Review Article

Prostate-specific membrane antigen in prostate cancer imaging and treatment

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Abstract: Despite the prevalence of prostate cancer (PC), conventional imaging such as computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy have significant limitations in identifying the disease, leading to problems with diagnosis and management. Prostate-specific membrane antigen (PSMA) is a membrane-bound protein that is heavily expressed on PC cells. Radiolabeled antibodies and small molecule inhibitors of PSMA have allowed for imaging with positron emission tomography (PET). These novel PET agents have been studied in a variety of clinical scenarios. Compared to conventional imaging, they are better able to detect localized disease and regional lymph nodes, reveal disease at the time of biochemical recurrence, and identify oligometastatic sites for targeted radiation therapy. While PSMA-PET appears superior to conventional imaging, it also has limitations with sensitivity in certain settings. Additionally, current reports on PSMA-PET imaging in PC are largely retrospective reviews. Well-designed prospective clinical trials should be conducted in order to understand the true potential of this novel imaging modality.

Keywords: Prostate-specific membrane antigen (PSMA); positron emission tomography (PET); prostate cancer imaging

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Introduction/background

Prostate cancer (PC) is the most common cancer and the third most common cause of cancer deaths in American men (1). Despite its prevalence and the recent advances in its treatment, the ability of standard imaging technologies, such as computed tomography (CT) and technetium-99m (^{99m}Tc) bone scintigraphy, to accurately identify PC continues to be a problem in the field (2). This limitation can result in management dilemmas at all stages of the disease, from initial detection (3) and biochemical recurrence (4), to the development of metastases (5). It has also led to issues in clinical trial design for PC in that standard imaging used for the Response Evaluation Criteria in Solid Tumors (RECIST) do not address key features of the disease (6), in part leading to the development of Prostate Cancer Clinical Trials Working Group (PCWG) recommendations for clinical trial design (7,8).

The limitations in standard imaging have led to the study of other imaging modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET). Novel radiotracers targeting different aspects of PC biology have been evaluated for PET imaging, including fluorodeoxyglucose (^{18}F-FDG), ^{18}F-sodium fluoride (^{18}F-NaF), ^{11}C-acetate, ^{11}C/^{18}F choline (9-12), and ^{18}F-FACBC (fluciclovine) (13), each with their advantages over standard imaging, but with ongoing limitations in terms of sensitivity and specificity (2,14).

Some of the most promising PET tracers are those that target prostate specific membrane antigen (PSMA). PSMA is a 100-kDa type II transmembrane zinc metalloenzyme receptor (15,16) expressed largely in the prostate and to a lesser degree in the duodenum, brain, salivary gland, kidney, colon, and the neovasculature of tumors including lung, colon, breast, and kidney cancers (17,18). While its biologic function in PC is unknown, PSMA expression is nearly 100-fold higher in the prostate than in other tissues

and is 10-fold higher in PC than in healthy prostate tissue (2,15). Its expression is further increased in higher-grade and metastatic cancers, and on development of castration resistance (19). Unlike prostate-specific antigen (PSA) and prostatic acid phosphatase that are secreted into the circulation, PSMA is membrane bound (20). In addition, its cytoplasmic domain contains an internalization motif that results in clathrin-mediated endocytosis that increases the uptake and deposition of radiotracers into cells. This feature may allow for a higher signal to noise ratio, making it an attractive target for imaging (19).

Initial targeting of PSMA used monoclonal antibodies, with ^{111}In-capromab pendetide (Prostascint) being the only FDA approved agent for PSMA imaging (21). However, it targets the cytoplasmic domain of the receptor and is thus only taken up by dying cells with disrupted membranes. As it is also excreted into the bowel and bladder, interpretation of scans, especially in the retroperitoneum where PC often metastasizes is limited by a poor positive predictive value (PPV) and specificity (22). Another antibody, J915, targets the extracellular domain of PSMA. Chelated with DOTA as a linker for radiotracers, it can be linked to ^{89}Zr, ^{64}Cu, ^{90}Y, ^{177}Lu, making it an agent that can be used both for imaging and targeted radionuclide therapy (23). However, one significant limitation of antibody-based imaging includes the long half-life of antibodies that results in high background signal and poor penetration into tumors (2).

Newer PSMA tracers are small molecule inhibitors targeting the extracellular portion of the molecule. These agents can be labeled with radioisotopes including ^{123}I, ^{18}F, ^{111}In, and ^{68}Ga. Because of their size, these molecules exhibit rapid extravasation, diffusion into extracellular spaces, and blood clearance allowing for a higher tumor-to-background signal within 1–2 hours after injection. These agents can be grouped into three different classes: those that are urea-based, thiol based, or phosphorous based (24). One of the most studied and widely used compounds is the urea-based Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (^{68}Ga-PSMA-HBED-CC, or ^{68}Ga-PSMA) initially described by Eder *et al.* (25). Urea based ^{18}F compounds have also demonstrated favorable imaging characteristics. *N*-[*N*-[(*S*)-1,3-dicarboxypropyl] carbamoyl]-4-[^{18}F]fluorobenzyl-L-cysteine (^{18}F-DCFBC), a first generation molecule developed at Johns Hopkins (26), has been followed by a second generation compound, 2-(3-(1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid ([^{18}F]DCFPyL), that demonstrates increased sensitivity and specificity for PC (27,28). These targeted imaging molecules have great promise for PC detection and management, and their application in different clinical scenarios will be reviewed here.

Local tumor detection

Not all men diagnosed with localized PC will die of the disease or even develop symptoms (29,30). Determining who requires therapy is critical because treatments, such as surgery or radiation, can result in long-term side effects including urinary incontinence and erectile dysfunction (31). However, unlike other early stage solid tumors that are diagnosed on biopsy of a lesion detected on imaging, PC is diagnosed by random sampling of the entire gland. This can lead to misclassification of a patient's initial disease stage or grade, both of which are necessary to guide appropriate management. The possibility of not sampling a clinically significant lesion is 10–46% (32), and up to 36% of PCs on biopsy are upgraded or upstaged at the time of surgery (33). As a result, an estimated 23–42% of men with PC are over-treated (34), leading to unnecessary complications and healthcare costs.

Multiparametric MRI (mpMRI) combines conventional T1 and T2 weighted images with functional MRI sequences such as diffusion weighted imaging, dynamic contrast enhancement, and MR spectroscopy, and has an improved ability over conventional imaging to detect localized PC (35-37). Targeting tumors for biopsy using mpMRI can improve the detection of clinically significant disease and reduce the detection of lower risk disease (38-42). However, in a retrospective analysis of mpMRI compared to tumor histology at the time of prostatectomy, the average sensitivity of detecting an index lesion was only 60.2% across six radiologists (43). In a prospective cohort study of 1,003 men undergoing both MRI-targeted and standard random biopsies, targeted biopsies detected 30% more high-risk cancers and 17% fewer low risk cancers (43,44). However, 15% of cases had higher risk pathology found only on standard biopsy, and in the subset of patients with no prior biopsies there was no difference between targeted and standard biopsies. Thus, with a sensitivity of 58–97% and specificity of 23–87% to detect clinically significant PC additional improvements are needed for mpMRI (38,45-47).

PSMA-PET has also been studied to detect localized PC (3,48-58). Rowe *et al.* prospectively evaluated 13 patients with ^{18}F-DCFBC PET and MRI prior to prostatectomy then correlated ^{18}F-DCFBC PET to histopathology on a per-segment (12 regions) basis. They found that for detection of PC ^{18}F-DCFBC PET had a sensitivity of 17% while that for MRI was 39%, however ^{18}F-DCFBC PET

had a specificity of 96% compared to 89% for MRI (3). Interestingly, ^{18}F-DCFBC uptake was associated with Gleason score (ρ=0.64) and ^{18}F-DCFBC uptake was significantly lower in benign prostatic hypertrophy than primary tumors (median SUV 2.2 *vs.* 3.5, P=0.004). Similarly, Turkbey *et al.* evaluated 13 patients with both ^{18}F-DCFBC PET/CT and MRI and correlated these findings to histopathology either from MRI-fusion biopsies (n=9) or prostatectomy (n=4) (59). They found that sensitivity to detect the largest and highest Gleason lesion for ^{18}F-DCFBC and MRI were 61.5% and 92%, respectively.

^{68}Ga-PSMA has a higher tumor-to-background signal ratio compared to ^{18}F-DCFBC (55), and studies evaluating this tracer demonstrate higher sensitivities and specificities for detecting disease. Rahbar *et al.* prospectively evaluated ^{68}Ga-PSMA PET in six patients who underwent prostatectomy for Gleason ≥3+4 tumors (55). They found that ^{68}Ga-PSMA PET had a sensitivity and specificity of 92% for identifying areas of PC. Fendler *et al.* also prospectively evaluated ^{68}Ga-PSMA PET in 21 patients with biopsy proven PC who underwent prostatectomy for Gleason 7 tumors (50). In this study, the prostate was sectioned based on a six-segment model. The sensitivity and specificity of ^{68}Ga-PMSA PET to detect cancer were 67% and 92%, respectively. False-negative results were noted in 6 of 12 segments with a Gleason score (GS) of 6, 12 of 27 segments with a GS of 7, 4 of 19 segments with a GS of 8, 10 of 41 segments with a GS of 9, and one segment with a GS of 10. Rhee *et al.* compared mpMRI and ^{68}Ga-PSMA PET in men scheduled to undergo radical prostatectomy (51). They compared the imaging results to whole mount specimens and found that the sensitivity, specificity, PPV, and negative predictive value (NPV) for mpMRI to be 44%, 94%, 81%, 76%, respectively, while the same values for ^{68}Ga-PSMA PET were 49%, 95%, 85%, 88%.

Determining the accuracy of an imaging modality to detect PC requires accurate registration between imaging and histopathology as the distribution of PC within the gland can be heterogeneous and deformations can occur during surgery and the histopathologic work up (45). Zamboglou *et al.* addressed this problem by conducting a prospective study of 9 men who went ^{68}Ga-PSMA PET/CT scans prior to prostatectomy. They meticulously performed co-registration studies between ^{68}Ga-PSMA scans and histopathology and found a statistically significant correlation of ^{68}Ga-PSMA PET/CT with histopathology in eight subjects and an average ROC AUC of 0.82 (48). A follow up study evaluated 10 men undergoing prostatectomy and compared ^{68}Ga-PMSA PET/CT and mpMRI to co-registered histopathology (60). They found that sensitivity and specificity for PC detected by ^{68}Ga-PMSA PET/CT and mpMRI were 75% and 87%, and 70% and 82%, respectively. They further found that the union of ^{68}Ga-PMSA PET/CT with mpMRI had a sensitivity and specificity of 82% and 67%, respectively, while that for the intersection of PSMA-PET and mpMRI were 55% and 99%, respectively.

Combining ^{68}Ga-PMSA PET and MRI has also been studied to evaluate whether additional multimodal imaging might improve the diagnostic performance. Using an integrated PET/MRI system, Eiber *et al.* performed simultaneous ^{68}Ga-PMSA PET/MRI on 66 patients with intermediate or high risk PC prior to prostatectomy (52). MRIs were read separately from ^{68}Ga-PMSA PET scans by different radiologists then together by a dual-board certified radiologist. Prostatectomy specimens were divided into sextants and the presence of tumor, size, and Gleason grade were noted for comparison to scans. Sensitivity and specificity for tumor detection were 43% and 95%, respectively for MRI, 64% and 94%, respectively for ^{68}Ga-PMSA PET, and 76% and 97%, respectively for combination ^{68}Ga-PMSA PET/MRI.

One problem with these initial studies to locate primary tumors in PC using ^{68}Ga-PMSA PET scans is that they were all conducted in patients who were candidates for treatment of clinically significant PC. The performance of this imaging modality may eventually need to be tested in a population undergoing screening for PC where not all men will be diagnosed with the disease.

Lymph node metastases

The presence of lymph node metastases at initial diagnosis is thought to represent systemic disease and signifies a poorer prognosis often necessitating a change in clinical management (61-63). Determining whether lymph nodes contain PC is challenging as standard imaging modalities rely on size and shape criteria. Specifically, round nodes larger than 8 mm in diameter or oval nodes with the short axis length greater than 10mm are considered metastatic. However, metastases can often be found in lymph nodes smaller than 8 mm in diameter resulting in a sensitivity of 36–40% using standard imaging methods (64).

PSMA-PET scans have been used to evaluate the presence of nodal metastases with varying success. Budäus *et al.* performed a retrospective analysis of 30 men with a nomogram-calculated risk of lymph node metastases greater

than 20% who had undergone a ^{68}Ga-PMSA PET prior to prostatectomy and extended pelvic lymph node dissection (65). The overall sensitivity, specificity, PPV, and NPV of ^{68}Ga-PMSA PET/CT to detect lymph node metastases were 33.3%, 100%, 100%, and 69.2%, respectively. They found that smaller intranodal tumor deposits were missed. The median size of ^{68}Ga-PMSA PET detected lymph node metastases was 13.6 mm compared to that of those missed measuring 4.3 mm.

The largest study to evaluate the ability of ^{68}Ga-PMSA PET to detect lymph node metastases reviewed scans and pathology of 130 men who were imaged with either a ^{68}Ga-PMSA PET/CT (n=95) or ^{68}Ga-PMSA PET/MRI (n=25) then underwent prostatectomy and standard template lymph node dissection (66). The sensitivity, specificity, and accuracy for standard imaging (MRI or CT) for nodal metastases were 43.9%, 85.4%, and 72.9%, respectively, while those for ^{68}Ga-PMSA PET were 65.9%, 98.9%, and 88.5%.

Another retrospective study of 42 men evaluated with mpMRI and ^{68}Ga-PMSA PET/CT prior to prostatectomy and pelvic lymph node dissection noted a patient based sensitivity, specificity, PPV, and NPV for nodal metastases detected by ^{68}Ga-PMSA PET of 93.33%, 96.30%, 93.33% and 96.30%, respectively (67). MRI had similar results for detecting nodal metastases with a patient-based sensitivity, specificity, PPV and NPV of 93.33%, 96.30%, 87.5% and 96.15%, respectively. These results might be explained by the larger lymph node sizes in this patient population with a mean size of 28.87 mm (range, 16–45 mm).

Biochemical recurrence

Within 10 years after curative therapy for localized PC, as many as 20–40% of patients will develop recurrent disease often in the form of a rising PSA (45). Also known as biochemical recurrence (BCR), this often precedes the appearance of clinical metastases by about 8 years (68). Whether BCR represents a local recurrence in the prostate or prostatectomy bed, or new metastatic disease is unclear as current standard imaging modalities are often unable to detect the presence of disease at these low PSA levels (4,69-71). As a result, management of BCR is controversial with recommendations including observation until the time of metastatic progression, early initiation of androgen deprivation therapy, participation on clinical trial, local ablation, or administration of salvage pelvic irradiation (4,5,72,73). As localization of recurrent disease is limited, salvage radiation plans have delivered varying doses to the prostatic and seminal vesicle bed and periprostatic tissues, and may or may not include the pelvic lymph nodes (72,74). And while this strategy may be effective in curing or delaying the need for systemic therapy, success rates remain poor at 10–40% (69).

Detecting the presence of malignancy in the setting of BCR after prostatectomy has been perhaps the most active area of research for PSMA-PET imaging. Numerous retrospective studies demonstrate the increased ability to detect suspicious lesions using PSMA-PET over standard imaging (12,75-84). Many of these studies evaluated cohorts ranging from 35 to 393 patients and focused on ^{68}Ga-PMSA PET, reporting the detection of suspicious lesions in 74.2–91.4% of their patients, significantly higher numbers when compared to conventional imaging (12,75-78,80,82). Various factors have been studied and found associated with increased PSMA-PET detection, the most reliable being an increased serum PSA level (12,75-77,82). While some have noted increased detection with a faster PSA velocity (12,76) and shorter doubling time (77), others have found no association with PSA doubling time (12,75) or Gleason score (75,82).

Bluemel *et al.* evaluated 139 patients with BCR who first underwent an ^{18}F-choline PET/CT (76). If that scan showed no evidence of malignancy, a ^{68}Ga-PSMA PET/CT was offered. Of the 41 patients with a negative ^{18}F-choline PET/CT, 32 agreed to the ^{68}Ga-PSMA PET/CT, 14 (43.8%) of whom were found to have uptake on the second scan suggesting that ^{68}Ga-PSMA PET/CT is a more sensitive test compared to ^{18}F-choline PET/CT. Schwenck *et al.* performed a similar study of 103 patients with BCR and evaluated all with ^{11}C-choline PET/CT followed by a ^{68}Ga-PSMA PET/CT 24 hours later (53). While 55% of the 458 lymph nodes suspicious for metastases were detected with both imaging modalities, 39% were seen only with ^{68}Ga-PSMA and tended to be smaller (6 *vs.* 11.7 mm). Interestingly, though ^{68}Ga-PSMA appeared to be more sensitive, 6% of the lymph nodes showed only ^{11}C-choline uptake.

Urinary excretion and accumulation of ^{68}Ga-PSMA in the bladder may obscure small pelvic lymph nodes involved with disease. Freitag *et al.* evaluated the utility of adding mpMRI to ^{68}Ga-PSMA PET/CT or ^{68}Ga-PSMA PET/MRI to detect local recurrences in 119 patients with BCR (78). The team measured the effect of urinary bladder proximity on the local recurrence detection rate and found that eight local recurrences were found on mpMRI and not on ^{68}Ga-PSMA PET scans. These local recurrences were within 1.3cm of the bladder and were not determined to be positive because of the high bladder SUV suggesting

that there may be a role to combine PET with mpMRI. Uprimny *et al.* also addressed this issue evaluating local recurrences in 203 patients with BCR (84). Subjects were imaged within minutes of ^{68}Ga-PSMA injection then again one hour after injection to test the hypothesis that with less bladder accumulation of radiotracer local recurrences might be more easily detected. Indeed they found that there was an increased detection rate for local recurrences within the pelvis of 24.6% and fewer equivocal lesions noted at the early time point compared to 12.8% at one hour after injection.

While the above studies demonstrate compelling data, only a handful included confirmation of disease status by histology or other clinical measures. Afshar-Oromieh *et al.* evaluated 319 patients with ^{68}Ga-PSMA PET/CT (75). Histologic verification was performed on 42 patients and on a lesion based analysis, sensitivity, specificity, PPV and NPV were 76.6%, 100%, 100%, and 91.4%, respectively. Hijazi *et al.* retrospectively evaluated the ability of ^{68}Ga-PMSA PET to detect lymph node metastases in 35 patients who underwent pelvic lymph node dissection either for biochemical recurrence (n=23) or for high-risk PC (n=12) (80). They found that for this cohort, ^{68}Ga-PMSA PET had a sensitivity, specificity, PPV, and NPV to detect lymph node metastases of 94%, 99%, 89%, and 99.5%, respectively.

With their increased sensitivity to detect local recurrences, PSMA PET scans may impact therapy. Schiller *et al.* selected 31 patients who had developed BCR after prostatectomy and were found to have lymph node involvement on ^{68}Ga-PSMA PET/CT or ^{68}Ga-PSMA PET/MRI. Of these patients, 21 had suspicious lesions found only on ^{68}Ga-PSMA PET imaging. Of the 28 nodes seen exclusively on ^{68}Ga-PSMA PET, 15 were outside of the standard lymph drainage radiation field, a concerning clinical implication. As a result of these data, 13 patients received a boost to a subarea of the prostate bed they would otherwise not have received with standard imaging, and 18 patients received radiation to uncommon lymph node sites. Similarly, van Leeuwen *et al.* reported 70 patients evaluated with ^{68}Ga-PMSA PET for BCR and found that the additional imaging changed salvage radiation therapy plans for 28.6% of patients (85). Eiber *et al.* evaluated 248 prostatectomy patients who had undergone ^{68}Ga-PMSA PET for BCR (12). Of these patients 35 had selective radiation to PSMA-positive lesions and experienced a PSA decline, clinically indicating disease involvement in those areas. In a retrospective study by Afshar-Oromieh *et al.* 50 subjects received targeted therapy as local therapy for their PSMA detected lesions (75). Twenty-seven received external beam radiation, and 17 with follow up data all had a decline in their PSA; 19 had surgery and 4 were treated with high intensity focused ultrasound, all with documented declines in their PSA. While these studies are compelling, well-designed prospective clinical trials and long-term follow up are needed to understand the true risks and benefits of PSMA-PET in this setting.

Metastatic disease

The standard treatment for metastatic PC includes the use of systemic therapies (86,87). Oligometastatic disease, often defined as five or fewer metastatic lesions, is thought to be an intermediate step between localized and widespread metastatic disease. There is an increasing interest to treat these limited metastatic lesions with local ablative methods with the hope that doing so may interrupt the natural progression of disease and offer improved outcomes (5,88,89). This strategy is predicated on the ability to accurately identify lesions, both to appropriately classify patients and to target lesions for treatment. Given the improved imaging of PSMA PET over standard CT, MRI, or ^{99m}Tm-bone scan, a number of groups have published on the treatment of oligometastatic PC detected with this imaging modality.

A case report by Schiavina *et al.* described a patient with BCR found to have three lymph nodes involved on ^{68}Ga-PMSA PET (90). An open lymph node dissection was performed and his PSA declined to <0.2 ng/mL and remained stable two months later. Of note, while metastatic disease was confirmed histologically in the three nodes found on imaging, another nine removed were also found to be involved, suggesting a concerning high false negative rate. Longer-term follow up was not provided and would be instructive. Maurer *et al.* presented a case series of 5 patients who underwent PSMA-radioguided surgery for metastatic PC (91). Lymph node metastases were identified with ^{68}Ga-PMSA PET, and using an ^{111}In labeled PSMA radiotracer and a gamma probe, metastatic lymph nodes were located intraoperatively. Interestingly, smaller tumor deposits in neighboring lymph nodes not seen on ^{68}Ga-PMSA PET were detected with the gamma probe intraoperatively and confirmed histologically. While the team demonstrated the feasibility of this procedure with few complications, no response or follow up data were presented.

Larger case series have noted variable long-term outcomes. A series of 29 patients with BCR and metastases

found using ^{68}Ga-PMSA PET/CT was presented by Henkenberens *et al.* (92). The disease sites included local recurrences (13.8%), isolated lymph node metastases (58.6%), isolated bone metastases (20.7%), and one with a single pelvic node and vertebral body metastasis, all of which were treated with radiotherapy and had PSA declines. There were two recurrences, 12 and 12.7 months later, outside the radiation fields suggesting good disease control. Casamassima *et al.* detected metastatic recurrences using ^{11}C- or ^{18}F-choline as a radiotracer, their cohort of patients had 3 years of survival follow up (93). They found 25 patients with node only metastases who were treated with radiotherapy. Progression of disease was noted in 10 patients, two developed bone metastases within 60 days and eight had lymph node recurrences outside the irradiated areas. This translated to a 17% disease free survival and 92% overall survival at 3 years. The poor disease free survival may be due to the less sensitive imaging technique used to detect metastatic disease, however later studies also note high recurrence rates even with ^{68}Ga-PMSA PET detection of disease.

Guler *et al.* evaluated 23 patients with BCR, 13 had castration sensitive and 10 had castration resistant disease, and were found to have 3 or fewer metastatic sites seen on ^{68}Ga-PMSA PET (94). These lesions were treated with radiation and at a median follow up of 7 months, 19 patients (83%) had no recurrence of disease, however the actuarial one-year progression free survival was 51%. Habl *et al.* evaluated 15 patients who were treated with radiation therapy for 20 lesions found on either ^{68}Ga-PMSA PET/CT or ^{11}C-choline PET/CT (95). With a median follow up after radiation therapy of 22.5 months, the median PSA progression free survival was only 6.9 months and the median distant progression free survival was 7.36 months. Siriwardana *et al.* performed robot assisted salvage lymphadenectomy on 35 patients who had 58 lesions detected on ^{68}Ga-PMSA PET/CT (96). A total of 32 patients had histopathologically proven metastatic disease with 87 lymph node metastases found at the time of surgery. A treatment response (PSA decline) was seen only in 43% of patients and PSA progression free survival at a median follow up of 12 months was only 23%. Similar to the case report by Schiavina *et al.* this study found more lymph nodes involved with disease than seen with ^{68}Ga-PMSA PET/CT suggesting a lower sensitivity than previously thought and may explain the low response rates and poor recurrence free survival in this cohort. Again, prospectively designed clinical trials are needed to fully understand the utility of PSMA PET scans in this clinical setting (*Table 1*).

Future directions

Though ^{68}Ga-PMSA PET demonstrates superior imaging qualities compared to other PET radiotracers (11), it has limitations in sensitivity and specificity. Newer PET tracers targeting PSMA are thus being developed. Particularly promising is a second generation small molecule inhibitor of PSMA, 2-(3-(1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid (^{18}F-DCFPyL) (27). It demonstrates a higher tumor to background uptake allowing it to detect significantly more metastatic lesions compared to conventional imaging modalities (139 *vs.* 45) (97), and has more favorable imaging characteristics compared to ^{68}Ga-PMSA PET/CT (98). In preliminary reports ^{18}F-DCFPyL demonstrated the ability to detect intraprostatic tumors with good correlation to whole mount specimens (99). A larger study of 25 men with high or very high risk PC imaged with ^{18}F-DCFPyL prior to prostatectomy and pelvic lymph node dissection demonstrated a sensitivity of 71.4% and specificity of 88.9% for detecting lymph node metastases (100).

The characteristics that make PSMA a good imaging target, particularly its specificity for PC and that ligands are internalized by clathrin mediated endocytosis, also allow it to be a target for delivery of radiopharmaceuticals, also known as endoradiotherapy. Several agents that target PSMA with bound radionuclide have been developed. Most of these agents use beta particle emitters including ^{177}lutecium (^{177}Lu), ^{90}yittrium (^{90}Y), and ^{131}iodine (^{131}I) (28), however agents using alpha particle emitter ^{225}actinium (^{225}Ac) are also being developed (101).

One of the first endoradiotherapeutic agents to be developed and studied was ^{177}Lu-labeled J951 (102,103). In a phase II study of 47 patients with metastatic castration resistant prostate cancer (mCRPC), 55.3% of whom had received chemotherapy, 59.6% experienced a PSA decline with 36.2% having a ≥30% PSA decline and 10.6% having a ≥50% PSA decline (102). Toxicities included grade 4 thrombocytopenia in 46.8% (29.8% requiring transfusions) and grade 4 neutropenia in 25.5% (one patient with febrile neutropenia). Another early endoradiotherapeutic agent targeting PSMA was (S)-2-(3-((S)-1-Carboxy-5-(3-(4-[^{131}I] iodophenyl)ureido)pentyl)ureido) pentanedioic acid, ^{131}I-MIP-1095, developed by Molecular Insight Pharmaceuticals (104). Tested in 34 men with mCRPC, 94.1% had a PSA decline with 70.6% having a ≥50% PSA decline (105). Of the 16 patients who had pain prior to therapy, 15 experienced a reduction in pain. Twenty-three patients received a second dose, and three patients received

Table 1 Summary of selected PSMA-PET studies, methods, and results

Population	Reference	N	Tracer	Methods	Results
Pts with localized disease	Rowe *et al.* (3)	13	^{18}F-DCFBC	PET and MRI prior to prostatectomy	PET Sens 17%, Sp 96%, uptake was associated with Gleason score MRI Sens 39% Sp 89%
	Turkbey *et al.* (59)	13	^{18}F-DCFBC	PET and MRI prior to prostatectomy (N=4) or MRI fusion biopsy (N=9)	PET detection of largest and highest Gleason lesion Sens 61.5% MRI Sens 92%
	Rahbar *et al.* (55)	6	^{68}Ga-PSMA	Prospective PET prior to prostatectomy for Gleason ≥3+4 disease	Sens 92%, Sp 92%
	Fendler *et al.* (50)	21	^{68}Ga-PSMA	Prospective PET for pts with biopsy proven disease and underwent prostatectomy for Gleason 7 disease; prostate sectioned into six segment model	Sens 67%, Sp 92%
	Rhee *et al.* (51)	20	^{68}Ga-PSMA	PET and MRI prior to prostatectomy; compared imaging to whole mount specimens	PSMA Sens 49%, Sp 95%, PPV 85%, NPV 88%; MRI Sens 44%, Sp 94%, PPV 81%, NPV 76%
	Zamboglou *et al.* (60)	10	^{68}Ga-PSMA	PET prior to prostatectomy; co-registration between PET and histopathology	PSMA Sens 75%, Sp 87%; MRI Sens 70%, Sp 82%
	Eiber *et al.* (52)	66	^{68}Ga-PSMA	PET/MRI for intermediate or high risk disease	PSMA Sens 64%, Sp 94%; MRI Sens 43%, Sp 95%, PSMA-MRI Sens 76%, Sp 97%
Pts undergoing prostatectomy with pelvic lymph node dissection	Budäus *et al.* (65)	30	^{68}Ga-PSMA	PET prior to prostatectomy and extended pelvic LND in pts with nomogram-calculated risk of LN metastases >20%	Sens 33.3%, Sp 100%, PPV 100%, NPV 69.2% for detection of LN metastases
	Maurer *et al.* (66)	130	^{68}Ga-PSMA	PET/CT (N=95) or MRI (N=25) prior to prostatectomy and standard template LND	Sens 65.9%, Sp 98.9%, Accuracy 88.5%
	Zhang *et al.* (67)	42	^{68}Ga-PSMA	PET/CT and MRI prior to prostatectomy and pelvic LND	Sens 93.33%, Sp 96.3%, PPV 93.33%, NPV 96.3%

Table 1 (*continued*)

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Population	Reference	N	Tracer	Methods	Results
Pts with biochemical recurrence	Bluemel *et al.* (76)	32	^{68}Ga-PSMA	^{18}F-choline PET/CT negative subjects had ^{68}Ga-PSMA PET/CT	43.8% had uptake on 68Ga-PSMA PET/CT
	Schwenck *et al.* (53)	103	^{68}Ga-PSMA	^{11}C-choline PET/CT then ^{68}GA PSMA PET/CT 24 hours later	39% of suspicious lesions were seen only with 68Ga-PSMA PET; LNs seen on ^{68}Ga-PSMA were smaller (6 *vs.* 11.7 mm)
	Freitag *et al.* (78)	119	^{68}Ga-PSMA	PET/CT *vs.* PET/MRI for local recurrence	8 local recurrences found on MRI and not on ^{68}Ga-PSMA PET within 1.3cm of the bladder
	Uprimny *et al.* (84)	203	^{68}Ga-PSMA	^{68}Ga-PSMA imaging within minutes of injection then after 1 hour	24.6% detection rate for local recurrence with immediate PET imaging *vs.* 12.8% at 1 hour after injection
	Afshar-Oromieh *et al.* (75)	42	^{68}Ga-PSMA	Histologic verification on a lesion based analysis	Sens 76.6%, Sp 100%, PPV 100%, NPV 91.4%
	Hijazi *et al.* (80)	35	^{68}Ga-PSMA	Pelvic lymph node dissection for BCR (N=23) or high risk PC (N=12)	Sens 94%, Sp 99%, PPV 89%, NPV 99.5%
Pts with oligometastatic disease	Maurer *et al.* (91)	5	^{68}Ga-PSMA	Lymph node metastases identified with ^{68}Ga-PSMA PET, using ^{111}In-PSMA and intraoperative gamma probe lymph nodes were removed	Neighboring lymph nodes not seen on ^{68}Ga-PSMA PET were detected with the intraoperative gamma probe and confirmed histologically
	Henkenberens *et al.* (92)	29	^{68}Ga-PSMA	Detection of oligometastatic disease treated with radiotherapy	All subjects had PSA declines, two recurrences 12 and 12.7 months after radiation
	Guler *et al.* (94)	23	^{68}Ga-PSMA	3 or fewer metastatic sites treated with radiotherapy	Median follow up of 7 months, 83% had no recurrence; 1-year PFS 51%
	Habl *et al.* (95)	15	^{68}Ga-PSMA or ^{11}C-Choline	20 lesions found on either scan modality treated with radiotherapy	Median follow-up 22.5 months after radiotherapy, median PSA PFS 6.9 months, median distant PFS 7.36 months
	Siriwardana *et al.* (96)	35	^{68}Ga-PSMA	58 lesions detected on PET underwent salvage LND	32 had histopathologically proven metastatic disease with 87 lymph nodes involved; PSA decline seen in 43%; PSA PFS at 12 months follow-up was 23%

PSMA, prostate-specific membrane antigen; LN, lymph node; LND, lymph node dissection; MRI, magnetic resonance imaging; NPV, negative predictive value; PET, positron emission tomography; PFS, progression-free survival; PPV, positive predictive value; PSA, prostate-specific antigen; Pts, patients; Sens, sensitivity; Sp, specificity.

a third dose at the time of PSA progression if they had had an initial response, however responses to subsequent doses were less effective. Hematologic toxicities after the first dose included grade 3 thrombocytopenia in 5.9% and grade 3 leukopenia in 2.9%, while non-hematologic toxicities included grade 1 or 2 xerostomia in 88.2% and fatigue in 5.9%. Despite the favorable efficacy and side effect profile of ^{131}I-MIP-1095, excitement has not been as robust as radioiodinated pharmaceuticals have poor *in vivo* stability due to dehalogenation (23,106).

DOTAGA-(I-y)fk(Sub-KuE), termed PSMA I&T (for Imaging and Therapy), was developed by Weineisen *et al.* (107). It is a PSMA targeting endoradiotherapeutic agent that can be tagged with ^{68}Ga or ^{177}Lu for imaging or endoradiotherapy, respectively. In a preliminary study imaging one patient with ^{68}Ga-PSMA I&T, uptake was seen in the primary tumor, regional lymph nodes, and bones with a lesion-to-background ratio of 17.6 for lymph node and 35.2 for bone metastases. One patient treated with ^{177}Lu-PSMA I&T had a decline in PSA from 40.2 to 0.7 ng/mL within 3 months of the first dose with a concomitant improvement in pain symptoms (107). In a follow up report of 56 patients with mCRPC treated with ^{177}Lu-PSMA I&T, 80.4% had a decline in PSA with 66.1% having a ≥30% PSA decline and 58.9% having a ≥50% PSA decline (108). The agent was well tolerated with grade 1 or 2 leukopenia in 9 patients but no other significant hematologic toxicities and only mild xerostomia in 2 patients. As a result 40 patients were able to receive more than one cycle of therapy. The median progression free survival was 13.7 months and median overall survival was not reached in the 28 months of follow up.

PSMA DKFZ-617 is another small molecule inhibitor of PSMA that can bind to both ^{68}Ga and ^{177}Lu for imaging and therapy. In an initial study of 10 patients, 70% had a decline in PSA with 5 having a ≥50% PSA decline and only one patient having a grade 3 anemia (109). A follow up report of 22 patients treated with at least two cycles of ^{177}Lu-PSMA DKFZ-617 showed that PSA responses were obtained in 79.1% after the first dose and 68.2% after the second dose with only two cases of grade 3 anemia (110). Alpha emitter ^{225}Ac has also been linked to PSMA DKFZ-617 with the thought that alpha radiation therapy may effectively treat disease that is resistant to beta emitters (101). In their initial report, Kratochwil *et al.* documented the administration of ^{225}Ac-PSMA DKFZ-617 in two heavily pre-treated patients, one with diffuse marrow infiltration and contraindicated to beta emitter therapy, and another who had disease progression on ^{177}Lu-PSMA DKFZ-617 with peritoneal carcinomatosis and liver infiltration (101). Quite remarkably, both patients had a decline in PSA to undetectable levels and a complete response on imaging with xerostomia as the only clinical side effect. The group later reported follow-up on 14 heavily pre-treated patients with poor risk features including ten patients with visceral metastases (111). Astonishingly nine of the 11 evaluable patients had either a radiographic response or PSA decline with therapy, however severe xerostomia did become a dose limiting toxicity (111).

PSMA imaging and targeting is an active field of research with at least 40 trials currently open and recruiting subjects on ClinicalTrials.gov, including NCT03042468 and NCT03042312, which further evaluate the use of ^{177}Lu-PSMA DKFZ-617, and NCT02552394, which explores additional applications of J591. Others combine this exciting field with the burgeoning field of immunotherapy such as NCT03089203, a phase I study of an intravenously administered dual PSMA-specific/TFGβ chimeric antigen receptor modified autologous T cell in patients with mCRPC, and NCT02262910, evaluating MOR209/ES414 (112), a bispecific antibody targeting PSMA and the T-cell receptor in patients with mCPRC.

Conclusions

The field of PC imaging has changed dramatically with the rapid development of PSMA-targeted imaging. With its increased ability to detect disease, the clearest application of this imaging modality appears to be in patients with biochemical recurrence when conventional imaging is unable to identify disease at very low PSA levels. Other areas where PSMA imaging appears promising is the detection and characterization of primary tumors, local staging of regional lymph nodes, and the identification of oligometastatic disease to allow for targeted treatment. PSMA-targeted treatment with endoradiotherapeutic agents is another emerging field. Results from preliminary reports with dramatic response rates and often tolerable side effects demonstrate the promise of targeting PSMA with radioligands. While results of many of these studies are compelling, they are also limited as they are largely retrospective and descriptive without clear controls, making it difficult to determine whether these agents affect outcomes. The true potential of this field can be better realized with well-designed prospective clinical trials.

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Footnote

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