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New Targets for PET Molecular Imaging of Prostate Cancer

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Prostate cancer (PCa) is the most common cancer in men worldwide, but it exhibits a highly variable biological behavior ranging from indolent to highly aggressive disease. The standard conventional imaging for staging PCa consists of CT, MRI, and bone scans, but this imaging has suboptimal accuracy for extraprostatic tumor detection, particularly in the scenario of early biochemical relapse when the prostate-specific antigen levels are still low indicating a low volume of recurrent disease. This gap between known disease (as indicated by a rising prostate-specific antigen) and the failure to detect it on conventional imaging, has led to the development of novel imaging probes most of which have positron emitting radioactive tags. In the last decade, multiple PET probes have demonstrated promising performance in detecting sites of recurrence and extent of disease in patients with PCa. The landscape of available PET radiotracers is changing rapidly and includes radiolabeled choline, anti1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F-fluciclovine), bombesin, dihydrotestosterone, and prostate-specific membrane antigen (PSMA) ligands, among others. Of these, radiolabeled PSMA-PET agents have shown the most encouraging results in terms of sensitivity and are likely to become universally available for imaging PCa within a few years Other PET radiotracers such as bombesin-based radiotracers and antagonist of gastrin releasing-peptide receptor (RM2) are emerging as possible alternatives for PCa imaging. This review article discusses the current and near-future of PET molecular imaging probes.

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Introduction

Prostate cancer (PCa) is the second most common cause of cancer-related deaths in men[1] and thus makes a compelling story for the development of new imaging agents. Imaging plays an increasingly important role in the clinical management of patients with PCa as they progress from localized to recurrent and metastatic disease. Conventional standard of care imaging, including CT, MRI, and bone scans often fail to detect sites of disease, especially early in the course of the progression of disease where it is most potentially treatable. Here it is important to note that this article will focus on disease that has recurred or spread from the original intraprostatic cancer. Detection of intraprostatic disease at diagnosis is generally well handled by multiparametric MRI (mpMRI) and fusion biopsy but is beyond the scope of this review. Instead we will focus on the disease once it has been treated and as recurred or at the time of diagnosis when it has spread outside the prostate as occurs in some high-risk cancers. There is a compelling need to understand the extent of disease so as to direct therapy including surgery, radiation, ablative, or systemic. Therefore, there is a need for more sensitive and specific imaging modalities to detect PCa, early tumor recurrence, and metastatic PCa. Imaging of PCa is challenging due to the complexity of the different stages of the disease. At initial diagnosis, it is not sufficient to simply visualize the cancer site, but also it is important to differentiate biologically aggressive cancers warranting life-altering therapies, from more indolent subtypes that may be observed by Active Surveillance. When a patient relapses after definitive curative therapy (ie, radiation or surgery), the serum prostate-specific antigen (PSA) rises, a phenomenon often referred to as biochemical recurrence (BCR). When this happens, there is a high likelihood that the patient has recurred somewhere in his body and imaging should be able to identify sites of recurrence and distinguish patients with limited local recurrence in the prostate bed from

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those with local nodal or distant metastases as treatments and prognosis are very different. Each type of recurrence carries a distinct prognosis and can be used to guide therapy. Finally, patients with metastatic disease can be assessed for the extent of their disease and their suitability for various therapies. For instance, metastatic disease can be of at least two types: castration sensitive or castration resistant and distinguishing these can be important from a prognostic perspective as well as providing guidance for treatment and treatment monitoring. Finally, the same or related molecular entities used to diagnose PCa may also be used to direct targeted radionuclide therapy, using therapeutic isotopes in place of diagnostic ones.

Several PET imaging agents have been developed to assess advanced PCa. They vary in their sensitivity and specificity for PCa. Most of the agents are not only insensitive for low grade primary cancer but also often are taken up in benign diseases such as benign prostatic hyperplasia or prostatitis. Additionally, many of the agents do not perform well late in the disease when adenocarcinomas undergo neuroendocrine differentiation. The exception to this latter rule is ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET imaging, which appears most useful in late castration resistant disease and is associated with a poor prognosis. For the majority of PCa, however, numerous PET agents are available that depend on the biology of choline, upregulation of amino acid transport, expression of prostate-specific membrane antigen (PSMA), and expression of gastrin releasing peptide receptor (GRPR), among others. Among these, the family of molecular probes targeting the PSMA has shown the highest sensitivity in staging of high-risk primary PCa, and in localizing sites of BCR. PSMA-based PET/CT have shown greater diagnostic performance compared to older agents, particularly at very low PSA levels as occurs in early BCR. The cancer detection rate as a function of PSA level in the recent postoperative state is an excellent comparator of agents, as PSA level at this stage correlates with PCa volume. In addition, PSMA, as a theranostic agent, allows for both radiolabeling with diagnostic (eg, ^{68}Ga, ^{18}F) or therapeutic nuclides (eg, ^{177}Lu, ^{225}Ac). Other emerging PET radiotracers for PCa include the bombesin group targeting the GRPR, 16β-^{18}F-fluoro-5α-dihydrotestosterone (^{18}F-FDHT) that binds to the androgen receptor (AR), and those targeting the urokinase plasminogen activator receptor (uPAR), the vasoactive intestinal polypeptide receptor 1, and the cell surface protein STEAP1, which are also overexpressed in PCa. Here we discuss these molecular probes in more detail.

^{11}C/^{18}F Choline

In the last decade, ^{11}C and ^{18}F radiolabeled choline PET/CT imaging have been widely used for detecting advanced PCa. Choline kinase is overexpressed in PCa, and choline serves as a substrate for this enzyme. Choline kinase helps the cells use choline to synthesize phosphatidylcholine, a key component of cell membranes and this metabolic pathway is limited to a few cancers including PCa.

^{11}C- Choline is identical chemically to endogenous choline and therefore, ideal as a PET tracer. However, this agent is only available in institutions with an on-site cyclotron and professional radiochemistry due to the short half-life (t1/2 = 20 min) and therefore, the requirement to quickly label the precursor of choline. By contrast, ^{18}F-labelled choline is more practical and widely available due to its longer half-life (t1/2 = 110 min), but it differs chemically from endogenous choline, for instance it has higher urinary excretion into the bladder than ^{11}C-choline, which may interfere with the interpretation of pelvic findings[2,3] such as local recurrence. However, from a performance standpoint both agents function well, and multiple studies have shown similar diagnostic performance for ^{11}C-choline and ^{18}F-choline for malignant lesions in different clinical settings.[4]

Localized PCa

One limitation of the choline-based PET imaging agents is that both benign and malignant entities in the prostate take up the agent. Thus, distinguishing tumor uptake from benign prostatic hyperplasia is usually not possible with either^{11}C/^{18}F-choline, therefore these agents have a limited role in primary PCa. The use of choline PET imaging should be limited in the initial staging of PCa high-risk and very-high-risk cancer to reduce the incidence of false-negative scans and to increase the yield of the scan.

Biochemical Recurrence

^{11}C/^{18}F-choline PET/CT is mainly used for restaging PCa patients in the setting of BCR, since it has shown better accuracy than conventional imaging.[5,6] In a recent meta-analysis of 29 studies with a total of 2686 patients, Fanti et al[7] found that ^{11}C-choline PET/CT had a lesion detection rate of 62% for any site of relapse (95% confidence interval [CI]: 53%-71%). Naturally, this detection rate is somewhat misleading as it depends on the mix of patients studied. Those with long standing recurrences with high PSA values are more likely to be detected than recent recurrences with low PSA values. However, detecting patients with lower PSA values is more meaningful as such patients are more likely to benefit from additional therapy such as salvage radiation. Stratifying by PSA in a series of 3203 BCR PCa patients using ^{11}C-choline PET/CT, Graziani et al[8] reported a sensitivity of 44.7% in patients with a PSA level between 1 and 2 ng/mL. This is substantially lower than the sensitivities of newer PSMA-based PET probes discussed below and raise questions as to the future of these agents. In the receiver operating characteristic curve analysis, a PSA of 1.16 ng/mL was the optimal cut-off value to predict a positive scan. Unfortunately, this PSA value in the recurrence setting after surgery is associated with a higher rate of treatment failure, whereas patients with lower PSA values do better. Nevertheless, ^{11}C/^{18}F-choline PET/CT findings influence decision-making in approximately 50% of cases in which the agent was used.[9-11] Recently, the European Association of Urology guidelines suggested the use of choline PET/CT in patients with BCR at PSA levels >1 ng/mL, and preferably between 1 and 2 ng/mL.[12]

The main limitations of choline PET/CT are related to low sensitivity in patients with low PSA levels (PSA < 1 ng/mL), where such scanning is most useful. The choline agents also demonstrate false positives in inflammatory nodes, for instance, in the inguinal region, an uncommon site for nodal PCa metastases. ^{11}C-Choline has the specific limitation of a very short half-life requiring an onsite cyclotron and radiochemistry facility.

It is generally understood that lymph node and bone metastases may behave differently on imaging. The diagnostic performance of choline PET/CT for the detection of bone metastasis in PCa has recently been evaluated in a meta-analysis by Guo et al[13] of 14 studies and a total 655 patients. On a per-patient basis, the reported sensitivity and specificity ranged from 50% to 100% and from 89% to 100%, respectively. On a per-lesion basis, eight studies involving 472 patients with 1619 lesions were included, and reported sensitivity and specificity ranged from 75% to 96% and from 92% to 100%, respectively.[13] Choline PET/CT imaging was found to exhibit excellent diagnostic performance for the detection of bone lesions; however, a negative choline PET result could not ensure the lack of bone metastases.[13] This point emphasizes the continued need for bone specific imaging agents.

Radiolabeled Amino Acid Analogs

Anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid, also known as ^{18}F-FACBC, recently renamed as ^{18}F-fluciclovine, or Axumin (brand name), is a synthesized amino acid L-leucine analogue, that targets amino acid transporters,[14] leading to intracellular accumulation in PCa cells.[15] ^{18}F-fluciclovine has a favorable dosimetry and biodistribution, that differs from choline as the activity in the urinary tract is negligible within one hour of injection, which reduces the possibility of missing small sites of disease relapse within the lower pelvis.[16,17]

Localized PCa

^{18}F-fluciclovine shares the problem of nonspecific prostate uptake, similar to choline. In a multicenter trial of 68 patients with primary PCa, ^{18}F-fluciclovine PET/CT was found to have high sensitivity and specificity of 92.5% and 90.1% for the focus of primary disease.[18] However, additional studies reported lower specificity for primary prostate detection as uptake was seen in benign entities as well as cancer.[19-21] In a comprehensive prospective trial, Turkbey et al[21] compared ^{18}F-FACBC PET/CT and MRI for the detection of primary PCa in 21 men, demonstrating higher sensitivity and specificity for MRI than ^{18}F-FACBC (73% vs 67% and 79% vs 66%, respectively). Prostate tumor uptake was significantly higher than the normal prostate gland, but without significant difference in uptake between prostate carcinoma and benign prostatic hyperplasia.[21] Similarly, another prospective study including 26 men with localized primary PCa, reported high sensitivity of 87% but low specificity of 56% for primary tumor identification, concluding that ^{18}F-fluciclovine PET failed to outperform MRI in primary lesion detection.[20] Therefore, it is unlikely that ^{18}F-fluciclovine PET will play a role in initial staging primary PCa.

Biochemical Recurrence

^{18}F-fluciclovine was granted approval by the US FDA in 2016 for the clinical indication of suspected recurrent PCa. A recent meta-analysis of six studies with 251 patients with BCR found a pooled sensitivity and specificity for ^{18}F-fluciclovine of 87% (95%CI: 80%-92%) and 66% (95%CI: 56%-75%), respectively for recurrent disease.[17] Similarly, high specificity of 96.7% and positive predictive value (PPV) of 95.7% was reported by Schuster et al[22] for extraprostatic detection of disease (eg, lymph nodes and bones) in patients with recurrent PCa (Fig. 1). This high PPV was mirrored by a large multicenter trial of 596 patients which showed a PPV of 92.3%.[23] Compared to diagnostic CT, the performance of ^{18}F-fluciclovine PET in detecting recurrent PCa was superior, providing better delineation of extraprostatic sites of recurrence.[24] However, like all agents, the ^{18}F-fluciclovine PET recurrence detection rate varies with PSA values, with reported detection rates of 72.0%, 83.3%, and 100% at PSA levels of <1 ng/mL, 1-2 ng/mL, and ≥2 ng/mL, respectively.[25] Results of a multicenter trial reported that ^{18}F-fluciclovine PET/CT tumor detection was broadly proportional to the prescan PSA, detecting lesions in 31%, 50%, 66%, and 84% of patients, with PSA 0-0.5 ng/mL, >0.5-1.0 ng/mL, PSA >1.0-2.0 ng/mL, and >2.0 ng/mL, respectively, in a

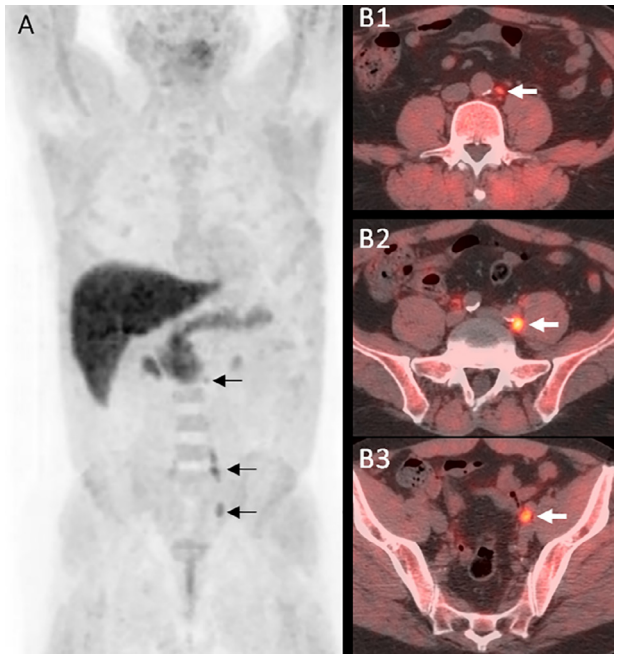

Figure 1 ^{18}F-fluciclovine PET/CT imaging in a patient with biochemical recurrence prostate cancer (PSA of 5.25 ng/mL). Maximal intensity projection (A), and axial fused ^{18}F-fluciclovine PET/CT (B) images show abnormal foci of uptake fusing to subcentimeter left paraaortic (B1), left common iliac (B2), and left internal iliac lymph nodes (B3).

per-patient basis. These values, however, are still somewhat lower than has been found with PSMA targeted imaging agents. For metastatic lymph nodes outside the pelvis, that is, retroperitoneal and other nodal distant sites, the scan positivity ranged from 3.7% at PSA ≤0.5 ng/mL to 42% at PSA >10 ng/mL, while the detection rate for bone metastases was 7.4% at PSA ≤0.5 ng/mL and 14% at PSA >2 ng/mL.[26] This prospective, multicenter LOCATE US trial enrolling 221 patients also assessed the impact of ^{18}F-fluciclovine on management plans for patients with BCR PCa after curative-intent primary therapy. Overall, 59% of the patients had a change in management after the scan, with 78% of these being major changes, that is, change from salvage or noncurative systemic therapy to watchful waiting (25%), or from noncurative systemic therapy to salvage therapy (24%) or from salvage therapy to noncurative systemic therapy (9%).[26]

Direct comparisons of ^{11}C/^{18}F-choline to ^{18}F-fluciclovine in the same patient cohort have been limited but in general demonstrated superior performance for ^{18}F-fluciclovine in BCR PCa. A prospective study from Nanni et al[27] including 89 BCR patients after radical prostatectomy, revealed sensitivity of 37%, specificity of 67%, PPV of 97%, neg predictive value (NPV) of 4%, and accuracy of 38% for ^{18}F-fluciclovine, versus 32%, 40%, 90%, 3%, and 32%, respectively for choline PET imaging.[27,28] In general, ^{18}F-fluciclovine outperforms choline, detecting a higher number of true positive and true negative lesions in the prostate bed, lymph nodes, and bones. Furthermore, ^{18}F-fluciclovine was found to be superior to choline for low, intermediate, and high PSA values.[28]. Practical advantages for ^{18}F-fluciclovine were reported in terms of biodistribution, image quality, and acquisition protocol, with lower physiologic background that improves lesion conspicuity.[29]

Overall, ^{18}F-fluciclovine appears to be a highly sensitive technique for detecting recurrent disease but suffers from low-to-moderate specificity with a relatively high false positive rate that could result in falsely upstaging disease. Despite its relatively good performance, the utility of this agent, similar to choline compounds, may need to be considered in the context of the newer promising PSMA-based PET agents.[30] In a small case series comparing both tracers, ^{68}Ga-PSMA-11 PET/CT outperformed ^{18}F-fluciclovine, by detecting positive findings in 50% (5/10) of patients who had a negative ^{18}F-fluciclovine scan, and detecting additional lesions in 20% of the patients who were positive with both scans.[31] Prospective larger trials designed to directly compare the 2 should be initiated.

PSMA PET/CT Imaging

In recent years, much attention has been focused on PSMA as a target for PCa PET imaging.[32] PSMA is overexpressed in intermediate high-grade tumors and increases in expression with increasing aggressiveness.[32-36] However, in highly evolved tumors with neuroendocrine features, expression may again be reduced. Although the term PSMA implies specificity for the prostate it is not entire prostate-specific, and it is expressed in other neoplasms and in infection-inflammation[37] and is physiologically expressed in normal cells including those in the small intestine, proximal renal tubules, and salivary and lacrimal glands.[36] PSMA is an excellent target for diagnostic imaging and therapy of PCa, due to its high expression in tumors, suitable binding affinity and internalization of PSMA ligands.

The first attempt to target PSMA for imaging was in the form of a radiolabeled monoclonal antibody (mAb), ^{111}Indium-7E11 (^{111}In-capromab; ProstaScint) that was investigated clinically as a SPECT imaging agent; however, it targeted the intracellular domain of PSMA, and thus, lacked sensitivity and specificity.[38] The humanized mAb hJ591 that binds to an extracellular domain of PSMA has also been investigated for PET diagnostic imaging in the form of ^{89}Zr-hJ591, and demonstrated higher affinity, and more efficient targeting,[39] and as ^{177}Lu-hJ591 for therapy in metastatic castrate-resistant PCa patients (mCRPC). The more recent development of PSMA radiopharmaceuticals have focused on small-molecule inhibitors (known as ligands) that target the active substrate recognition site of the PSMA folate hydrolase enzyme. These ligands, that have a urea binding motif, bind with high affinity to the PSMA receptor and also exhibit rapid plasma clearance and high tumor-to-background ratios. A variety of PSMA ligands have translated into the clinic over recent years, but none has yet been approved by the US FDA although they are used clinically in many countries in Europe, Asia, and Australia. The most widely used PSMA compound in clinical studies (PSMA-HBED-CC) is labeled with ^{68}Ga and is known as ^{68}Ga-PSMA-11,[40] which has quickly evolved in Europe. PSMA have been also labeled with other tracers like ^{68}Ga, ^{18}F, ^{111}In, and ^{99m}Tc, such as ^{18}F-DCFBC/^{18}F-DCFPyL, ^{18}F-PSMA-1007, ^{68}Ga/^{111}In-PSMA-617, or ^{123}I-MIP-1095 among others.

Localized PCa

In patients eligible for curative-intent primary therapy, the decision to proceed with a further staging work-up is guided by the available treatment options, considering patient's preference and comorbidity. In the assessment of intraprostatic primary malignancy, PSMA PET/CT has been compared with multiparametric MRI (mpMRI) in several cohorts (Fig. 2), for instance by Giesel et al[41] which revealed concordance between positive findings on each modality.[41] Combined ^{68}Ga-PSMA-11 PET/MRI was analyzed in 53 patients with intermediate to high-risk PCa, and the PET agent demonstrated superior accuracy with the hybrid approach compared to either modality alone, with sensitivities and specificities of 76% and 97% for hybrid ^{68}Ga-PSMA-11 PET/MRI; 58% and 82% for mpMRI alone; and 64% and 94% for ^{68}Ga-PSMA-11 PET/CT alone.[42] Similarly, Zamboglou et al[43] proved that the combination of PSMA PET with mpMRI increased the accuracy of PET or mpMRI performed alone for primary tumors, showing a sensitivity of 82% and a specificity of 89%. Furthermore, when comparing to histology, PSMA PET/CT uptake, measured by maximum standard uptake value, increases with increasing tumor grade

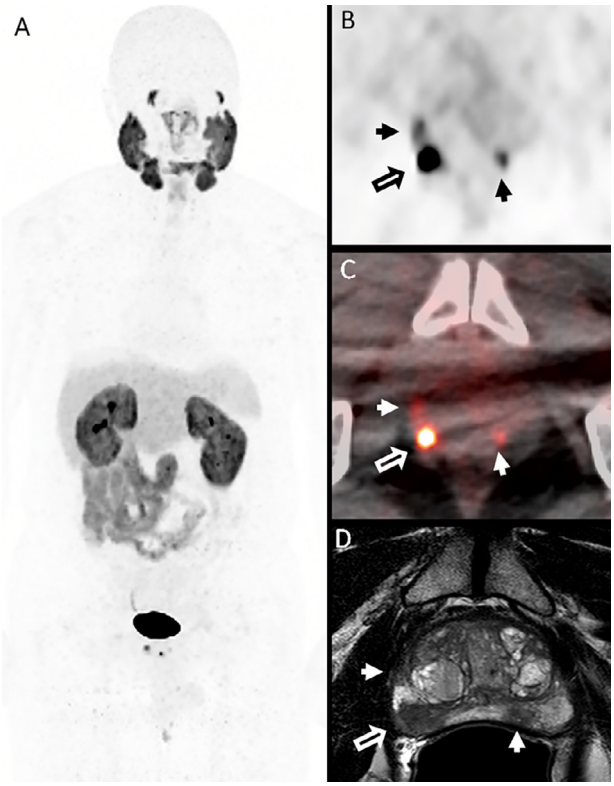

Figure 2 ^{18}F-DCFPyL PET/CT in a patient with high-risk primary prostate cancer. Maximal intensity projection (A), axial ^{18}F-DCFPyL PET (B), and axial-fused PET/CT (C) images demonstrate a dominant DCFPyL-avid focus at the right apical-mid peripheral zone (PZ) (open arrow), and additional smaller abnormal foci of uptake at the right anterior mid PZ, and left mid PZ (small arrows), all concordant with the T2W MRI findings (D).

demonstrating positive correlation with Gleason score,[44] although considerable overlap exists for any Gleason category. In addition, PSMA PET can discriminate clinically significant high-grade PCa from BPH nodules which usually fail to take up the agent.[45,46] Compared to histology, the sensitivity of PSMA PET tracers on a voxel-wise basis ranged from 67% to 79%[47,48] indicating not all parts of a tumor will express PSMA; however, the majority of cells will express at least at some detectable level. This has implications for the guidance of focal therapies, as it demonstrates that PSMA PET/CT tends to underestimate the tumor volume.

Preoperative assessment of lymph node status is important in intermediate and high-risk PCa patients. Conventional imaging performs poorly for the detection of pelvic lymph node metastases,[49] almost 80% of which measure less than 8 mm and thus, cannot be detected on conventional imaging. Maurer et al[50] compared ^{68}Ga-PSMA-11 imaging with conventional imaging, that is, CT and mpMRI for lymph node staging showing that the sensitivity, specificity, and accuracy for the detection of nodal metastases was 65.9%, 98.9% and 88.5%, respectively for ^{68}Ga-PSMA-11, compared with 43.9%, 85.4%, and 72.3% for morphological imaging.[50] A recent meta-analysis found a pooled sensitivity, and specificity of 71% and 95% for lymph node staging in patients with newly diagnosed intermediate to high-risk PCa; however, such values must be stratified by PSA value.[51-53] Budaus et al[53] retrospectively compared preoperative ^{68}Ga-PSMA PET/CT with histology in 30 patients and proved that nodal detection rates were substantially influenced by the lymph node size, with a significantly different median nodal size for PSMA-avid nodes versus undetected lymph node metastases (1.36 vs 0.43 cm).

For the assessment of bone metastatic disease in intermediate high-risk primary patients, a meta-analysis indicated that PSMA-PET/CT outperformed bone scan.[54] ^{68}Ga-PSMA uptake showed higher diagnostic performance in detecting osteolytic and bone marrow metastases than osteoblastic metastases.[55] Data from PSMA PET and CT complement each other for the diagnosis of different types of bone metastases.[55]

The routine use of PSMA PET/CT in staging PCa should be reserved for patients with intermediate or high-risk cancers based on PSA and Gleason scores, where there is a reasonable likelihood of extraprostatic disease (Fig. 3).

Biochemical Recurrence

The most extensive experience with PSMA PET/CT imaging has been in the setting of BCR following therapy (PSA $\geq$0.2 ng/mL after radical prostatectomy, or a 2 ng/mL rise above the PSA nadir postradiation). Detection of sites of recurrence guides therapy, as it could ultimately determine whether to use aggressive loco-regional salvage therapy or systemic palliative therapy. This is most important at low serum PSA values, when there are potential curative salvage radiation therapy (RT) options, which remain most effective at serum PSA values less than 0.5-1.0 ng/mL.[56]

Several reports have demonstrated superiority of PSMA PET to conventional imaging, including CT and MRI for detecting sites of recurrent disease. For instance, Giesel et al[57] showed the ability of PSMA PET to detect positivity in two-thirds of patients with nodes with a short axis <8 mm

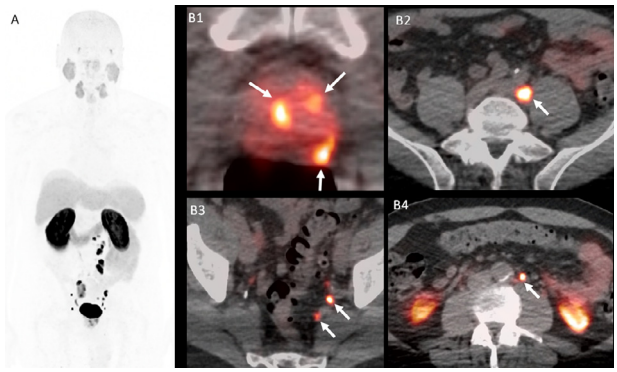

Figure 3 ^{18}F-DCFPyL PET/CT in a patient recently diagnosed of high-risk primary prostate cancer. A 66-year-old man with biopsy-proven adenocarcinoma of the prostate, Gleason 9 (4-+5) and PSA of 7.1 ng/mL. Maximal intensity projection (A), and axial fused ^{18}F-DCFPyL PET/CT images (B) demonstrate multiple DCFPyL-avid foci at the prostate gland (B1), and additional multiple DCFPyL-avid bilateral pelvic (A, B2, and B3) and left retroperitoneal lymph nodes (A and B4).

with BCR.[57] Similarly, in another study, PSMA-PET was able to detect nodal metastases in 78% of the histologically proven metastatic nodes, whereas morphological imaging was positive in only 26.9% of the same patients.[58] PSMA-PET is not only able to detect small nodes but depicts the distribution of extrapelvic nodes in a noncontiguous pattern including small supraclavicular nodes (Fig. 4) or even small bone sites (Fig. 5). The sensitivity of PSMA-PET depends on PSA values; in a recent meta-analysis performed by Perera et al[59] including data from 16 studies, the overall percentage of positive ^{68}Ga-PSMA-11 PET was 76%. The tumor detection rates for the PSA categories of 0-0.2 ng/mL, 0.2-1.0 ng/mL, 1-2 ng/mL, and >2 ng/mL were 42%, 58%, 76%, and 95%, respectively; and ^{68}Ga-PSMA PET positivity was associated with shorter PSA doubling time (PSAdt).[59] In another meta-analysis by Von Eyben et al,[60] overall detected sites of recurrence were seen in 81% of patients, with detection rates of

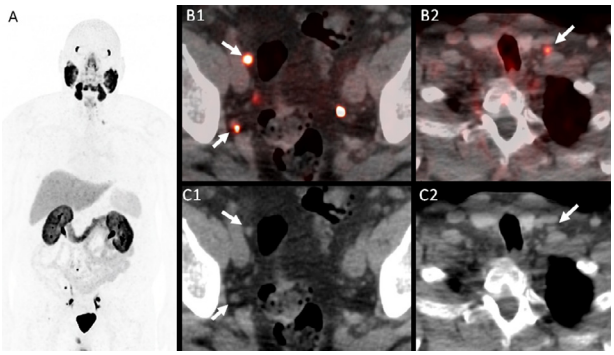

Figure 4 ^{18}F-DCFPyL PET/CT in a patient with biochemical recurrence PCa. A 67-year-old man with history of PCa, Gleason 8 (5 + 4), status post-prostatectomy and salvage radiation 6 years ago, with rising PSA (4.8 ng/mL). Maximal intensity projection (A), axial ^{18}F-DCFPyL fused PET/CT (B), and low-dose CT (C) images demonstrate small subcentimeter pelvic nodes (B1 and C1) and a small left supraclavicular node (B2 and C2). Physiologic urinary uptake is noted in the bilateral distal ureters.

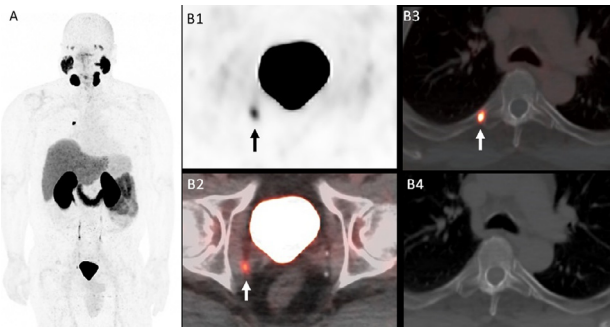

Figure 5 ^{18}F-DCFPyL PET/CT in a patient with biochemical recurrence PCa. A 63-year-old man with history of PCa, Gleason 9 (5 + 4), status post-prostatectomy a year ago, with rising PSA (0.44 ng/mL). Maximal intensity projection (A), axial ^{18}F-DCFPyL PET, fused PET/CT, and CT images demonstrate a small 4 mm DCFPyL-avid right pelvic wall lymph node (B1 and B2), and a small focus of intense uptake at the posterior right fifth rib (B3), without definitive abnormality on the corresponding CT (B4). Biopsy was performed on the rib resulting in metastatic prostate cancer.

50%, and 53% for PSA of 0.2-0.49, and 0.50-0.99 ng/mL, respectively.[60] The largest retrospective study with 1007 patients reported tumor detection rates for ^{68}Ga-PSMA-11 PET/CT of 79.5%.[61] However, multivariate analysis found no relevant correlation with PSAdt or PSA velocity or between Gleason score and PET positivity. Ceci et al[62] identified an association between PSA level and PSAdt with a positive ^{68}Ga-PSMA-11 PET/CT in 70 patients with BCR after radical prostatectomy. Receiver operating characteristic analysis showed that a PSAdt of 6.5 months and a PSA of 0.83 ng/mL were optimal cut-off values for ^{68}Ga-PSA PET-positivity, which was observed in 85% of patients with PSA <2 ng/mL and PSAdt >6.5 months. Similarly, Verburg et al[63] proved that a shorter PSAdt was significantly associated with the presence of pelvic and extrapelvic lymph node (LN), bone, and visceral metastases, and that higher PSA levels and shorter PSAdt were independently associated with scan positivity and extrapelvic metastases, which could be used for selecting patients for ^{68}Ga-PSMA-11 PET imaging.[63] These data are important as they imply that positive PSMA scans are associated with clinically significant PSA recurrences.

Salvage lymph node resection are also performed in the setting of BCR. In this setting, specificities of up to 100% have been reported in presurgical nodal assessment prior to nodal salvage surgery using ^{68}Ga-PSMA.[58,64-66] This figure is somewhat misleading as there is a clear verification bias in such studies. Radio-guided surgical detection can be augmented with hand-held gamma probes detection of nodes both in the primary and salvage settings. Although data are limited, the use of a gamma probe to detect ^{111}In-PSMA injected preoperatively appeared promising in detecting PSMA-avid but imaging-occult nodal micrometastases.[67,68] PSMA PET imaging has also shown promise for guiding salvage RT.[31,69] A change in radiotherapy planning occurred in 20%-60% of patients after imaging with ^{68}Ga-PSMA PET/CT.[70,71] PSMA PET can identify sites of disease in patients after external beam radiation,[72] which allows for potential salvage therapy if the recurrence site is outside a prior RT field or it is possible to reirradiate the site of recurrence. In the setting of BCR, a negative PSMA PET scan is associated with favorable RT response compared with patients with a positive scan.[73]

Comparison of PSMA-Based Radiopharmaceuticals With Other Agents

Over the last few years, PSMA PET imaging has proven to be a potential game changer compared to the other radiotracers discussed. In an early pilot study comparing ^{68}Ga-labeled PSMA ligand to ^{18}F-fluoromethylcholine in the detection of BCR PCa, a higher sensitivity with the PSMA-targeted radiotracer (86% vs 70%) was found.[74] In a prospective comparison study with both tracers, ^{68}Ga-labeled PSMA-PET/CT detected lesions in 66% of patients, whereas ^{18}F-fluoromethylcholine was positive in only 29% of the same BCR patients. Importantly, the superiority of PSMA PET for lesion detection was demonstrated across all PSA levels.[75] Similarly, a retrospective study of 66 patients selected for salvage lymphadenectomy compared the PSMA-

PET findings against choline-PET using post-lymphadenectomy histology for validation. PSMA PET demonstrated significantly better accuracy and higher negative predictive value than choline-PET (92% vs 83% and 97% vs 89%, respectively).[76] There is limited experience in comparing FDG PET with PSMA PET imaging. In a recent study, Hofman et al[77] used both FDG and PSMA PET imaging to evaluate treatment responses in patients with mCRPC treated with ^{177}Lu-PSMA-617; by excluding patients with lesion sites of low or absent PSMA expression and high FDG avidity, higher response rates were achieved.[77] This suggests that FDG positivity is associated with a more aggressive phenotype of metastatic disease than PSMA positivity alone.

There is some debate over the most optimized PSMA PET agent. Some PSMA PET agents are labeled via chelate with ^{68}Ga while others are directly labeled with ^{18}F. ^{68}Ga has a shorter half-life (68 min) and higher positron energies resulting in slightly blurrier images compared to ^{18}F with a 110-min half-life and lower positron energies. ^{18}F- labeled PSMA agents have the logistical advantage of production at a central source whereas ^{68}Ga-labeled PSMA agents are usually labeled on site. However, one advantage of the Ga-labeled compounds is that they include a chelate which can also be used to attach 177Lu or ^{225}Ac isotopes as therapeutic agents, thus constituting a true theranostic agent. A direct comparison between different radiolabeled PSMA ligands had also been made by Dietlein et al,[78] resulting in comparable distribution patterns for both tracers. However, in one study ^{18}F-DCFPyL PET imaging detected 36% additional lesions and the sensitivity increased abruptly when PSA values exceeded 0.5 ng/mL, being 88% for ^{18}F-DCFPyL and 66% for ^{68}Ga-PSMA-11 when PSA ranged from 0.5 to 3.5 ng/mL.[78]

Impact in Clinical Decision Making

As PSMA-PET tracers are increasingly implemented into clinical practice, it is clear that this technology will have profound effects on patient treatment. For instance, a prospective, multicenter study among 4 Australian sites assessed whether ^{68}Ga-PSMA PET/CT affected clinical management of patients with primary and recurrent PCa.[79] The study included 431 patients with PCa, 25% being staged for high-risk primary disease, and 75% being restaged for BCR. ^{68}Ga-PSMA PET/CT scan led to a change in planned management in 51% of patients, with higher impact in the group of patients with biochemical failure than those undergoing primary staging (62% vs 21% change in management intent).[78] In a prospective study including 38 patients, Morigi et al[75] reported change of management in 63% of patients undergoing both ^{18}F-Fluoromethylcholine and ^{68}Ga-PMSA, with the bulk of the changes due to ^{68}Ga-PSMA imaging alone. Similar high clinical impact of ^{68}Ga-PSMA/PET was reported in other several retrospective, single-institution studies,[70,80,81] for instance Bluemel et al[70] assessed the impact of ^{68}Ga-PSMA-11 PET/CT before salvage RT in 45 patients with BCR. Suspicious lesions were detected in 53% of patients; of those, 62% of lesions were detected by ^{68}Ga-PSMA-11 PET alone. Accordingly, treatment was changed in 42.2% of patients by extending the RT field, dose escalation, or change to systemic therapy.[70] Similarly, in another retrospective study including 57 patients, PSMA-PET/CT led to a change in RT management in 50.8% of cases.[82] In a cohort of 131 patients, ^{68}Ga-PSMA PET/CT led to change of clinical management in 76% of patients. The authors found a positive scan in 45% of patients with a PSA level of $\leq$0.5 ng/mL and in 75% with PSA level of 0.5-1.0 ng/mL.[83]

Although PSMA-PET/CT agents are found to alter the patients' clinical management, the impact of enhanced metastatic detection on the overall survival is still not clear. Designed trials evaluating patient outcome are clearly needed. This is especially important in patients at the very early stages of BCR, whom PSMA-PET scan is positive.

^{18}F-Fluorodihydrotestosterone

The overexpression of AR plays an important role in growth of PCa, especially early in the disease when it is castration sensitive castrate sensitive prostate cancer (CSPC). AR still plays a role in CRPC but is often independent of androgen binding by this point. Thus, AR-targeted imaging can play a useful role in characterizing the status of PCa, predicting AR binding to androgens, and potentially assessing the therapeutic effect of AR-targeted blocking drugs. 16beta-^{18}F-fluoro-5alpha-dihydrotestoterone (^{18}F-FDHT) is a radiolabeled analogue of dihydrotestosterone, the AR's primary activating binding ligand, which offers the possibility to delineate PCa cells with high expression of wild-type AR. ^{18}F-FDHT has been tested in a variety of settings particularly for optimal dosing of anti-androgen therapies specifically, enzalutamide which functions to block DHT binding.[84,85] Decreases in uptake of ^{18}F-FDHT suggest a positive pharmacodynamic effect to DHT binding site inhibitors in the class of enzalutamide.[86] To date, there are only a limited number of sites producing ^{18}F-FDHT. Larson et al[87] first established the feasibility of using ^{18}F-FDHT to detect lesions in a small group of patients with metastatic PCa. In this group of patients ^{18}F-FDHT was found to have lower sensitivity than ^{18}F-FDG (78% vs 97%) although this was due to patient selection with many end stage CRPC patients. Vargas et al[88] also compared both tracers, ^{18}F-FDHT and ^{18}F-FDG, in 38 patients with mCRPC, concluding that patients whose lesions showed higher ^{18}F-FDHT uptake had significantly shorter overall survival, whereas the intensity of ^{18}F-FDG uptake was not associated with overall survival. However, in a larger group of 133 patients with mCRPC naïve to anti-androgen therapies, Fox et al[89] tested the combination ^{18}F-FDHT and ^{18}F-FDG as prognostic biomarkers. Patients whose lesions demonstrated concordant ^{18}F-FDHT and ^{18}F-FDG uptake were found to have the best survival rates, whereas patients whose disease manifested with a preponderance of ^{18}F-FDHT-negative lesions had the poorest prognosis, possibly due to androgen deprivation therapy resistance.[89] This agent remains as part of the portfolio of PCa imaging agents as it is the only one that informs about the status of the AR, which plays a central role in PCa but its limited role makes it unlikely to enter the realm of a commercialized, widely produced PET agent.

Emerging PET Radiotracers

Bombesin and GRPR Binders

An emerging PET tracer for PCa imaging is an analogue of bombesin or antagonist of the gastrin releasing-peptide (GRP) receptor, a natural 14-amino acid peptide, that has been radiolabeled with ^{68}Ga, ^{64}Cu, and ^{18}F for visualization of GRP receptor-expressing tumours.[90,91] GRP receptor antagonists have shown more favorable characteristics with higher tumor to background ratio, without inducing adverse effects,[92] and are more sensitive than GRP receptor agonists.[93-95] GRP is reported to be overexpressed in 63%-100% of primary PCa lesions, and in 50%-85% of nodal and osseous metastases.[96,97] By contrast, a low density of GRP receptors has been reported in benign prostatic hyperplasia and normal prostate tissue.[98]

In the setting of staging PCa, radiolabeled GRP receptor antagonist, ^{68}Ga-RM2 (previously known as BAY 86-7548) was assessed in a first-in-human clinical trial of 14 patients, 11 of whom were scheduled for radical prostatectomy and three who had biochemical relapse. ^{68}Ga-RM2 demonstrated a sensitivity, specificity, and accuracy of 89%, 81%, and 83%, respectively for the detection of primary PCa, and sensitivity of 70% for nodal metastases using histology as the gold standard; however, it failed to detect skeletal disease in a hormone-refractory patient and incorrectly detected six false positive foci due to BPH.[98] Recently, Zhang et al[99] assessed the clinical diagnostic value of using another GRP-receptor antagonist, ^{68}Ga-RM26, and compared it with a GRP receptor agonist, ^{68}Ga-BBN; ^{68}Ga-RM26 PET/CT successfully identified positive prostate tumors in 88.2% (15/17) of the patients with newly diagnosed PCa. Compared with ^{68}Ga-RM26 PET/CT, GRPR agonist ^{68}Ga-BBN PET/CT detected fewer primary lesions and lymph node metastases and demonstrated lower tracer accumulation. There was a significant positive correlation between standard uptake value derived from ^{68}Ga-RM26 PET and the expression level of GRPR.[99] A fluorinated bombesin PET radiotracer, ^{18}F-BAY 86-4367, was also investigated in a small pilot study with favorable dosimetric values. The tracer was able to delineate tumors in three of five patients with primary tumors and in two of five patients with BCR.[91] A ^{64}Cu-labeled GRP receptor antagonist, ^{64}Cu-CB-TE2A-AR-06, has also shown some promising preliminary results, successfully delineating the primary tumors in three out of four patients with newly diagnosed PCa.[90]

In the setting of BCR, a recent prospective trial with ^{68}Ga-RM2 PET/MRI imaging investigated 32 patients and negative conventional imaging. ^{68}Ga-RM2 PET identified recurrent PCa in 71% of the patients, whereas the simultaneous MRI scan identified findings compatible with recurrent PCa in only 34% of the patients.[100] As with prior comparisons, correlation must be made with PSA in order to fairly compare agents. Comparison of ^{68}Ga-RM2 has been made with other PET imaging radiopharmaceuticals, for instance ^{68}Ga-RM2 was compared with ^{68}Ga-PSMA-11 PET in a small pilot study including seven patients with BCR PCa, reporting similar but not identical patterns of uptake in the abnormal tissue, with the exception of one false negative case with ^{68}Ga-RM2 PET,[101] possibly reflecting differing aspects of tumor biology worthy of further study. ^{68}Ga-RM2 was compared to ^{18}F-fluoroethylcholine (^{18}F-ECH) PET/CT in a cohort of 16 patients with BCR with negative or inconclusive ^{18}F-ECH PET/CT. ^{68}Ga-RM2 PET/ CT successfully localized PCa recurrence in 62.5% (10/16) of the patients, with histology or further imaging confirmation in 7 of the 10 positive ^{68}Ga-RM2 scans. However, the median PSA at the time of ^{18}F-ECH PET/CT was lower than that at the time of ^{68}Ga-RM2 PET/CT (2.4 vs 5.5 ng/mL, respectively). Another GRP receptor-targeting PET radiopharmaceutical, ^{68}Ga-SB3 has recently been reported in a small cohort of 9 patients with PCa. ^{68}Ga-SB3 did not produce adverse effects and identified lesions in five of nine patients (55%) with PCa.[102] An improved version of this radiopharmaceutical, ^{68}Ga-NeoBOMB1, is showing promising data in preliminary studies.[103] Future work should explore the role of the radiolabeled bombesin receptor antagonist relationship to PSMA PET. Potentially both agents could be used in tandem. Furthermore, the advantageous characteristics of these compounds are particularly attractive for peptide receptor targeted therapy.

Urokinase Plasminogen Activator

The serine protease urokinase-type plasminogen activator (uPA) and its receptor (uPAR) have been shown to be up-regulated in a variety of human cancers, including PCa,[104] and it is associated with advanced disease and poor prognosis.[105] High preoperative plasma uPAR levels have been shown to correlate with early progression.[105] Radiolabeled uPAR agents with ^{64}Cu, ^{68}Ga, and ^{18}F have been developed and used for PET imaging in various human xenograft PCa models.[106,107] The first-in-human phase I clinical trial with ^{64}Cu-DOTA-AE105, a radiolabeled chelated small peptide ligand of the uPAR receptor, was successful in four patients with primary PCa and two with bone metastatic disease.[107,108] These preliminary results are encouraging and support larger scale clinical trials to determine the utility of uPAR PET in the management of patients with PCa.

Other PET Agents

Various additional PET tracers may play a future role in PCa imaging. For instance, ^{64}Cu-TP3805 has demonstrated high affinity for the vasoactive intestinal polypeptide receptor 1 receptor, a G-protein coupled receptor that is overexpressed in PCa.[109] The cell surface protein STEAP1 has also been identified as a target for castration-resistant PCa. A PET radiotracer ^{89}Zr-2109A, derived from a fully humanized mAb targeting STEAP1, was tested as an imaging agent to measure changes in STEAP1 expression in a preclinical castration-resistant PCa model. ^{89}Zr-2109A was able to localize STEAP1-positive human PCa models, and sensitively measured treatment-induced changes in STEAP1 expression.[110] Although these new tracers are promising, much work needs to happen to establish their role in clinical practice.

Conclusion

During the past two decades, many PET probes have been developed to address staging of PCa. Novel imaging agents have allowed for the identification of tiny foci of PCa, particularly in the setting of early BCR, greatly surpassing the limitations of traditional morphological imaging. To date, PSMA-based PET is so far proving to have higher sensitivity than any other previously tested PET agent for localizing the site of recurrence in the setting of BCR PCa. Other applications showing promising results include the characterization of intermediate to high-risk primary PCa and staging for metastatic PCa to improve identification of patients with oligometastatic disease. PSMA-based PET imaging may be also useful in guiding salvage-extended lymph node dissection, radiotherapy planning and identifying patients who could benefit from PSMA targeted radiotherapy, increasingly being used in advanced PCa. With encouraging data, the PSMA-based radiolabelled ligands are likely to become universally available in clinical practice for imaging PCa in the near future. In coming years, large and well-defined prospective trials would determine the true utility of PSMA-based PET to improve management and outcomes of patients with PCa.

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