

# Keeping up with the prostate-specific membrane antigens (PSMAs): an introduction to a new class of positron emission tomography (PET) imaging agents

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**Abstract:** Prostate-specific membrane antigen (PSMA) targeted positron emission tomography (PET) is an emerging prostate cancer imaging method, which has been reported to have a higher sensitivity and specificity than the currently approved PET imaging agents. Multiple PSMA ligands are being investigated around the world and applications range from primary tumor characterization, to local staging, biochemical recurrence, metastasis, and image-guided interventions. The most investigated PET tracers are labelled with 68-Gallium or 18-Fluoride and are discussed in this review. Additionally, <sup>99m</sup>Tc labeled PSMA agents for single photon emission computed tomography (SPECT) imaging are elucidated as an alternative method of PSMA image acquisition.

**Keywords:** Positron emission tomography/computed tomography (PET/CT); nuclear medicine; prostatic neoplasms; tomography; emission-computed, single-photon; gallium

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## Introduction

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, which is present in the epithelium of surrounding prostatic ducts (1). Its coding domain is usually expressed in patients with clinically significant prostate cancer (PCa) and its over-expression on the cell membrane of prostatic epithelial cells has been shown to be a sensitive biomarker of aggressive disease. PSMA expression increases with both increasing stage and tumor grade and its radiolabeling has been investigated in a variety of PCa settings including local staging, metastasis, biochemical recurrence (BCR), and image-guided interventions (2-4).

PSMA ligands that are used in imaging bind to the surface receptor and are then internalized within cells. Due to their small size, unbound ligands are rapidly cleared by the body leading to high tumor to background ratios (5). PSMA is not specific to PCa, and its uptake is observed in normal organs including salivary/lacrimal glands, small bowel, proximal renal tubular cells, as well as the neovasculature of some tumors (transitional cell carcinomas, renal cell carcinomas, colon, esophageal, thyroid, lung and brain cancer) (6,7). Labeling the ligand with either 68-Gallium (<sup>68</sup>Ga) or 18-Fluoride (<sup>18</sup>F) results in an agent that is rapidly taken up in PCa and rapidly cleared. PSMA

radioligands are administered as an intravenous bolus and scanning commences 1–2 hours post injection. Most PSMA agents are excreted via the urinary system except for PSMA-1007 which is excreted via the hepatobiliary system. The first PSMA agents to be reported in humans were  $^{68}\text{Ga}$  labeled tracers.  $^{68}\text{Ga}$  requires a generator and only a limited number of doses can be extracted per day; however, once obtained, labeling of the PSMA targeting ligand is straightforward (8).  $^{68}\text{Ga}$  has a 68-minute half-life, making it challenging to deliver from a centralized facility and its high positron energy leads to a slightly decreased spatial resolution. On the other hand,  $^{18}\text{F}$  can be produced in large batches at a centralized facility with a cyclotron, conjugated to its ligand and then shipped to local nuclear medicine departments making production simpler. Moreover,  $^{18}\text{F}$  has lower positron energies resulting in sharper imaging. Both agents are being currently commercialized.

Although thousands of patients have been scanned to date, none of the PSMA radioligands have been approved by the U.S. Food and Drug Administration or European Medicines Agency. Thus, PSMA positron emission tomography (PET) imaging lacks consensus regarding its indications. European guidelines suggest its use in the setting of staging and BCR (9). In the U.S., the only approved PSMA imaging agent is a radiolabeled anti-PSMA antibody, capromab pentetide (ProstaScint; EUSA Pharma) which has been available since the late 1990s. Unfortunately, this agent has multiple drawbacks including its very slow clearance and its targeting of the intracellular domain of PSMA causing low uptake and increased background signal (10,11). Moreover, capromab is labeled with 111-Indium ( $^{111}\text{In}$ ) which is a long-lived single photon emission computed tomography (SPECT) agent resulting in lower resolution images. For these reasons, this agent is not commonly employed in the clinic. The new generation of small molecule PSMA-based tracers show outstanding sensitivity and specificity for PCa detection, and are likely to become available in the clinic in the next few years.

A variety of other PET tracers have been proposed for imaging PCa. The most widely used oncologic PET/CT imaging agent,  $^{18}\text{F}$ -fluorodeoxyglucose (FDG), is not useful for prostate imaging because of its low uptake in most PCa (12). European guidelines mention the use of  $^{18}\text{F}$  choline PET/CT in patients with recurrent PCa; however, its sensitivity is relatively poor and most patients must have PSA >2 ng/mL before  $^{18}\text{F}$  choline PET/CT turns positive (13). A recent study by Afshar *et al.* compared  $^{68}\text{Ga}$ -

PSMA-11, to  $^{18}\text{F}$ -fluoromethylcholine PET/CT in a cohort of 37 men with biochemically recurrent PCa (13,14) and showed that  $^{68}\text{Ga}$ -PSMA-11 PET/CT was more sensitive than  $^{18}\text{F}$ -fluoromethylcholine PET/CT (87% *vs.* 70%). Moreover, the detection rate in  $^{68}\text{Ga}$ -PSMA-11 PET/CT group was significantly higher (78 lesions detected in 32 patients *vs.* 56 lesions in 26 patients,  $P=0.04$ ). All 56 lesions observed in  $^{18}\text{F}$ -fluoromethylcholine PET/CT studies were also visualized in  $^{68}\text{Ga}$ -PSMA-11 PET/CT, indicating its superior performance in this small cohort. In line with this publication, more recent studies of PSMA tracers demonstrate superior performance consistent with this study over both  $^{18}\text{F}$  choline-based radiotracers (such as  $^{18}\text{F}$ -fluoromethylcholine) and fluciclovine (a recent FDA approved  $^{18}\text{F}$  radiotracer for detection of recurrent PCa by mechanisms of amino acid transport).  $^{11}\text{C}$  choline is approved in the U.S. for recurrent PCa but its use is limited by the short half-life of the agent (20 min) and the requirement for an onsite cyclotron and radiochemistry capabilities (15).

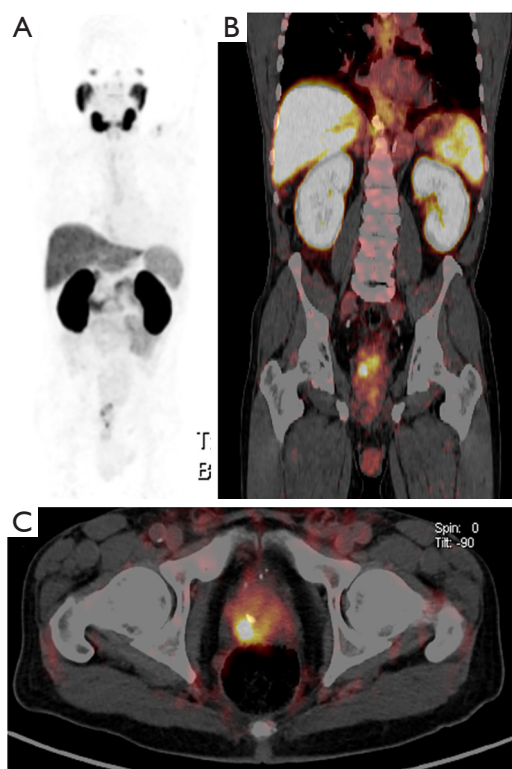
A variety of PSMA radioligands have been developed with slightly different properties. Almost all PSMA-based PET agents are urea-based molecules which bind with high affinity to the enzymatic portion of PSMA. Examples include  $^{68}\text{Ga}$ -PSMA-HBED-CC (PSMA-11),  $^{68}\text{Ga}$ -PSMA-617,  $^{68}\text{Ga}$ -PSMA-I&T,  $^{18}\text{F}$ -DCFBC,  $^{18}\text{F}$ -DCFPyL, and  $^{18}\text{F}$ -PSMA-1007, all of which will be discussed in this review. Additionally, new SPECT-based markers which are investigated in a few centers will be discussed as a feasible alternative for PSMA-PET imaging (16). Theranostic applications of PSMA are briefly discussed, but are beyond the scope of this article.

## PSMA-PET tracers

### $^{68}\text{Ga}$ -PSMA-11

$^{68}\text{Ga}$ -PSMA-11 (also known as  $^{68}\text{Ga}$ -HBED-CC-PSMA) was introduced in humans in 2012 and is the most widely used and studied PSMA-ligand (5,17,18) (Figure 1).  $^{68}\text{Ga}$  is eluted from a  $^{68}\text{Ge}/^{68}\text{Ga}$  generator system and added to a binding kit containing the precursor (19). Many centers label the compound on-site because of the relatively short 68-minute half-life of  $^{68}\text{Ga}$  (20).

This agent has been investigated in all stages of PCa. It was histologically validated in a cohort with localized primary PCa by Eiber *et al.* which compared multiparametric magnetic resonance imaging (mpMRI),



**Figure 1**  $^{68}\text{Ga}$ -PSMA-11 PET/CT in primary localized PCa. A 77-year-old man with newly diagnosed high-risk prostate cancer; Gleason 3+3, PSA: 22 ng/mL. He underwent  $^{68}\text{Ga}$ -PSMA-11 PET/CT including maximal intensity projection (A), fused coronal, axial PET/CT (B,C), respectively. The images revealed a local focus of uptake in the right peripheral zone of the prostate, with an otherwise negative scan. PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen; PCa, prostate cancer.

PET and combined  $^{68}\text{Ga}$ -PSMA-11 PET/MRI for localization of primary PCa in 53 men with biopsy-proven PCa (21). In this study, Eiber *et al.* showed that simultaneous  $^{68}\text{Ga}$ -PSMA-11 PET/MRI was superior to mpMRI or PET alone for PCa localization, with a sensitivity and specificity of 58% and 82% for mpMRI; 64% and 94% for PET; 76% and 97% for  $^{68}\text{Ga}$ -PSMA-11 PET/MRI, respectively.  $^{68}\text{Ga}$ -PSMA-11 PET images have been used to direct biopsy in patients with a high suspicion for localized PCa. This study additionally introduced the possibility of incorporating  $^{68}\text{Ga}$ -PSMA PET/MR into image-guided biopsy.

The role of  $^{68}\text{Ga}$ -PSMA-11 PET/CT is controversial for lymph node staging in primary diagnosed PCa. In the setting of primary PCa staging Herlemann *et al.*

showed that  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan provides high accuracy for preoperative lymph node staging in patients with intermediate to high risk PCa (22). This study was validated by nodal histopathology obtained at surgery in all 71 reported lymph node regions from 34 patients and it concluded that PSMA PET/CT was superior to CT for identifying lymph node metastases with a sensitivity of 84% *vs.* 65% and specificity of 82% *vs.* 76%, especially in nodes not fulfilling the size criteria on CT. A similar study performed PSMA-11 PET/CT imaging in 30 patients prior to radical prostatectomy and extended pelvic lymph node detection, found that 67% of patients were found to have false negative findings (23). The study images were not re-evaluated by imaging subspecialists, which raised a concern for under-reporting with considerable inhomogeneity in initial reports. Nevertheless, the use of PSMA in lymph node staging appears to have an added value to the previously available CT size criteria.

It is estimated that BCR occurs in at least 20–30% of patients after definitive treatment of PCa (24). In this setting, PSMA PET/CT demonstrates the greatest advantage over other imaging methods, with multiple studies showing that  $^{68}\text{Ga}$ -PSMA-11 PET can detect the likely site of recurrence (local, nodal or distant) in most cases (25,26).  $^{68}\text{Ga}$ -PSMA-11 PET/CT can be effective even when PSA values are low (0.2–1.0 ng/mL) (27). At these prostate-specific antigen (PSA) levels, most other available tracers fail to detect metastasis. The patient gains the most from early diagnosis and the likelihood of cure decreases with advancing metastatic burden (17). The sensitivity of PSMA-11 depends on PSA doubling times and initial Gleason scores, indicating that even lower PSA values may still be possible to detect on imaging if the doubling time is rapid or the tumor grade is high (26). Afshar *et al.* analyzed data from 319 men with BCR, and found that  $^{68}\text{Ga}$ -PSMA-11 PET/CT was highly specific for PCa (25). Further analysis revealed an overall sensitivity of 88%, which was dependent on the PSA value. Eiber *et al.* correlated the efficacy of the  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan and PSA concentration in 248 men (28). Among subjects with PSA values  $\geq 2$ , 1–2, 0.5–1 or 0.2–0.5 ng/mL the efficacy was 97%, 93%, 73% and 58%, respectively. For instance, even when the PSA level was as low as  $<0.2$  ng/mL or between 0.2 and  $<0.5$  ng/mL the sensitivity was 44.4% and 72% respectively. Thus,  $^{68}\text{Ga}$ -PSMA-11 PET/MRI scan could be used for the detection of locally recurrent PCa. This result exceeds the sensitivity of other

available non-PSMA PET tracers in the recurrence setting or for conventional imaging (29,30).

In the setting of metastatic disease, Pyka *et al.* compared standard plain  $^{99m}\text{Tc}$  bone scintigraphy and  $^{68}\text{Ga}$ -PSMA-11 PET/CT scan for the detection of bone metastases in 126 patients with PCa (30).  $^{68}\text{Ga}$ -PSMA-11 PET/CT was shown to perform with a significantly higher diagnostic accuracy than bone scintigraphy for the assessment of overall bone involvement (PET/CT and scintigraphy sensitivity were 99–100% and 87–89%, respectively; specificity 88.2–100% and 61–96%, respectively).

### $^{68}\text{Ga}$ -PSMA-617

The use of PSMA-targeted therapy has been revolutionized by modifying the most widely used Gallium-based ligand, PSMA-11, to PSMA-617. This altered PSMA-ligand, which has similar pharmacokinetic properties as PSMA-11, may be labelled with Actinium-225,  $^{68}\text{Ga}$ ,  $^{177}\text{Lu}$ ,  $^{111}\text{In}$ , or Yttrium-90, and has gained considerable interest in the scientific community (31).

The compound has been evaluated in phase I studies for its dosimetry, safety, and efficacy as a diagnostic agent, as well as response and tolerability in its therapeutic form (32,33). Its excretory characteristics, which show rapid renal clearance in preclinical studies has thus far shown to be slower than PSMA-11 (34,35). For this reason, it is currently hypothesized that  $^{18}\text{F}$ -PSMA-1007, a compound which is structurally similar to PSMA-617 may serve as a better surrogate marker for imaging and therapy monitoring than PSMA-11 (36). A more recent study analyzed lesion-based parameters (i.e.,  $\text{SUV}_{\text{max}}$ , metabolic tumor volume) which were shown to correlate well with Gleason score and PSA levels indicating that it may be used to predict metastatic PCa, but has not been compared head-to-head to PSMA-11 or other compounds (37).

The use of  $^{177}\text{Lu}$ -PSMA-617 for radionuclide treatment in metastatic castration-resistant PCa has been an area of interest, as this population had most therapeutic options exhausted. A study by Hofman *et al.* on a group of 30 patients, as part of a prospective phase II trial showed its potential benefit in this cohort (38). The results showed that the treatment was well tolerated, with 37% of patients experiencing a minimum of a ten-point improvement in global health score, including a decrease in pain severity. The most commonly experienced toxic effects included dry mouth (87%), low-grade nausea and fatigue (50%), all of which were attributed to the treatment. Similarly, favorable

results were shown from a study that retrospectively analyzed 145 patients previously treated with multiple cycles of  $^{177}\text{Lu}$ -PSMA-617 (39). This study also identified that patients with very advanced disease with a high alkaline phosphatase (>220 IU/L) and visceral metastasis poorly responded to the treatment, and were more likely to relapse.

The marker's robust capabilities to be conjugated with either diagnostic (e.g.,  $^{68}\text{Ga}$ ) or therapeutic (e.g.,  $^{177}\text{Lu}$ ) radioisotopes is currently being investigated in a large multi-center trial in patients with metastatic castrate-resistant PCa as part of the VISION trial (40), and its adoption in Europe is rapidly growing. Larger, multi-center studies will help elucidate its role in imaging and therapy, especially in patients with metastatic castrate-resistant disease.

### $^{68}\text{Ga}$ -PSMA-I&T

$^{68}\text{Ga}$ -PSMA-I&T demonstrates similar biodistribution and imaging properties as  $^{68}\text{Ga}$ -PSMA-11, with I & T referring to "imaging and therapy" (41). Thus, this compound can be used both for imaging and, when labeled with a therapeutic radioisotope, for treatment. Both tissue distribution pattern and time of accumulation are comparable to PSMA-11. However, biodistribution studies showed slightly lower physiologic tracer uptake in the liver, spleen and intestine and a slightly higher uptake in the proximal tubules of the kidneys and salivary glands. The standard injected activity has been determined to be about the same when compared to  $^{68}\text{Ga}$ -PSMA-11 (150 MBq) (42). These changes have an impact on the effective dose coefficients for specific organs (1.71E-02 vs. 1.99E-02 mSv/MBq, for total body, 1.73E-01 vs. 6.74E-02 mSv/MBq for urinary bladder wall, and 1.22E-01 vs. 2.20E-01 mSv/MBq for kidney, respectively) (42,43). Similar to  $^{68}\text{Ga}$ -PSMA-11,  $^{68}\text{Ga}$ -PSMA-I&T demonstrates predominantly renal excretion. To overcome this problem, an intravenous diuretic injection just after imaging at 60 min was shown to lower mean urine activity at 180 min, especially for prostatic bed assessment, as well as improve detection of pelvic lymph nodes by ureteric wash-out (44).

Similar to  $^{68}\text{Ga}$ -PSMA-11 PET/CT,  $^{68}\text{Ga}$ -PSMA-I&T PET/CT has been used for assessment of primary PCa before prostatectomy (45) and BCR (46). In a study published by Schmuck *et al.*, 240 men with BCR were scanned with  $^{68}\text{Ga}$ -PSMA-I&T. Cancer detection rates were 94.2% for PSA value  $\geq 2$  ng/mL; 72% for 1 to <2 ng/mL; 59% for 0.5 to <1 ng/mL; 56% for >0.2 to <0.5 ng/mL and 39% for 0.01 to 0.2 ng/mL. In their retrospective analysis

of 83 men, Berliner *et al.* demonstrated, that  $^{68}\text{Ga}$ -PSMA-I&T PET/CT detection rate also positively correlated with PSA serum levels, and were 100% for PSA  $\geq 10.0$  ng/mL, 100% for 5.0 to  $<10.0$  ng/mL, 93% for 2.0 to  $<5.0$  ng/mL, 70% for 1.0 to  $<2.0$  ng/mL, 55% for 0.5 to  $<1.0$  ng/mL, and 52% for  $<0.5$  ng/mL, thus both findings are comparable to the performance of  $^{68}\text{Ga}$ -PSMA-11 (47).

$^{68}\text{Ga}$ -PSMA-I&T differs from  $^{68}\text{Ga}$ -PSMA-11 in its chemical structure which results in slightly higher receptor affinity leading to a slightly higher diagnostic accuracy when compared  $^{68}\text{Ga}$ -PSMA-11 (48). PSMA-I&T can be labelled with  $^{177}\text{Lu}$  or Actinium-225 without significant changes in affinity and thus, can be used in PCa therapy (41). Nevertheless, most research on PCa theranostic ligands is performed with a compound closely related to PSMA-11; PSMA-617 (41).

### $^{18}\text{F}$ -DCFBC and $^{18}\text{F}$ -DCFPyL

These two  $^{18}\text{F}$ -labeled PSMA agents arose from the same laboratory.  $^{18}\text{F}$ -DCFBC was the first-generation agent and was also a small-molecule urea-derivative PSMA-targeted inhibitor of PSMA. The second generation agent is known as  $^{18}\text{F}$ -DCFPyL {2-(3-(1-carboxy-5- $^{18}\text{F}$ fluoro-pyridine-3-carbonyl)-amino)-pentyl)-ureido)-pentanedioic acid} (49) and was developed in part to overcome the limitation of  $^{18}\text{F}$ -DCFBC which bound serum proteins. Thus, it had a long clearance time from the blood pool which interfered with lymph-node detection in the retroperitoneum and pelvis adjacent to large blood vessels. The next generation radiotracer,  $^{18}\text{F}$ -DCFPyL, not only exhibits substantially greater binding affinity for PSMA but also had much less blood pool activity than its predecessor. Because of these enhanced characteristics, the focus of development is now shifted to  $^{18}\text{F}$ -DCFPyL which is in the process of commercialization and approval.

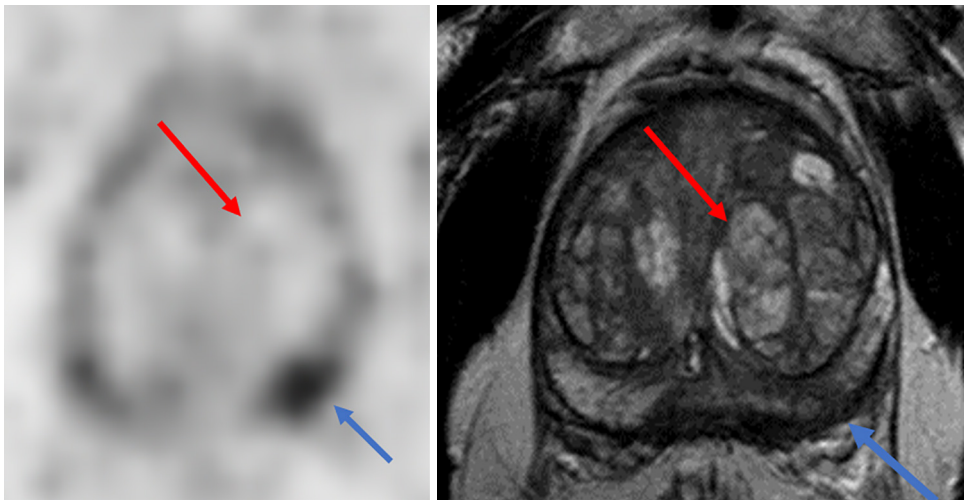
Like the gallium-labeled compounds, the family of fluorinated compounds are small, urea-based molecules, that binds to the extracellular domain of PSMA. Unlike the gallium compounds which have a chelate attached to the PSMA-binding moiety, the fluorinated compounds are directly labeled resulting in a slightly smaller molecular weight. The absence of a chelate, however, means that the interchangeability of radioisotopes, including therapeutic radioisotopes, is more limited. As small molecules, these PSMA agents are predominantly excreted through the urinary tract, consequently the bladder shows the highest activity, followed by the stomach, heart and kidneys, but like the

gallium compounds, it also accumulates in the salivary glands, kidneys, urinary bladder, liver, spleen, and small intestines (50). The effective dose is 0.0165 mSv/MBq for a 370 MBq dose, with the kidneys receiving the highest estimated radiation dose (0.0945 mGy/MBq) followed by the urinary bladder wall (0.0864 mGy/MBq), submandibular glands (0.0387 mGy/MBq), and liver (0.0380 mGy/MBq) (50). These dose-limiting organs should be taken into consideration for the potential use of this compound in the PSMA treatment setting (51).

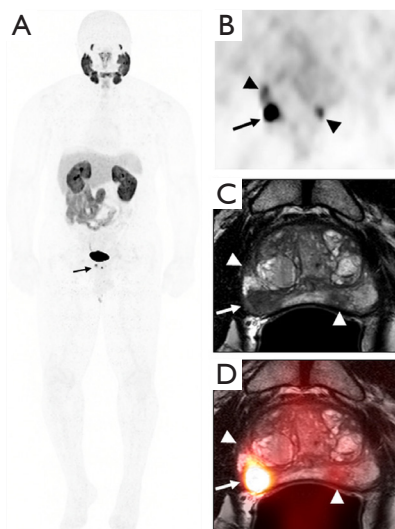
Currently, more studies have been published with  $^{18}\text{F}$ -DCFBC than  $^{18}\text{F}$ -DCFPyL. Turkbey *et al.* (4), showed that localized PCAs were detected by  $^{18}\text{F}$ -DCFBC and mpMRI and these lesions were subsequently validated with MRI/transrectal ultrasound guided biopsy or radical prostatectomy. Tumor uptake was noted to be very high with maximum standardized uptake values ( $\text{SUV}_{\text{max}}$ ) greater than 100 in some lesions 1 and 2 h post-injection (50). The method was highly sensitive for intermediate and high-grade primary cancers (4) (Figure 2).  $^{18}\text{F}$ -DCFPyL PET uptake, was contingent on higher Gleason pattern 4 within tumors, whereas lower-grade PCa with Gleason pattern 3 tended to have much lower radiotracer uptake (52) (Figure 3) (2).

These agents have also been used in PCa staging. Gorin *et al.* (3) prospectively evaluated the diagnostic performance of  $^{18}\text{F}$ -DCFPyL PET/CT in staging high-risk PCa in 25 men (53). In the study,  $^{18}\text{F}$ -DCFPyL-PET correctly identified 5 of the 7 cases with otherwise clinically occult positive lymph nodes when compared with surgical pathology, while over staging the remaining two cases. In these two cases, this may have been caused by attributing ureteric uptake as focal lymph node uptake, and thus assigning it to a false-positive finding. In the metastatic setting, this series of  $^{18}\text{F}$ -DCFPyL-PET identified sites of distant disease in 12% of the patients (53).

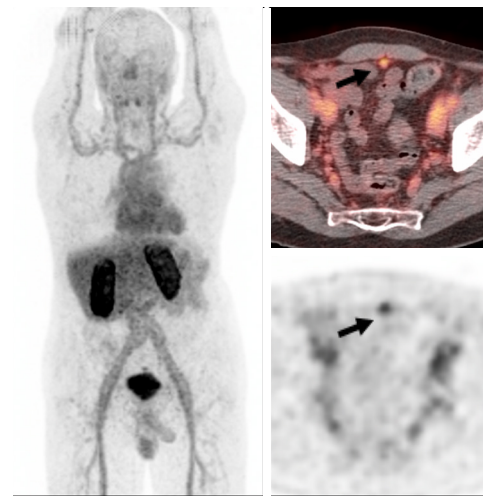
In the BCR setting, Turkbey *et al.* (4) demonstrated that  $^{18}\text{F}$ -DCFBC could detect recurrences (either local or lymph node) in 60.3% of patients without evidence of disease on conventional imaging (Figure 4). Imaging detection rate correlated to PSA values with a threshold PSA of 0.78 ng/mL or above, highly predictive of a positive scan. Interestingly, focal  $^{18}\text{F}$ -DCFBC results changed clinical management in 51.2% of patients due to the detection of more-than-expected disease. This compelling application for non-invasive detection of recurrent disease by radiolabeled PSMA binding agents is promising in advancing therapeutic strategies. Subsequently, it was shown that the sensitivity of both  $^{18}\text{F}$ -DCFPyL (n=62) and  $^{68}\text{Ga}$ -PSMA-11 (n=129) was significantly associated with absolute



**Figure 2**  $^{18}\text{F}$ -DCFBC in localized disease.  $^{18}\text{F}$ -DCFBC with focal uptake in left apical-mid peripheral zone prostate cancer lesion (blue arrows) but not in benign prostatic hyperplasia (red arrows). Left image is axial PET of prostate and right image is axial T2 MRI.



**Figure 3**  $^{18}\text{F}$ -DCFPyL in primary localized PCa. A 64-year-old man newly diagnosed of high-risk prostate cancer, Gleason 5+4, PSA: 8 ng/mL.  $^{18}\text{F}$ -DCFPyL PET maximal intensity projection (A) and axial PET (B) imaging demonstrates a dominant focus in the right apical-mid peripheral zone of the prostate gland with intense  $^{18}\text{F}$ -DCFPyL, concordant with a 1.5-cm PIRADS 5 lesion reported on MR-T2W axial imaging (arrows in A,B,C,D) (C). MRI shows two additional PIRADS 4 lesions in the left apical-mid peripheral zone and right anterior transition zone, with moderately intense  $^{18}\text{F}$ -DCFPyL uptake (arrowheads in B,C,D). All DCFPyL-avid lesions were concordant with MRI findings as seen on the fused PET-MRI image (D). PCa, prostate cancer; PSA, prostate-specific antigen.



**Figure 4**  $^{18}\text{F}$ -DCFBC in biochemical recurrence. A 59-year-old man status post prostatectomy with biochemical recurrence, PSA 2 ng/mL.  $^{18}\text{F}$ -DCFBC shows focal uptake in 8-mm mesenteric node (arrows). Left image is maximum intensity projection of  $^{18}\text{F}$ -DCFBC PET. Right top image is axial PET/CT fusion of pelvis and right bottom is corresponding axial PET of pelvis. PSA, prostate-specific antigen.

PSA levels (54). In this study, Dietlein *et al.* showed that for a PSA range of 0.5–3.5  $\mu\text{g/L}$ , the PSA-stratified sensitivity of  $^{18}\text{F}$ -DCFPyL significantly exceeded that of  $^{68}\text{Ga}$ -PSMA-11 (88% *vs.* 66%). Outside of this range, sensitivity was comparably low (for PSA <0.5  $\mu\text{g/L}$ ) or high (for PSA

>3.5 µg/L). After radiotherapy, tracer sensitivity was largely PSA-independent. In a subsample of 25 patients examined with both tracers, the distribution patterns of <sup>18</sup>F-DCFPyL and <sup>68</sup>Ga-PSMA-11 were comparable, but <sup>18</sup>F-DCFPyL scans detected additional lesions in 36% of the patients (54). Since both radiotracers target the same epitope on the PSMA molecule, the improved lesion detection efficiency of <sup>18</sup>F-DCFPyL relative to the <sup>68</sup>Ga-labelled PSMA agent may reflect the intrinsic advantages of <sup>18</sup>F as a PET radionuclide or subtle pharmacokinetic differences. <sup>18</sup>F-DCFPyL has the advantages of being cyclotron-based and has a longer half-life and more favorable energy levels, resulting in improved spatial resolution, owing to lower background activity in non-target tissues (54).

The fluorinated compounds have also been used in the metastatic setting. <sup>18</sup>F-DCFBC outperformed conventional imaging and detected a larger number of lesions in lymph nodes, bone and soft tissue with a sensitivity of 92% compared to 71% for traditional imaging modalities (55). In the metastatic setting, Rowe *et al.* (56) also showed that <sup>18</sup>F-DCFPyL PET/CT outperformed conventional imaging by detecting an overall larger number of positive sites of either local recurrence, lymph nodes, or bones (138 definitive sites and 1 equivocal versus 30 definitive sites with 15 equivocal) (56). Several prospective and multicenter trials are currently under way to better determine the diagnostic performance of <sup>18</sup>F-DCFPyL PET for distant sites of PCa (Figures 5,6).

Imaging of metastatic bone disease has yielded intriguing findings. In comparison to the highly sensitive but nonspecific <sup>18</sup>F-NaF, the detection of metastatic bone lesions by <sup>18</sup>F-DCFBC or <sup>18</sup>F-DCFPyL depends on the treatment status and disease stage (57) (Figure 7). In patients on androgen deprivation therapy, <sup>18</sup>F-NaF identifies more bone lesions than <sup>18</sup>F-DCFBC in the early, castrate sensitive phase but as disease advances to castration resistance, detection rates are similar in both tracers. This is thought to occur due to hormonal suppression of PCa cells leading to senescence and reduced PSMA expression which is reactivated when resistance develops. The secondary effects of bone remodeling appear to persist throughout and are consequently visible with <sup>18</sup>F-NaF but not PSMA PET/CT (58). The implication is that PSMA radiotracers may be able to distinguish castration sensitive and castration resistant disease of the bones when combined with a cross sectional bone scan method. This may provide insights into the origins of castration resistance.

### <sup>18</sup>F-PSMA-1007

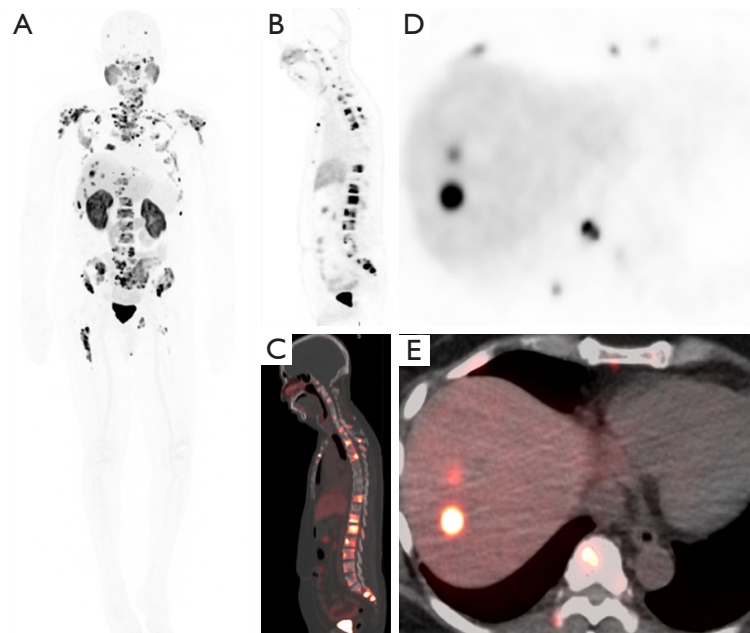
Recently, a compound based on <sup>68</sup>Ga-PSMA-617, which is <sup>18</sup>F-labeled has been introduced with a similar diagnostic and therapeutic potential to <sup>68</sup>Ga-PSMA-11 or <sup>68</sup>Ga-PSMA-I&T (36). PSMA-1007 presents a unique biodistribution compared to the other known PSMA-ligands as excretion follows the hepatobiliary pathway, instead of the more common urinary route (59). This provides several advantages with regard to primary staging and local recurrence, as there is less uptake in the anatomical area of the prostate and surrounding tissue. Also, the radiation dose is comparable to other PSMA-ligands, but due to hepatobiliary excretion there is a slightly different organ dose distribution with a higher dose to the liver parenchyma and lower radiation dose to the urinary bladder (Figure 8). In preliminary studies, this excretory pathway is beneficial in the visualization of prostate and ureter region as well as pelvis for metastatic lymph nodes (59-61), but comparative studies have not been done. When PSMA-1007 was compared to mpMRI for local staging, both modalities exhibited similar accuracy (60). Paddubny *et al.* presented its use in the setting of BCR and equivocal findings on MRI (Figure 9). In this study, the <sup>18</sup>F-PSMA-1007 PET/CT scan allowed identification of local PCa recurrence, which was otherwise not seen on mpMRI (62).

A recent publication with PSMA-1007 showed a high sensitivity in BCR patients with low (0.5–1 ng/mL) and very low (0.2–0.5 ng/mL) PSA of 74% and 62%, respectively. This study demonstrated an improved detection rate in over 150 BCR patients with a PSA-level between 0.2–0.5 ng/mL of over 60%, which was most likely due to the different energy profile using fluorine *vs.* gallium (63).

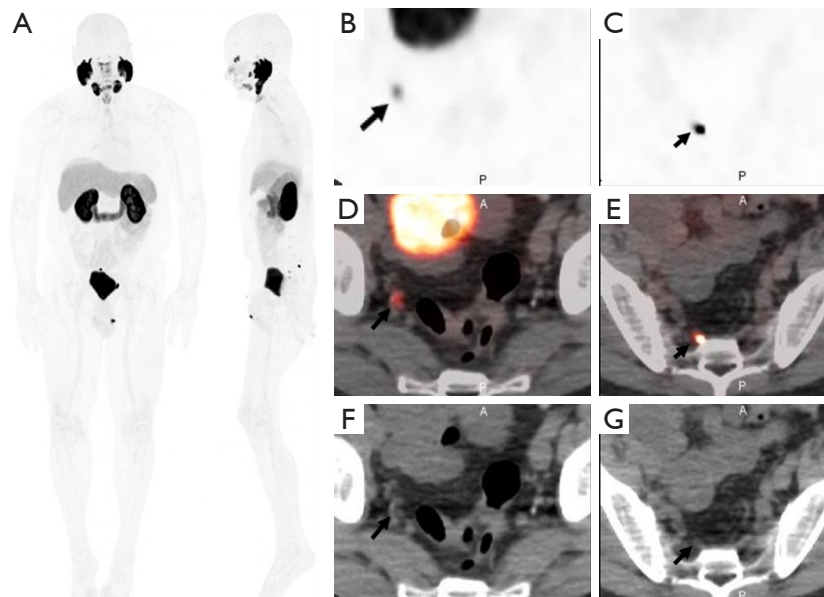
PSMA-1007 has shown high sensitivity in specific cases. Nodes as small as 1mm were detected with a very high sensitivity reaching 95% (59). Since PSMA-1007 has a similar structure to PSMA-617, it can also be used as a theranostic with <sup>177</sup>Lu-PSMA-617 and future studies will define the clinical importance of this compound (36,64).

### SPECT PSMA

SPECT is a broadly available imaging technique. SPECT is widely used in myocardial perfusion and functional brain imaging (65). The modality uses a conventional gamma camera, which has a relatively lower unit price making SPECT more economical. Instead of planar views, which are used in scintigraphy, a set of several 2D

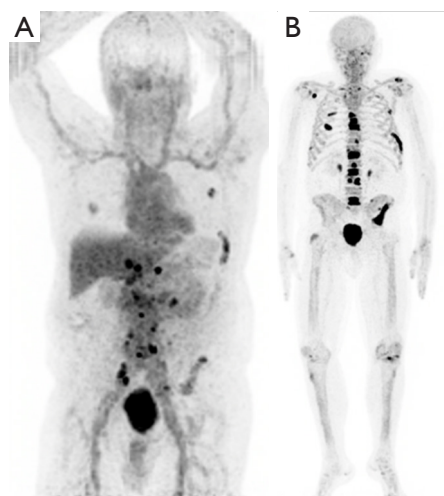


**Figure 5**  $^{18}\text{F}$ -DCFPyL in metastatic PCa. A 62-year-old man with metastatic castrate-resistant prostate cancer, status post-prostatectomy, salvage radiation, and chemotherapy, with elevated PSA 135 ng/mL and testosterone <20 ng/dL.  $^{18}\text{F}$ -DCFPyL PET/CT imaging including maximal intensity projection (A), sagittal PET and fused PET/CT (B,C), and axial PET and fused PET/CT (D,E) show widespread bone metastatic disease and several metastatic liver lesions. PCa, prostate cancer; PSA, prostate-specific antigen.

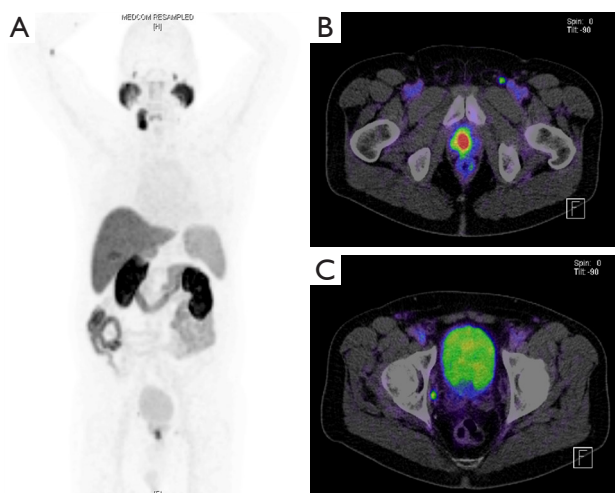


**Figure 6**  $^{18}\text{F}$ -DCFPyL in metastatic PCa. A 60-year-old man with history of prostate cancer, Gleason 9 (4+5), status post-prostatectomy, and rising PSA (0.4 ng/mL) 6 years after surgery.  $^{18}\text{F}$ -DCFPyL PET imaging including maximal intensity projection (A), axial PET (B,C), axial fused PET/CT (D,E) and axial low dose CT (F,G) show suspicious sub-centimeter right internal iliac and pre-sacral lymph nodes (arrows) at a very low level of PSA. PSA, prostate-specific antigen; PCa, prostate cancer.





**Figure 7**  $^{18}\text{F}$ -DCFBC compared to  $^{18}\text{F}$ -NaF in metastatic prostate cancer. A 74-year-old man with castrate resistant metastatic prostate cancer and PSA 388.1 ng/mL.  $^{18}\text{F}$ -DCFBC (A) detects most bone lesions concordant with  $^{18}\text{F}$ -NaF (B) in addition to soft tissue disease. PSA, prostate-specific antigen.



**Figure 8**  $^{18}\text{F}$ -PSMA-1007 PET/CT of a 72-year-old man with high-risk prostate cancer [Gleason 9 (4+5), Grade Group 5] and rising PSA levels (latest PSA level: 11.2 ng/mL). Coronal maximal intensity projection PET image shows the primary excretion of the tracer by the hepatobiliary system, which may decrease the amount false positive findings from uptake within the ureters and urethra (A). In addition to intraprostatic uptake inguinal (B) and pararectal lymph nodes and one lymph node next to the right distal ureter was shown (C). PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen.

projections are acquired and used to create 3D images using tomographic reconstruction. The additional use of CT, as in PET imaging, may then be applied for improved spatial colocalization.

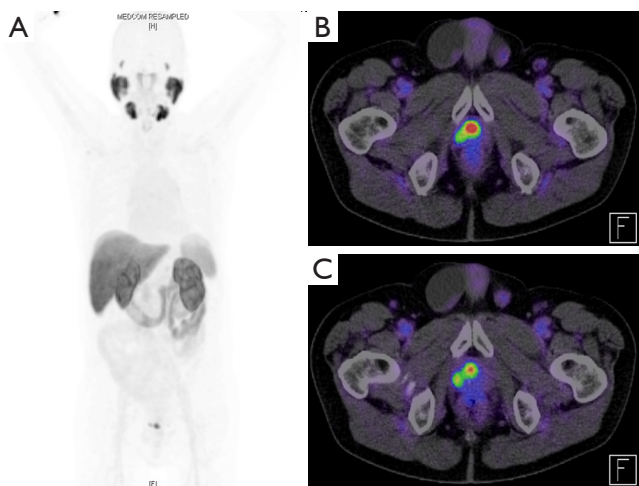
The emergence of PSMA as a prostate-specific marker, and its recent developments in  $^{68}\text{Ga}$  and  $^{18}\text{F}$ -labelled PET imaging have been encouraging for possible developments of Technetium-based PSMA radiotracers which could be used in SPECT. One PSMA radiotracer,  $^{99\text{m}}\text{Tc}$ -MIP-1404 has demonstrated low blood pool and hepatobiliary excretion in a phase I clinical trial (66). A more recent phase II clinical trial of 105 patients with intermediate and high-risk PCa prior to radical prostatectomy was found to perform with an overall detection rate of 94%, and showed tumor-to-background ratios of lesions correlating with Gleason score. Lymph node invasion (LNI) was detected with a sensitivity of 50% and specificity of 87% (67). Another study by Reinfelder *et al.*, had slightly lower overall detection of 77% for cancer, but this cohort was restricted to patients with BCR (68,69).

With the widespread availability of SPECT scanners, and the relatively low cost compared to PET, there is a possibility that the current clinical practice of using  $^{99\text{m}}\text{Tc}$  bone scintigraphy (bone scan) may be replaced with a PSMA-specific  $^{99\text{m}}\text{Tc}$  marker for PCa staging.  $^{68}\text{Ga}$ -PSMA PET has previously shown to perform better than bone scan in the detection of bone metastasis (70). The use of PSMA-PET for bone staging, though was superior with the use of the anatomical colocalization with CT, which essentially doubles the radiation dose compared to the classic planar bone scan. SPECT/CT with PSMA ligand  $^{99\text{m}}\text{Tc}$ -MIP-1427 was compared to conventional bone scans by Rathke *et al.* in 21 patients with metastatic disease. The study showed an advantage for PSMA SPECT/CT, mainly by decreasing the number of equivocal findings and by its higher specificity, as it does not readily accumulate in degenerative bone disease (71).

All current Technetium-based PSMA ligands are experimental, with clinical trials ongoing in Europe. In the United States, they remain to be approved for diagnostic purposes, and therefore adoption of the technique has been overshadowed by the larger ongoing trials of PET-based PSMA ligands.

## Conclusions

The introduction of PSMA PET ligands has been nothing



**Figure 9**  $^{18}\text{F}$ -PSMA-1007 PET/CT in a man following radiation therapy with biochemical recurrence (PSA 3.7 ng/mL). The study revealed two intraprostatic PSMA-avid foci, without evidence of extraprostatic disease (A,B,C). PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen.

short of transformational for the imaging of PCa. When comparing PSMA PET ligands to other tracers, substantial advantages to PSMA are seen including higher positive predictive values and higher sensitivity (28). However, there are now many PSMA PET ligands to choose from and it's impossible to compare them without head-to-head studies which are expensive to conduct. The general impression is that they all perform comparably. Current guidelines are inconsistent and do not reflect the use of PSMA in the United States, with European use in the setting of staging and BCR. The ongoing trials and studies will most likely determine the fate of PSMA compounds and their place in PCa detection and staging. Prior to its broad approval, PSMA PET will remain somewhat of a mystery for most clinicians. Hopefully, this review casts some light on the variety of PSMA-based radionuclides that are now undergoing clinical testing.

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### Footnote

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

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