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Novel PET Imaging Methods for Prostate Cancer

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Abstract

Prostate cancer (PCa) exhibits highly variable biological behavior ranging from indolent to highly aggressive based on its grade and stage. Conventional imaging consists of computed tomography (CT), magnetic resonance imaging (MRI), and single photon bone scans, but imaging has traditionally played a secondary role in managing prostate cancer patients. Thus, many of the treatment decisions rely on PSA levels and "best guesses" of disease status. The gap between what conventional imaging shows and the suspected status of disease based on clinical factors has encouraged the development of more sensitive molecular imaging probes based on positron emitting radioactive tags. Such Positron Emission Tomography (PET) probes have high sensitivity owing to the nature of PET imaging and several PCa-focused agents have been developed, particularly for detecting sites of recurrence and staging patients with PCa. The expanding list of available PET radiotracers now includes radiolabeled ^{11}C and ^{18}F choline agents, anti1-

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amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F-fluciclovine or ^{18}F-FACBC), ^{68}Ga and ^{18}F bombesin and derivatives, ^{18}F dihydrotestosterone (^{18}F DHT), ^{68}Ga and ^{18}F prostate-specific membrane antigen (PSMA) ligands, and ^{18}F Fluorodeoxyglucose (^{18}F FDG) among others. Of these, radiolabeled PSMA PET agents have emerged as having the best sensitivity and specificity for PCa. However, as use of PSMA PET increases, false negative scans as well as false positives are reported. As a result, it is important to consider the wide range of potential molecular imaging agents that may fill in where PSMA is suboptimal. For instance, PET radiotracers such as bombesin-targeted or antagonist of gastrin releasing-peptide receptor (GRP)-targeted (RM2) and ^{18}F FDG are potential alternatives. Herein, we review the agents currently available or in development for molecular imaging of PCa.

Keywords

Prostate cancer; molecular imaging; prostate specific membrane antigen; biochemical recurrence; staging

Introduction

Prostate cancer (PCa) is a major cause of cancer-related deaths in men and one of the few cancers where imaging, until recently, has not played a major role in the standard diagnostic and risk stratification process (1). Conventional imaging including CT, MRI, and bone scans often fail to detect sites of disease especially at lower PSA levels and may overstate the amount of active disease as PSA rises. Molecular imaging becomes especially important. Detection of intra-prostatic disease at diagnosis is generally handled by multiparametric MRI and fusion biopsy and is covered in detail elsewhere in this special edition. While there may be a role for molecular imaging in early diagnosis, here, we focus on the disease once it has been initially treated and has recurred based on rising PSA or for high risk patients, for optimized staging at the time of initial diagnosis. In the setting of biochemical recurrence (BCR) imaging should be able to distinguish local recurrence in the prostate bed from nodal or distant visceral or osseous metastases. Finally, the same or related molecular entities used in molecular imaging of prostate cancer may also be used to direct targeted radionuclide therapy (TRT), using therapeutic isotopes in place of diagnostic isotopes.

There has been much effort devoted to developing new PET imaging agents for PCa. A distinct problem with many PET agents is that they are often taken up in benign conditions such as benign prostatic hyperplasia or prostatitis, reducing their value for initial diagnosis. Many of the agents lose sensitivity later in the disease when adenocarcinomas undergo neuroendocrine trans-differentiation. The one exception is ^{18}F-FDG PET imaging, which is taken up more avidly in less well differentiated tumors, perhaps a reflection of increased metabolic turnover. As a result 18F-FDG is increasingly used in late castration resistant prostate cancer (CRPC) and increasing uptake is associated with a poor prognosis.

Here, we discuss these molecular probes and compare them using existing literature.

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

Choline kinase (CK) is overexpressed in PCa, and choline serves as a substrate for this enzyme. CK helps the cells use choline to synthesize phosphatidylcholine, a key component of cell membranes. Therefore, radiolabeled choline is taken up in PCa cells. ^{11}C and ^{18}F radiolabeled choline PET/CT imaging have both been widely used for detecting advanced PCa. Thus, when CK is upregulated radiolabeled choline will be taken up by tumors.

^{11}C-Choline is theoretically an ideal PET tracer because its label, ^{11}C, does not alter the essential chemistry of choline. However, due to the short half-life (t1/2= 20 min) of ^{11}C, it can only be made in institutions with an on-site cyclotron and clinical radiochemistry facility, heavily restricting its use and requiring patients to travel to such institutions simply for a diagnostic test. ^{18}F-labelled choline is a more practical alternative due to its longer half-life (t1/2=110 min.), but this small change in labeling isotope makes the compound chemically and physiologically different from endogenous choline. It has higher urinary excretion into the bladder than ^{11}C-choline, which may obscure visualization of the prostate bed (2,3). Nonetheless, both agents function satisfactorily, and multiple studies have shown similar diagnostic performance for ^{11}C-choline and ^{18}F-choline for malignant lesions in different clinical settings (4). While ^{11}C-choline was approved by the FDA in 2012, ^{18}F-choline is not approved and has no commercial supplier in United States.

In localized disease a central limitation of Choline PET is that its uptake is non-specific. Benign prostatic hyperplasia takes up $^{11}C/^{18}F$-choline indistinguishably from cancer. Thus, use is generally restricted to staging/restaging patients with intermediate-high-risk or very-high-risk cancer.

The major role of $^{11}C/^{18}F$-choline PET/CT is for detecting recurrence in the setting of BCR, where it has shown better accuracy than conventional imaging (5,6). For instance, among 2686 patients (7) ^{11}C-choline PET/CT had an overall detection rate for recurrent disease of 62% (95%CI: 53%–71%). Such overall numbers, however, are misleading as they are influenced by the distribution of PSA levels in the studied population, therefore, a more meaningful measure is obtained by stratifying patients by their PSA level. Patients with high PSA levels will have their disease easily detected on most imaging methods. However, detecting disease in patients with lower PSA values could be of more use as such patients are more responsive to salvage radiation and therefore, still have a “therapeutic window”. Among 3203 PCa patients with BCR ^{11}C-choline PET/CT (8) achieved a sensitivity of 44.7% in patients with a PSA level between 1 and 2 ng/mL. $^{11}C/^{18}F$-choline PET/CT findings in the setting of recurrent disease change clinical decision-making in approximately 50% of cases in which the agent is used (9–11) and it has been incorporated into several professional association guidelines(12). However, this measure of efficacy is limited as a change in management is not necessarily a measure of improved outcome.

The diagnostic performance of choline PET/CT for the detection of bone metastasis in PCa was evaluated in a meta-analysis of 14 studies involving 655 patients(13). 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, among 1,619 lesions from 472 patients 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 did not guarantee that bone metastases were not present (13). Thus, choline PET was among the first molecular imaging agents for PCa that demonstrated improved sensitivity over conventional imaging but is comparatively insensitive when compared to newer agents.

Radiolabeled Amino Acid Analogs

Anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid, chemically referred to as ^{18}F-FACBC, and recently renamed ^{18}F-fluciclovine, or Axumin™ (Blue Earth Diagnostics, UK), is a synthetic amino acid L-leucine analogue, that binds to amino acid transporters which are heavily upregulated in PCa (14, 15). ^{18}F-fluciclovine exhibits delayed excretion into the urinary tract, thus improving detection of disease near the prostate bed (16,17).

^{18}F-fluciclovine, like choline PET, exhibits non-specific prostate uptake in benign conditions such as BPH. Among 68 patients with primary PCa, ^{18}F-fluciclovine PET/CT was found to have a sensitivity and specificity of 92.5% and 90.1% (18). However, when a more realistic mix of patients and diagnostic criteria are applied the specificity is lower (19−21). In a comparison study (21) of ^{18}F-fluciclovine PET/CT and MRI for the detection of primary PCa in 21 men, MRI had a higher sensitivity and specificity than ^{18}F-fluciclovine (73% vs 67% and 79% vs 66%, respectively). PCa uptake was significantly higher than the normal prostate gland, however, PCa could not be distinguished from benign prostatic hyperplasia (21). This was confirmed in another study in which the high sensitivity of 87% but low specificity of 56% for primary tumor identification was seen with ^{18}F-fluciclovine. Therefore, it is unlikely that ^{18}F-fluciclovine PET will play a role in initial staging of primary PCa.

^{18}F-fluciclovine was granted approval by the US FDA in 2016 for suspected recurrent PCa. In 251 patients with BCR a pooled sensitivity and specificity of 87% (95%CI: 80–92%) and 66% (95%CI: 56–75%), respectively was found with ^{18}F-fluciclovine for recurrent disease (17). Similarly, a high specificity of 96.7% and positive predictive value (PPV) of 95.7% was reported (22) for nodal and boney disease in patients with recurrent PCa (figure 1). This high PPV was confirmed in a trial of 596 patients where the PPV was 92.3% (23). ^{18}F-fluciclovine surpassed the performance of CT in detecting recurrent PCa (24). However, when results were stratified by PSA value, ^{18}F-fluciclovine PET had cancer recurrence 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). When the strata were even more carefully defined, ^{18}F-fluciclovine PET/CT tumor had a detection rate of 31 %, 50%, 66%, and 84% of patients, for PSA 0–0.5ng/mL, >0.5–1.0ng/mL, PSA >1.0–2.0ng/mL and >2.0ng/mL, respectively, on a per patient-basis(26). ^{18}F-fluciclovine results can have a major impact on patient management and 59% of patients in one study had their treatment altered, in some cases significantly, by this PET scan (26). Again, however, altered treatment plans does not necessarily predict better outcomes.

Few studies directly compare $^{11}C/^{18}F$-choline and ^{18}F-fluciclovine in the same patient but generally, the performance of ^{18}F-fluciclovine is superior. A prospective study comparing the two scans (27) in 89 BCR patients after radical prostatectomy, revealed sensitivity of 37%, specificity of 67%, PPV of 97%, 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 detects a higher rate of true positive and true negative lesions in the prostate bed, lymph nodes, and bones. Furthermore, ^{18}F-fluciclovine was superior to choline PET at all levels of PSA (28). The longer lived nature of ^{18}F and the commercial availability of an FDA-approved product provide practical advantages for ^{18}F-fluciclovine (29).

^{18}F-fluciclovine, however, has some limitations. It shows only low-to-moderate specificity with a relatively high false positive rate in many patients(30). As a prelude to the next section ^{68}Ga-PSMA-11 PET/CT outperformed ^{18}F-fluciclovine, by detecting findings in half of patients who had a negative ^{18}F-fluciclovine scan, and detecting additional lesions in the 20% of patients who were positive with both scans (31).

Prostate-specific membrane antigen (PSMA) PET/CT imaging

Prostate-specific membrane antigen (PSMA) is a well-known target of PCa but has become the most well known target for PET imaging relatively recently (32). PSMA is overexpressed in most intermediate-high-grade PCa and its expression increases as the disease progresses (32–36). However, in transdifferentiated tumors with neuroendocrine features, PSMA expression may be reduced or absent. In addition to prostate cancer, PSMA is also is expressed in some normal tissues (salivary gland, kidney, small bowel), other neoplasms (especially in the neovasculature) and in some cases of inflammation (37, 36). PSMA is an excellent target for diagnostic imaging and therapy of PCa, due to its high expression in tumors, low background and internalization within cells.

The first clinical attempt to target PSMA for imaging was a radiolabeled monoclonal antibody (mAb), ^{111}Indium-7E11 (^{111}In-capromab; ProstaScint™) that was approved in 1999. Unfortunately, the antibody targeted the *intracellular* domain of PSMA, which is usually inaccessible to exogenously injected antibodies and thus, lacked sensitivity and specificity (38). Another antibody, hJ591, developed by Neil Bander at Cornell University, binds to an extracellular domain of PSMA and has also been investigated for PET diagnostic imaging in the form of ^{89}Zr-hJ591. While this agent demonstrated higher affinity, and more efficient targeting (39), and was used as a theranostic in the form of ^{177}Lu-hJ591 for therapy in metastatic castrate-resistant PCa patients (mCRPC), it has never advanced commercially. Any of the agents discussed can be labeled with therapeutic isotopes such as the beta particle emitting^{177}Lu or the alpha particle emitting ^{225}Ac. Many other isotopes fall into this therapeutic category and they vary in their emitting energy and half life as well as their “decay” scheme which can release additional therapeutic isotopes.

The more recent development of PSMA radiopharmaceuticals are small-molecule, urea-based inhibitors that bind the active substrate recognition site of the folate hydrolase enzyme which is part of the external domain of the PSMA complex. These ligands bind with high

(subnanomolar) affinity and also exhibit rapid plasma clearance producing high tumor-to-background ratios. A variety of PSMA PET agents have been translated into the clinic over recent years, but none has yet been approved by the US FDA. Among the most widely used PSMA compounds in clinical studies, PSMA-HBED-CC is labeled with ^{68}Ga and is known as ^{68}Ga-PSMA-11 (40), which has quickly become the dominant agent worldwide because of the widespread commercial availability of the substrate. However, ^{68}Ga labeling is not ideal in all circumstances due to its short half-life, high energy positron and the need for an onsite generator. An alternative, where labeling can be made off-site with ^{18}F is desirable. To date, the most common labels used for PSMA imaging are ^{68}Ga, ^{18}F, (both PET emitters) and ^{111}In, and ^{99m}Tc (both SPECT emitters), such as ^{18}F-DCFBC/^{18}F-DCFPyL, ^{18}F-PSMA-1007, ^{68}Ga/^{111}In-PSMA-617, or ^{99m}Tc -MIP-1095 among others.

Unlike other agents discussed, PSMA is highly specific for PCa and is not taken up in benign prostatic hyperplasia. Thus, PSMA PET/CT can be used in localized disease. Some have gone so far as to suggest PSMA PET/CT could guide biopsy and focal therapy of localized prostate cancer (figure 2), (41). Of course, PSMA PET/CT may benefit from being combined with MRI as in PET/MRI since both modalities are useful in PCa diagnosis. Combined ^{68}Ga-PSMA-11 PET/MRI was analyzed in 53 patients with intermediate to high-risk PCa, and PSMA demonstrated superior accuracy with MRI 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 multi-parametric MRI alone, and 64% and 94%, for ^{68}Ga-PSMA-11 PET/CT alone (42). Similarly, other studies. (43) have shown that PSMA PET/MR increased the accuracy of both modalities resulting in a sensitivity of 82% and a specificity of 89%. There is a correspondence between PSMA maximum standard uptake value (SUVmax) and Gleason score at histology, although there is considerable overlap among different Gleason scores. (44). The ability of PSMA PET to discriminate clinically significant high-grade PCa from BPH makes it especially valuable in localized disease (45,46). Even within a specific primary tumor there can be heterogeneity of uptake (47,48) indicating not all parts of a tumor will express PSMA. The significance of non-expression within parts of the tumor is not yet well understood.

Preoperative staging is important in intermediate and high risk patients as the risk of nodal or bone disease is much higher. Conventional imaging performs poorly for the detection of pelvic lymph node metastases (49), mainly because most nodes measure less than 8 mm and thus, cannot be reported as positive on conventional imaging. When PSMA and CT are compared for lymph node staging (50) PSMA shows its true strength. For instance, 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, again, results must be stratified by PSA values (51, 52,53). In a comparison of ^{68}Ga-PSMA PET/CT with histology in 30 patients (53) it was shown that nodal detection rates were substantially influenced by lymph node size (Fig 3).

For initial staging, PSMA PET/CT outperforms conventional bone scan in intermediate-high risk primary patients (54). ^{68}Ga-PSMA uptake showed even higher diagnostic performance for osteolytic lesions than osteoblastic metastases (55).

The most extensive experience with PSMA PET/CT imaging has been in the setting of BCR (PSA ≥0.2 ng/ml after radical prostatectomy, or a 2 ng/ml rise above the PSA nadir post radiation). Early detection of recurrence can guide therapy, and assist in the decision to use aggressive loco-regional salvage therapy or systemic palliative therapy. PSMA-driven changes in management have not yet been shown to positively influence outcomes. This is most important at low serum PSA values, when there are potential curative salvage RT options, which remain most effective at serum PSA values less than 1.0 ng/mL (56).

PSMA PET/CT has shown clear superiority to conventional imaging. (57). PSMA PET/CT was able to detect nodal metastases in 78% of patients with histologically proven metastatic nodes, whereas conventional imaging was positive in only 27% (58). PSMA PET can be used to identify metastatic nodes from the low pelvis to the supraclavicular node chain (figure 4) (figure 5). When PSMA PET/CT data is stratified by PSA a clear relationship between PSA and PSMA PET can be seen. ^{68}Ga-PSMA-11 PET 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 seen more in patients with shorter PSA doubling time (PSAdt) (59). Using similar strata, a meta-analysis showed a sensitivity of PSMA PET of 50% for PSA of 0.2 to 0.49 and 53% for PSA of 0.50 to 0.99 ng/mL (60). Several large studies with over 1000 patients have been reported (61) and some have found no correlation between PSMA PET/CT uptake and PSAdt or PSA velocity or between Gleason score and PET positivity. However, most studies draw associations between PSA level and PSA doubling time (PSAdt) and a positive ^{68}Ga-PSMA-11 PET/CT (62). A PSAdt of 6.5 months and a PSA of 0.83 ng/ml were optimal cut-off values for predicting ^{68}Ga-PSA PET-positivity, which was observed in 85% of patients with PSA < 2 ng/ml and PSAdt > 6.5 months. Others (63) have confirmed that a shorter PSAdt was significantly associated with the presence of pelvic and extrapelvic LN, bone, and visceral metastases on PSMA PET/CT, and that higher PSA levels and shorter PSAdt were independently associated with scan positivity and extrapelvic metastases(63). The association between positivity and more aggressive disease implies that PSMA positivity has an independent prognostic value in patients with prostate cancer. Likewise, negative PSMA scans carry a favorable prognosis.

In the setting of salvage lymph node resection, PSMA PET/CT can be very useful in guiding surgical assessment (58,64–66). PSMA PET/CT has also been used to guide surgical resection using hand held gamma probes to detect positive nodes. For instance, experimentally, a gamma probe was used in conjunction with ^{111}In-PSMA to facilitate node sampling (67,68). PSMA PET imaging has also shown promise for guiding salvage radiation therapy (RT) (31,69) When a PSMA PET/CT was obtained prior to RT, a change in radiotherapy planning occurred in 20–60% of patients (70,71). PSMA PET obtained after RT can identify sites of residual disease (72), which allows for potential re-irradiation if feasible. In the setting of BCR, a negative PSMA PET scan is associated with favorable RT response compared with patients with a positive scan (73).

PSMA PET imaging has proven more effective than other PET probes heretofore developed. In two studies comparing ^{68}Ga-labeled PSMA-11 ligand to ^{18}F-fluoromethylcholine, the PSMA probe had a higher sensitivity (86% vs 70% and 66% vs 29%) in both and was seen at all PSA strata (74,75). In a similar study of lymphadenectomy specimens (therefore, verified histologically) PSMA PET demonstrated significantly better accuracy and higher negative predictive value than choline-PET (92 vs 83% and 97 vs 89%, respectively) (76). In one study (77) comparing FDG and PSMA PET imaging in patients with advanced metastatic disease (mCRPC) it was shown that discordant studies (FDG positive PSMA negative) were associated with a very poor prognosis.

Some PSMA PET agents are labeled via a chelate with ^{68}Ga while others are directly labeled with ^{18}F. Importantly, in both cases the binding site to PSMA is identical. ^{68}Ga has a shorter half-life (68 min.) and higher positron energies resulting in less sharpness compared to ^{18}F with a 110 min. half-life and lower positron energies. ^{18}F-labeled PSMA agents have advantages of central production and distribution which enables smaller local hospitals without radiopharmacies to offer PSMA PET to their patients. In contrast, ^{68}Ga-labeled PSMA agents require onsite ^{68}Ge/^{68}Ga generators and expertise in radiolabeling thereby favoring hospitals with more resources. One advantage of ^{68}Ga PSMA compounds is that they include a chelate which can also bind therapeutic isotopes such as ^{177}Lu or ^{225}Ac thus creating a theragnostic agent. Only a few studies have been published compare different radiolabeled PSMA ligands in the same patients. In one study ^{18}F-DCFPyL PSMA PET imaging detected 36% more lesions and had a higher sensitivity (88% vs. 66%) for PSA values > 0.5 ng/mL (78) but the study was small and the doses of the agents were not equivalent.

In one prospective, multicenter study ^{68}Ga-PSMA PET/CT scan led to a change in management in 51% of patients with highest impact in the group of patients with biochemical failure vs. those undergoing primary staging (62 vs 21% change) (78) Similar high clinical impact of ^{68}Ga-PSMA/PET was reported in other several retrospective, single-institution studies (70,80, 81), where the rate of management change ranged from 42–76% (70,82,83). However, clinicians should be aware that PSMA PET scans are likely to lead to more complicated workups.

Although PSMA PET/CT agents are found to alter the patients' clinical management, the impact of enhanced detection on overall survival is yet to be proven. Prospective trials evaluating patient outcome are clearly needed. This is especially important in patients at the very early stages of biochemical recurrence, who would ordinarily be missed with conventional imaging.

Emerging PET radiotracers

^{18}F-Fluorodihydrotestosterone (^{18}F-FDHT)

In addition to the agents previously discussed there are a number of agents that have been developed and used in patients but in small numbers and at limited sites. One of these, 16beta-^{18}F-fluoro-5 alpha-dihydrotestoterone (^{18}F-FDHT) targets the androgen receptor (AR) with radiolabeled dihydrotestosterone. AR plays an important role in growth of PCa

since it is a transcription factor that influences many other genes including the genes responsible for PSA. Dihydrotestosterone binds to AR in the cytoplasm mediating its migration to the nucleus of the cell and causing downstream genes to be activated. As the disease progresses the cancer cell may become “androgen independent” especially in the castration resistant (CRPC) phase when the tumor no longer responds to androgen deprivation therapy (ADT). AR still plays a role in CRPC but is often independent of androgen binding by this point. Thus, AR-targeted imaging can play a role in assessing whether androgens can still bind to the AR. ^{18}F-FDHT is a radiolabeled analogue of dihydrotestosterone that has been tested mostly in the context of the development of novel second generation anti-androgen therapies, specifically enzalutamide, which blocks DHT binding to AR (84,85). Decreases in uptake of ^{18}F-FDHT suggest a positive pharmacodynamic effect by enzalutamide and other DHT binding site inhibitors (86). To date, only a few sites around the world produce ^{18}F-FDHT. Larson et al. (87) first developed ^{18}F-FDHT as a method of detecting prostate cancer metastases but it had a lower sensitivity than ^{18}F-FDG (78% vs 97%) in late stage patients. This study actually showed the value of FDG PET in this setting. When ^{18}F-FDHT and ^{18}F-FDG were compared in the same patients (88) with mCRPC, it was initially found that patients whose lesions showed higher ^{18}F-FDHT uptake had significantly shorter overall survival whereas ^{18}F-FDG uptake was not associated with overall survival. However, when a larger group of mCRPC patients were compared (89) it was found that patients with mostly concordant ^{18}F-FDHT and ^{18}F-FDG uptake were found to have the best survival rates, whereas patients whose disease manifested as ^{18}F-FDG >> ^{18}F-FDHT-had the poorest prognosis, reflecting the increased metabolism of late stage prostate cancer (89). ^{18}F-FDHT remains part of the conversation regarding 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 so far has not offered the sensitivity of other agents in detecting recurrent and metastatic disease. It certainly has increased understanding of the dynamics occurring within metastatic PCa cells.

Bombesin and Gastrin Releasing Peptide Receptor Ligands—Another potential target for imaging is the gastrin releasing peptide receptor (GRPR). Bombesin (derived from a rain forest frog) is a natural 14-amino acid peptide, that can be radiolabeled with ^{68}Ga, ^{64}Cu, or ^{18}F, binds to GRPR as a receptor agonist (90,91). GRP receptor antagonists have shown more favorable imaging characteristics with higher tumor to background ratios, without inducing adverse effects (92), and are more sensitive than GRP receptor agonists (93–95). GRPR 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, GRPR is expressed at low levels in benign prostatic hyperplasia and normal prostate tissue (98).

^{68}Ga-RM2 (previously known as BAY 86–7548) is the agent most widely reported upon. It demonstrates a sensitivity, specificity, and accuracy of 89%, 81%, and 83 %, respectively for the detection of primary PCa, and a 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 revealed 6 false positive foci due to BPH (98). In the setting of BCR, ^{68}Ga-RM2 PET/MRI detected recurrent PCa in 71% of the patients, whereas MRI identified findings compatible with recurrent PCa in only 34% of the patients (99,100). Results were not broken

down by PSA strata so direct comparison with other agents is difficult. When comparing ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET in a small pilot study of only 7 patients with BCR the two scans had similar results overall, but the patterns of uptake were different (101), possibly reflecting differing aspects of tumor biology worthy of further study. In a comparison of ^{68}Ga-RM2 and ^{18}F-fluoroethylcholine (^{18}F-ECH) PET/CT in 16 patients with BCR ^{68}Ga-RM2 PET/ CT localized PCa recurrence in 62.5% (10/16) of the patients in which the choline scan was negative. One flaw was that 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) biasing in favor of the ^{68}Ga-RM2 scan. Another GRP receptor-targeting PET radiopharmaceutical, ^{68}Ga-SB3 identified lesions in 5 of 9 patients (55%) with PCa (102). An improved version of this radiopharmaceutical, ^{68}Ga-NeoBOMB1, is being developed (103). While radiolabeled bombesin receptor antagonists are showing encouraging results they clearly must be compared to PSMA PET, the current gold standard. It may be possible that these two agents together cover a larger percentage of patients than either alone but this remains to be proven. If true, it could have implications not only for imaging but also for combination targeted radionuclide therapy of PCa.

Other GRPR antagonists, ^{68}Ga-RM26, and ^{68}Ga-BBN have been developed; ^{68}Ga-RM26 PET/CT was superior to ^{68}Ga-BBN identifying more patients and showing a positive correlation between uptake and GRPR expression(99). Only a small early clinical experience is available for a fluorinated bombesin PET radiotracer, ^{18}F-BAY 86–4367 and there are insufficient results to assess(91). A ^{64}Cu labeled GRP receptor antagonist, ^{64}Cu-CB-TE2A-AR-06, has also shown promising preliminary results, successfully detecting primary tumors in 3 out of 4 patients with newly diagnosed PCa (90).

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 its presence is associated with advanced disease and poor prognosis (105). Plasma uPAR levels 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 human xenograft prostate cancer models (106,107) and only recently, a first-in-human phase I clinical trial was conducted with ^{64}Cu-DOTA-AE105, a radiolabeled chelated small peptide ligand of the uPAR receptor (107,108). These preliminary results are encouraging and support larger scale clinical trials to determine the potential role of uPAR PET in PCa.

Other PET Agents—It is possible that additional experimental tracers will play a role in the future. Among those with preliminary data are ^{64}Cu-TP3805 which targets the VPAC1 receptor, a G-protein coupled receptor that is overexpressed in PCa (109). The cell surface protein 6 transmembrane epithelial antigen of prostate 1 (STEAP1) has also been identified as a target for castration-resistant PCa and antibody imaging against this antigen has been developed using the PET radiotracer, ^{89}Zr-2109A. The STEAP1 antibody was derived from a fully humanized monoclonal antibody targeting STEAP1, and 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 is needed before they can even be considered for wider clinical use.

Conclusion

During the past two decades, prostate cancer has provided fertile ground for the development of novel PET tracers. Novel imaging agents have allowed for the identification of foci of PCa, particularly in the setting of early biochemical recurrence where the PSA detects small amounts of disease but unfortunately is not able to localize it. To date, PSMA-based PET has shown the best performance among all the candidate probes and has rapidly been adopted across the world. It has also been extended as a targeted radionuclide therapy by adding therapeutic radioisotopes to the PSMA-binding ligand. With this encouraging data, the PSMA-based radiolabelled ligands are likely to become universally available in clinical practice for imaging PCa in the near future. Where they are widely available now they are avidly used by clinicians. In coming years, large and well-defined prospective trials will be needed to understand the impact of PSMA-based PET on the outcomes of patients with PCa.

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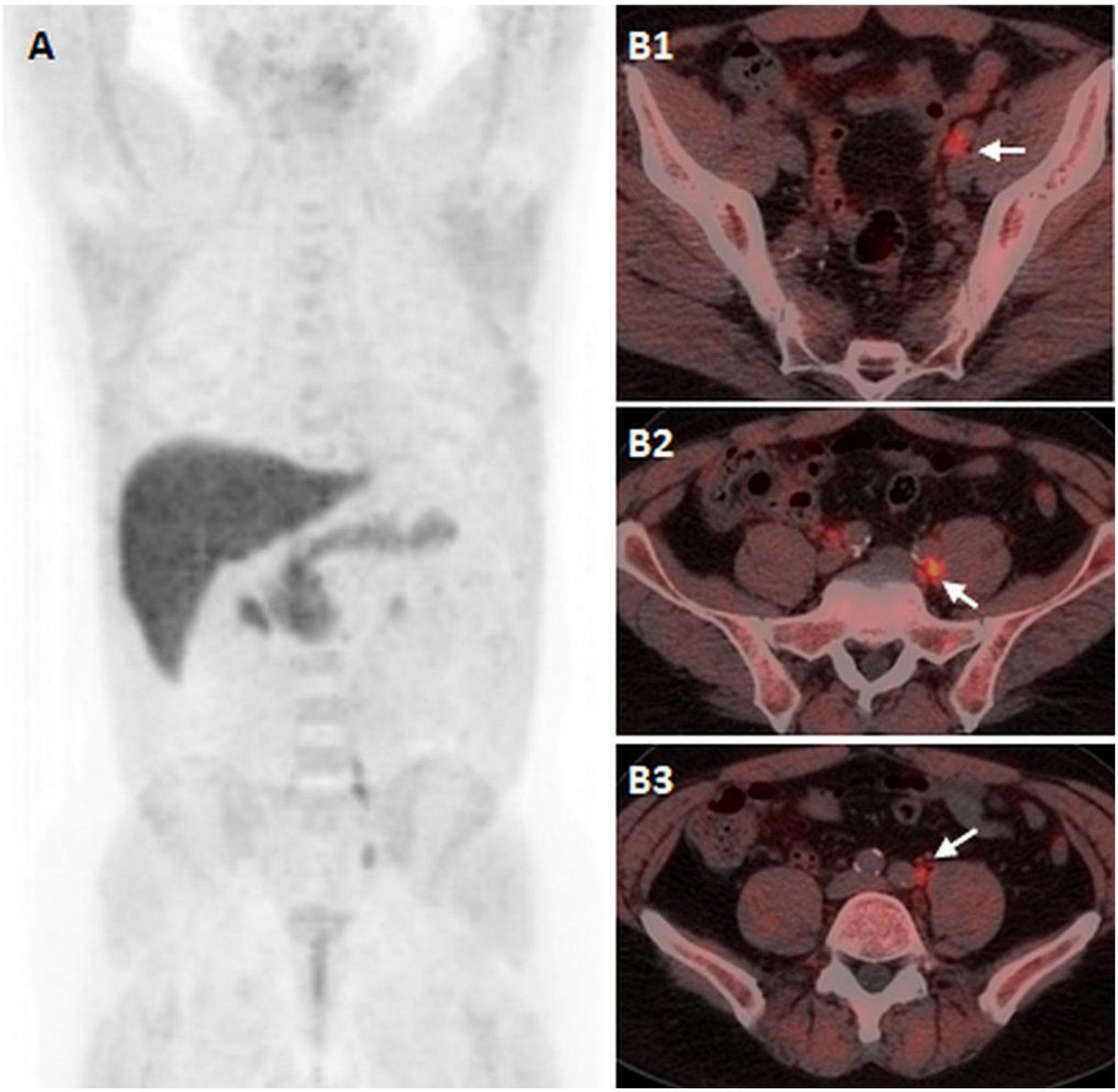

Figure 1:
61-years old man with biochemical recurrent prostate cancer, status post HIFU and salvage IMRT 5 ears ago, and recent rising PSA of 2.5ng/ml. 18F-Fluciclovine PET/CT imaging, including maximal intensity projection (A) and axial fused PET/CT images (B1, B2, 3) demonstrates focal increased uptake fusing to sub-centimeter left external iliac (B1), and left common iliac (B2, B3) lymph nodes.

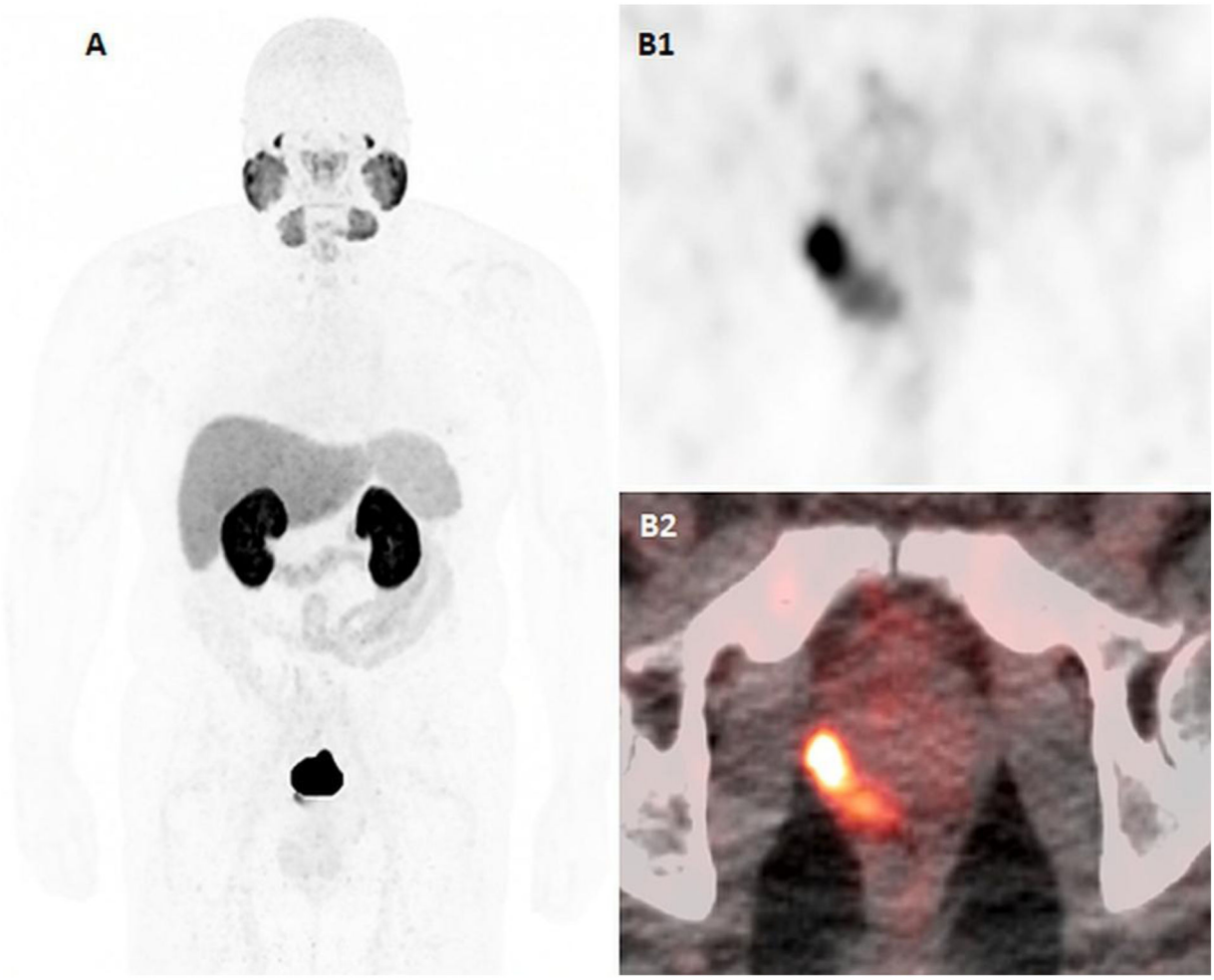

Figure 2:

55-years-old man with newly diagnosed high-risk prostate cancer, Gleason 9 (4+5) and PSA of 20.95ng/ml. 18F-DCFPYL PET/CT imaging, including maximal intensity projection (A), axial PET (B1) and axial fused PET/CT (B2) images demonstrate intraprostatic DCFPYL-avid focus at the right mid-base posterolateral peripheral zone of the prostate, consistent with the biopsy-proven primary malignancy. There are no suspicious DCFPYL-avid focus to suggest metastatic disease.

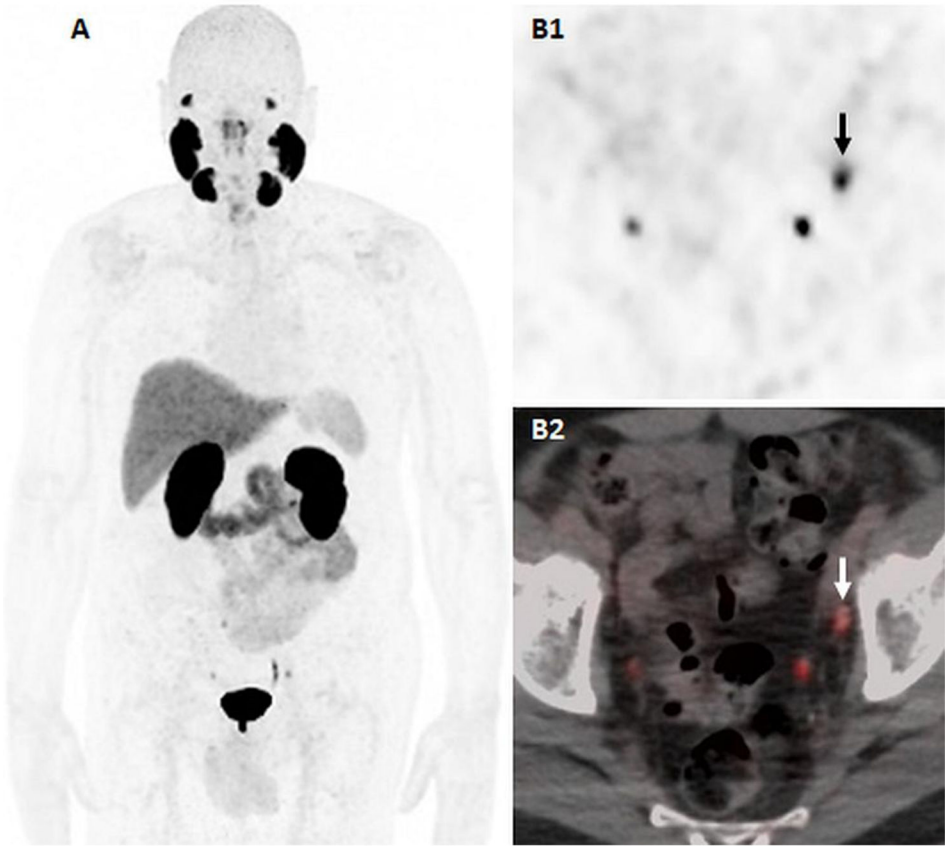

Figure 3:

74-years-old man with biochemical recurrence prostate cancer, status post-prostatectomy 5 yers ago, with rising PSA of 2.23ng/ml at the time of the scan. 18F-DCFPYL PET/CT including maximal intensity projection (A), axial PET (B1) and axial fused PET/T (B2) images demonstrate a 0.5cm DCFPYL-avid left obturator lymph node. Physiologic uptake is seen in bilateral ureters.

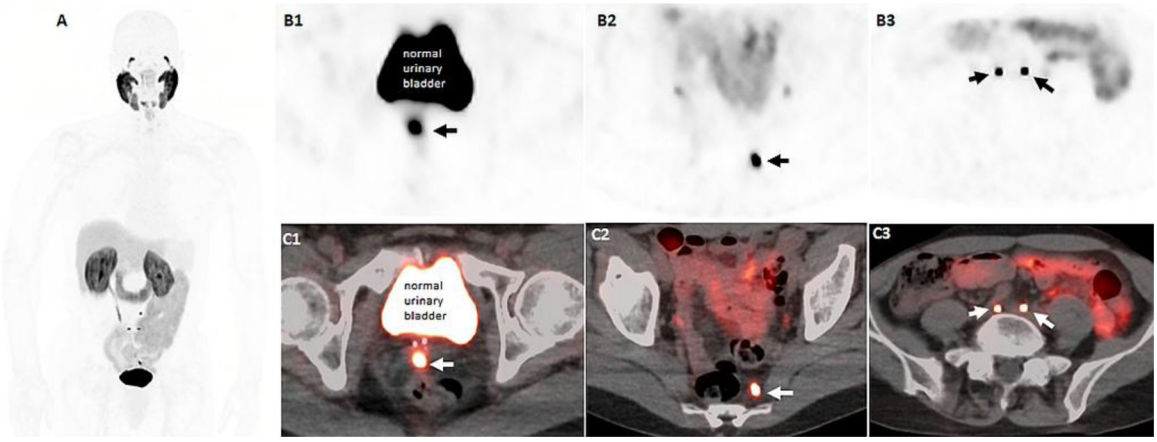

Figure 4:

64-years-old man with history of prostate cancer, Gleason 9 (4+5), status post EBRT and 1 year of ADT with PSA nadir of 0.4ng/ml, and recent rising PSA of 2.86ng/ml. 18F-DCFPYL PET/CT imaging, including maximal intensity projection (A), axial PET (B row) and axial fused PET/CT (C row) images demonstrate an intense DCFPYL avid focus at the midline of the seminal sevicles (B1, C1) and several subcentimeter pelvis lymph nodes including left presacral (B2, C2) and bilateral common iliac nodes (B2, C3).

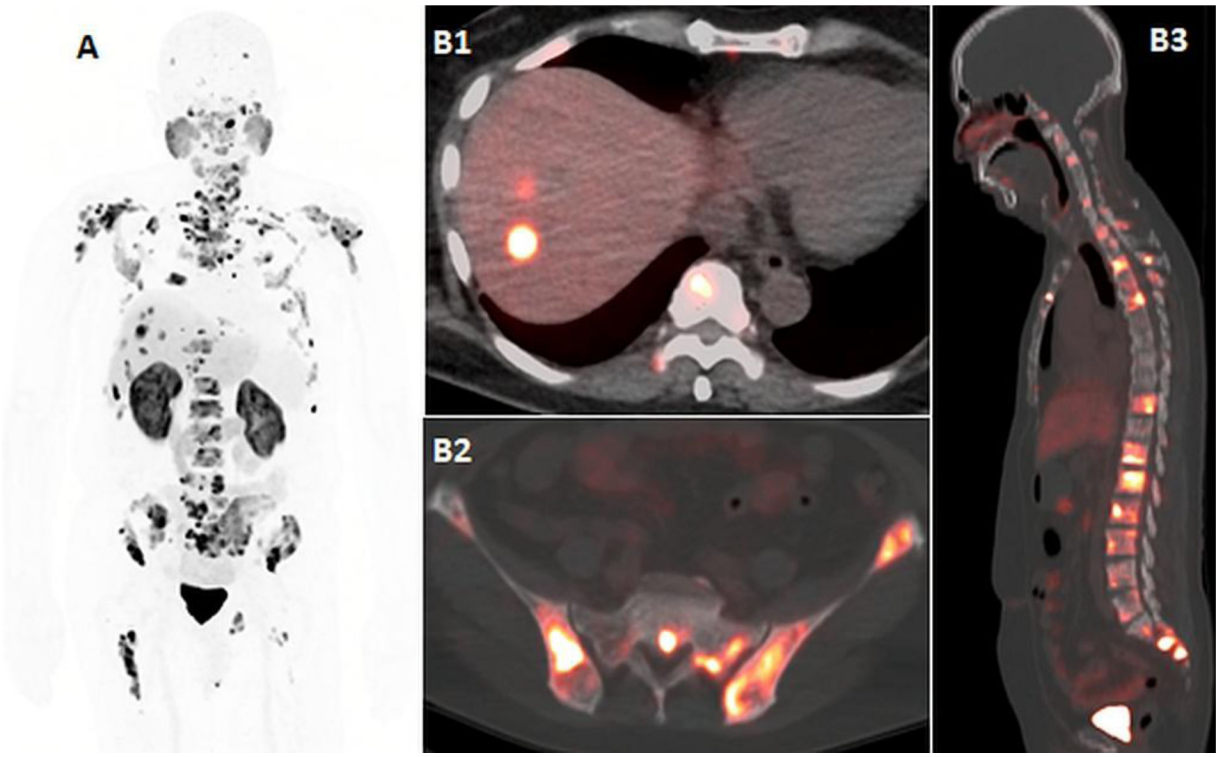

Figure 5:
62-year-old man with metastatic castrate resistant prostate cancer, and PSA of 134ng/ml. 18F-DCFPYL imaging, including maximal intensity projection (A), and axial and sagittal fused PET/CT images (B1, B2, B3) demonstrate liver metastases (B1) and wide-spread osseous metastatic disease (A, B2, B3).

Table 1

Comparison of PET tracers in prostate cancer

PET Agent	Advantages	Disadvantages	Comments
^{11}C or ^{18}F Choline	Min urinary excretion Availability	Lower sensitivity Non specific uptake	^{11}C Choi ine approved by US FDA
^{18}F FACBC	Improved sensitivity Local recurrence	Lower sensitivity Non specific uptake	^{18}FACBC is approved by US FDA (Axumin)
^{68}Ga or ^{18}F PSMA	High sensitivity High specificity	False positive uptake	Soon to be available in US, Current gold standard
^{18}F DHT	Reports AR activity	Difficult synthesis Noisy scans	Not commercially available
^{68}Ga or ^{18}F Bombesin	High sensitivity	False positive uptake	Not commercially available
^{18}F FDG	Prognostic indicator Widely available	Insensitive in early dz.	^{18}F FDG is approved by US FDA