. systemic disease). Several studies have investigated the impact of PSMA ligand PET/CT on patient management and therapy. Most studies have focussed on the value of PSMA ligand PET/CT in patients with BCR after curative treatment and report changes in therapeutic management depending on the specific clinical scenario and the extent of treatment modification (69-74). Most recently, an overall change in the therapeutic management in 75% of 131 patients after primary treatment was shown (69). Similar results were found in a smaller patient cohort of 45 patients resulting in a change of treatment in 19 of 45 patients (42.2%) including extension of RT field or administration of dose escalation to local recurrence. In 2 of 19 patients, salvage RT was replaced by systemic treatment due to multiple metastatic lesions (70). In a well-defined patient cohort prior to salvage RT, a major management change in 20 of 70 (28.6%) patients with a PSA level < 1 ng/mL was demonstrated by van Leeuwen et al. (74).

In the setting of primary treatment a small cohort of 15 patients underwent PSMA ligand PET/CT and the imaging was found to influence clinical TNM stage in 53.3% and RT plan in 33.3% of patients, respectively (71). Combining both the setting of RT planning in primary and recurrent...
disease, two recent publications reported an impact of PSMA ligand PET/CT in 50.8% and 53.7% of patients, respectively (72, 73).

PSMA ligand PET/CT may also be used to guide salvage lymph node dissection (sLND), an emerging concept that may spare some patients ADT in early BCR. With the rise of PSMA ligand PET/CT, there is increasing interest both based on the high specificity as well as improved sensitivity for detection of recurrent disease. Rauscher et al. have demonstrated high specificity (>95%) and superior sensitivity (78%) compared to standard of care imaging (27%) in patients who underwent sLND (75). Preliminary results showed the feasibility of radioguided surgery (RGS) exploiting pre-operative labeling of lymph node metastases with a gamma emitting PSMA-ligand (e.g. 111In-PSMA I&T) allowing detection and resection of even very small metastatic lesions (76, 77). The recent introduction of 99mTc-PSMA I&S might facilitate dissemination of this promising technique (78).

**Patient Preparation and PSMA ligand PET/CT Image Acquisition**

**Patient Preparation**

Patients should be well hydrated before the study and during uptake time (e.g. 500 mL of water orally during a 2 h period prior to acquisition). To reduce artifacts due to high tracer activity in the urinary system (potentially resulting in “halo artefacts” as well as false positive findings) it is beneficial to co-inject furosemide at the time of tracer injection and to empty the bladder immediately prior to image acquisition (79). Rectal filling with a negative contrast agent (100–150 mL) is optional to improve anatomical delineation of the rectum and differentiation of e.g. lymph nodes and seminal vesicles from adjacent structures.

**PET/CT Acquisition**
68Ga-labelled PSMA ligands are applied intravenously using a recommended activity of 2 MBq per kilogram bodyweight. 68Ga-PSMA-11 PET/CT is routinely conducted 1h p.i. according to its first described clinical set-up (27). However, the same article already demonstrated that late images conducted at 3h p.i. show the majority of PCa lesions with higher contrast due to an ongoing decrease of the background signal and increase of tracer uptake in the majority of PCa lesions. Recently, one study demonstrated that the higher uptake and contrast of PC lesions in scans at 3h p.i. result in a higher number of lesions detected by 68Ga-PSMA-11 PET/CT as well as in a higher number of patients with an overall positive PET result (80). In contrast, most recently, another large retrospective study showed no clear advantage of delayed imaging (81). However, delayed imaging might be considered in cases of equivocal findings or in the context of low PSA levels. Imaging with 18F-labelled agents has been described at 60 minutes p.i. and 120 minutes p.i., with preliminary evidence indicating an improvement in lesion detection with later time point imaging (32,82).

Depending on previous imaging, either a low dose or a diagnostic CT scan with or without i.v. contrast agent is performed. The PET acquisition should be performed in 3D-mode with an acquisition time of 3-4 min per bed position. Technical details on correction of emission data, image reconstruction, and post-processing for 68Ga-labelled PSMA ligands have been recently published (79).

**Practical Issues**

1. Image Display and Reading

Hybrid PET/CT image review is recommended on a dedicated post-processing workstation allowing parallel visualization of PET-, CT-, and PET/CT fused images in the axial, coronal, and sagittal planes as well as maximum intensity projections (3D cine mode). PET and CT should be linked at the same table position to help localize PET-positive findings. For PET interpretation,
both uncorrected and attenuation-corrected images need to be assessed to identify artifacts (e.g. from contrast agents, metal implants, patient motion). Further, dynamic variation of SUV-treshold by changing display windowing is necessary to adjust e.g. the uptake of PSMA-ligands in/or adjacent to organs with high background such as the kidneys, ureter or the urinary bladder. Otherwise findings such as local recurrence near the urinary bladder might be missed. Semi-quantitative information of suspicious lesions (SUV\textsubscript{mean/max}) can be derived on all slices of the attenuation corrected PET using a 3D volume-of-interest. Notably, currently no SUV-thresholds have been stringently defined that reliably aid in differentiation between benign and malignant lesions. Diagnostic contrast-enhanced CT should be evaluated separately according to established radiological criteria on a dedicated post-processing workstation.

2. Physiological PSMA Uptake and Variants

All low-molecular-weight PSMA ligands for PET-imaging demonstrate typical physiologic PSMA ligand uptake in the lacrimal glands, parotid glands, submandibular glands, liver, spleen, small intestine, kidneys, and colon (for an image example see Figure 3). Notably, PSMA ligand uptake in the salivary gland is not finally proven to be related to PSMA-expression in the tissue. In addition, PSMA is synonymous with N-acetyl-L-aspartyl-L-glutamate peptidase I which is an enzyme expressed in human brain tissue and has a role of regulating Glutamate concentration.

All \textsuperscript{68}Ga- and \textsuperscript{18}F-labelled PSMA ligands are excreted via the kidneys with subsequent high radiotracer uptake in kidneys and urinary collection (16). Limited preliminary data indicate that \textsuperscript{18}F-PSMA 1007 might have reduced urinary clearance within the first two hours post injection potentially allowing for improved assessment of the prostate within this time window (33).

3. Pathologic PSMA uptake related to PC and metastases
The excellent specificity of PSMA ligands especially for lymph node metastases was demonstrated in several studies (21,39,46,83-85). Therefore, any focal uptake of the PSMA-ligand higher than the surrounding background in morphologically visible lesions and not associated with physiological uptake should be considered suspicious.

The pathologic uptake should be reported as low, moderate or intense by comparison to the background uptake e.g. compared to liver or spleen as recently described (86). Besides local involvement (primary tumor vs. local recurrence), the typical metastatic pattern is primarily the regional pelvic lymph nodes. This is often followed by distant lymph nodes (above the aortic bifurcation) and bone metastases. In advanced disease, PC can even spread to the liver, lungs or other visceral organs.

4. Limitations and Pitfalls in Clinical Interpretation

It is also well known that the neovasculature of many solid tumors can also expresses PSMA (22). Accordingly, there is increasing evidence that PSMA ligand uptake is not exclusively specific for PC. A large number of case series and reports describe increased PET-signal in benign lesions (e.g. neurogenic tissue, Paget’s disease, thyroid adenoma, granulomatous disease, adrenal adenoma, etc.) as well as in malignant pathologies (e.g. renal cell carcinoma, lung cancer, glioblastoma, hepatocellular carcinoma, and thyroid cancer) (87-95). Table 1S (supplemental data) summarizes the current evidence in the literature. As many of these potential pitfalls can be solved in clinical context or by adding further imaging, increased PSMA ligand uptake in ganglia is the most common pitfall (for an image example see Figure 4). Their sites (especially sacral and coeliac) are near the typical locations of lymph node metastases. Thus, knowledge of the CT-characteristics (e.g. size, shape, and specific location) is crucial for reliable differentiation. In a recent investigation, at least one coeliac ganglion with increased PSMA ligand uptake mimicking retroperitoneal lymph node disease was found in 89% of patients.
undergoing $^{68}\text{Ga}$-PSMA-11 PET/CT examinations (96). Another important limitation is the absent PSMA-overexpression in the primary tumor and/or its metastases in up to 10% of patients with primary PC or (as mentioned above) decreased PSMA-expression in advanced disease (21). Side-by-side interpretation of the diagnostic CT scan as part of the PSMA ligand PET/CT examination is important. An example of a patient with a PSMA-positive rib fracture can be seen in Figure 5.

5. Current regulatory status for PSMA-ligands

Currently PSMA-ligands are not approved for clinical use in any country. In many European countries (especially Germany and Austria) the use of non-approved agents for PET-imaging is possible within certain limitations. For the use, the number of sites offering PSMA-ligands is currently increasing as many institutions are evaluating PSMA-ligands in prospective trials either for staging or restaging of PC. Most of the protocols for $^{68}\text{Ga}$-PSMA-11 are harmonized under a multi-centric approach headed by the clinical trials network (CTN) of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) which is intended to trigger a new drug application and potential FDA-approval. In addition, $^{18}\text{F}$-DCFPyL is currently in multicenter phase II/III trials. Finally, an increasing number of clinical guidelines adopt the use of PSMA-ligand PET especially for BCR.

Conclusion

PSMA ligand PET/CT has become a clinically accepted technique for PC imaging worldwide and provides high diagnostic efficacy in recurrent PC as well as in staging of high risk PC. Evidence is emerging that it substantially influences treatment decisions by detection of sites of recurrence and nodal/distant metastases that are often occult on standard of care imaging. Intraprostatic tumor localization, therapy stratification and treatment monitoring of advanced disease are
potential future indications. Standardized criteria for image interpretation of PSMA ligand PET are evolving, facilitating its use in clinical practice. Several prospective trials are underway to support final market approval and reimbursement.

**Conflict of interest**

MGP is a coinventor on a U.S. Patent covering $^{18}$F-DCFPyL, and as such is entitled to a portion of any licensing fees and royalties generated by this technology. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict-of-interest policies. MGP and SPR have received research support from Progenics Pharmaceuticals, the licensee of $^{18}$F-DCFPyL.
References


Figure 1:

63 year old patient with biochemical recurrence (PSA of 0.21 ng/ml) after radical prostatectomy (initially pT2c N0 M0 L1/V1 R1 G1, Gleason score of 7), local radiation treatment, and antiandrogen therapy. $^{68}$Ga PSMA ligand PET/CT exhibits a solitary left iliac radiotracer-positive lymph node. Transaxial (A) CT, (B) PET, (C) fused PET/CT. Patient was referred for salvage lymph node dissection.
Figure 2:

78 year old patient with biochemical recurrence (PSA of 0.54 ng/ml) after radical prostatectomy (initially pT3b N0 M0 R0 G2). $^{68}$Ga PSMA ligand PET/CT reveals focal uptake in the left paramedian prostatic fossa indicating local recurrence. Transaxial (A) CT, (B) PET, (C) fused PET/CT. Patient was referred for salvage radiation treatment.
Figure 3:

Maximum intensity protection (MIP) images displaying typical PSMA ligand biodistribution (images were acquired with A $^{18}$F-DCFBC and B $^{18}$F-DCFPyL). Physiologic accumulation is seen in lacrimal and salivary glands, nasal mucosa, liver, spleen, bowel, kidneys, ureter on the left side, and bladder.
Figure 4:

Transaxial CT (A), PET (B), and fused PET/CT (C) $^{68}$Ga-PSMA ligand PET/CT scan demonstrating moderately increased, focal PSMA ligand uptake in a comma-shaped soft tissue structure between the left adrenal gland and the aorta, indicating normal variant uptake in a coeliac ganglion.
Figure 5:

$^{68}$Ga-PSMA ligand PET/CT scan exhibiting moderate, focal PSMA ligand uptake in a left-sided rib in transaxial PET (B) and fused PET/CT images (D). Corresponding CT images (A, C) confirm a minimally displaced fracture of the rib.
### Table 1: PSMA-ligand positive non-PC lesions

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Specific entities</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuroectodermal tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcortical infarct</td>
<td></td>
<td>(1,2)</td>
</tr>
<tr>
<td>Meningioma</td>
<td></td>
<td>(3,4)</td>
</tr>
<tr>
<td>Schwannoma</td>
<td></td>
<td>(5,6)</td>
</tr>
<tr>
<td>Cervicothoracic (stellate), coeliac and sacral ganglia</td>
<td></td>
<td>(7,8)</td>
</tr>
<tr>
<td><strong>Head and Neck</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign thyroid nodule (follicular adenoma)</td>
<td></td>
<td>(9-11)</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td></td>
<td>(12-15)</td>
</tr>
<tr>
<td>Oro-pharyngeal squamous cell carcinoma</td>
<td></td>
<td>(16)</td>
</tr>
<tr>
<td>Adenoid Cystic Carcinoma</td>
<td></td>
<td>(17)</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td></td>
<td>(18)</td>
</tr>
<tr>
<td>Pseudoangiomatous stromal hyperplasia</td>
<td></td>
<td>(19)</td>
</tr>
<tr>
<td><strong>Lungs and granulomatous disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis and inflammatory disease</td>
<td></td>
<td>(20)</td>
</tr>
<tr>
<td>NSCLC</td>
<td></td>
<td>(21,22)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
<td>(23-26)</td>
</tr>
<tr>
<td>Wegener</td>
<td></td>
<td>(27)</td>
</tr>
<tr>
<td>Activated tuberculosis</td>
<td></td>
<td>(22)</td>
</tr>
<tr>
<td>Anthracosis</td>
<td></td>
<td>(28)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumor</td>
<td></td>
<td>(29)</td>
</tr>
<tr>
<td>Pancreatic serous cystadenoma</td>
<td></td>
<td>(30)</td>
</tr>
<tr>
<td>Hepatic capillary hemangioma</td>
<td></td>
<td>(31)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td></td>
<td>(32,33)</td>
</tr>
<tr>
<td>Adrenal adenoma</td>
<td></td>
<td>(34)</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td></td>
<td>(35)</td>
</tr>
<tr>
<td>Rectal carcinoma</td>
<td></td>
<td>(36,37)</td>
</tr>
<tr>
<td><strong>Genitourinary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell carcinoma (different subtypes)</td>
<td></td>
<td>(38-46)</td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td></td>
<td>(47)</td>
</tr>
<tr>
<td>Penile cancer</td>
<td></td>
<td>(48)</td>
</tr>
<tr>
<td><strong>Skeleton</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. Paget</td>
<td></td>
<td>(49-53)</td>
</tr>
<tr>
<td>Acute/healing fracture</td>
<td></td>
<td>(54,55)</td>
</tr>
<tr>
<td><strong>Soft-tissue lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatofibroma</td>
<td></td>
<td>(56)</td>
</tr>
<tr>
<td>Nodular fasciitis</td>
<td></td>
<td>(57)</td>
</tr>
<tr>
<td>Desmoid tumor</td>
<td></td>
<td>(58)</td>
</tr>
<tr>
<td>Subcutaneous hemangioma</td>
<td></td>
<td>(59)</td>
</tr>
<tr>
<td><strong>Systemic disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td></td>
<td>(60,61)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td></td>
<td>(62)</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td></td>
<td>(63)</td>
</tr>
</tbody>
</table>


PSMA Ligands for PET-Imaging of Prostate Cancer

Sarah M. Schwarzenböck, Isabel Rauscher, Christina Bluemel, Wolfgang P. Fendler, Steven P. Rowe, Martin G. Pomper, Ali Afshar-Oromieh, Ken Herrmann and Matthias Eiber

J Nucl Med.
Published online: July 7, 2017.
Doi: 10.2967/jnumed.117.191031

This article and updated information are available at:
http://jnm.snmjournals.org/content/early/2017/07/07/jnumed.117.191031

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml

JNM ahead of print articles have been peer reviewed and accepted for publication in JNM. They have not been copyedited, nor have they appeared in a print or online issue of the journal. Once the accepted manuscripts appear in the JNM ahead of print area, they will be prepared for print and online publication, which includes copyediting, typesetting, proofreading, and author review. This process may lead to differences between the accepted version of the manuscript and the final, published version.

The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

© Copyright 2017 SNMMI; all rights reserved.