REVIEW

Special Focus Issue: Prostate Cancer Imaging

PET imaging of recurrent and metastatic prostate cancer with novel tracers

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Early detection of recurrent prostate cancer (PCa) is of paramount importance to deliver prompt and accurate therapy reducing the chance of progression to metastatic disease. However, current imaging modalities such as conventional computed tomography, MRI and PET scanning do not provide sufficient sensitivity, especially at lower prostate-specific antigen values. Moreover, biological characterization of PCa has become increasingly important to provide patient-specific therapy and current imaging poorly characterizes disease aggressiveness. The current uprise of novel PET tracers in recurrent and metastatic PCa shows promising, yet variable sensitivities and specificities in detection, indicating the need for further studies. In this review, we highlight current and new PET tracers that have been developed to improve the detection of recurrent and metastatic PCa.

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Prostate cancer (PCa) is the most common noncutaneous malignancy in American men with 180,890 new cases and 26,120 deaths estimated in 2016 alone [1]. Recent advances in detection, monitoring and treatment of the disease include the growing use of multiparametric MRI, transrectal ultrasound/fusion MRI-guided biopsies and new focal therapies. Primary definitive therapy options for PCa remain radiation therapy (RT) and radical prostatectomy (RP), which are used with curative intent, although both methods have improved over time. Despite the high success rates in primary treatment, 15–25% of patients still experience biochemical recurrence (BCR), following primary definitive therapy with RP or RT [2–7]. The definition of BCR varies between therapy methods. For instance, following RP a rising PSA above 0.2 ng/ml defines BCR whereas following RT BCR is defined as a PSA change of 2.0 ng/ml above the nadir following RT and is known as the Phoenix criteria [7]. As rising PSA in post primary therapy patients is an indicator of PCa BCR, close monitoring of serum PSA levels following treatment is critical [7,8]. In the case of BCR, early detection and initiation of therapy is a key to better long-term outcomes. Early intervention is associated with a lower rate of metastatic disease. Thus, accurate and early detection of recurrence leading to earlier treatment will aid in hindering the progression of BCR to metastatic disease.

Multiple imaging modalities exist for the detection of recurrent PCa including computed tomography (CT), bone scintigraphy, MRI and PET. However, the need for more sensitive and specific imaging modalities to detect early recurrent and metastatic PCa has been prompted by evidence supporting early treatment. In addition to more sensitive and specific imaging, there has been a ‘thrust’ toward personalized and targeted management to discover disease phenotype and predict clinical outcomes earlier, which PET/CT has answered the call [9]. The future demands more

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than a traditional approach in disease assessment and staging; it requires the exploration of tumor biology in conjunction with existing structural imaging methods to deliver personalized medicine in the case of BCR and metastatic PCa [9]. In turn, accurate localization of recurrent PCa at low PSA values is a major challenge as patients with BCR are best treated as early as possible [10–13]. Current imaging modalities, aside from PET/CT, are limited in detection of recurrence or metastasis for PSA values <5 ng/ml [14]. PET imaging is unique in that it is highly sensitive and it has the ability to evaluate metabolic and molecular processes [15]. However, a major challenge among this class of agents is their low specificity and the inability to differentiate between indolent and aggressive disease [15,16]. Current favored tracers of PET imaging include bone scintigraphy with ^{99m}Tc -labeled phosphonates and 2-deoxy-2- ^{18}F fluoro-D-glucose, or ^{18}F -FDG; however, these tracers are limited by sensitivity, specificity, metabolism and excretion methods [17–19]. Thus, the purpose of this review is to highlight the advantages and limitations of current novel PET tracers in the detection of biochemical recurrent and metastatic PCa.

^{11}C - & ^{18}F -choline tracers

Choline kinase is overexpressed in PCa cells, and choline is used to synthesize phosphatidylcholine, an integral component to cell membranes. Investigators have sought to radiolabel choline with ^{11}C or ^{18}F to detect early recurrent PCa on PET/CT. Choline PET/CT has been shown to have high sensitivity in the detection of recurrent disease [20]. The primary mechanism of increased uptake of ^{11}C - and ^{18}F -choline tracers is the upregulated cell membrane synthesis of PCa cells and the uptake of choline in cancer cells. Though both ^{11}C - and ^{18}F -choline tracers are similar in concept and use, they differ in half-life and urinary tract excretion [21]. For instance, ^{11}C -labeled choline, which has only a 20 min half-life, is primarily excreted via the hepatobiliary route. This means that the bladder has minimal activity reducing artifacts in the pelvis [21–23]. The short half of ^{11}C mandates that it be produced on site, requiring both a cyclotron and synthetic radiochemistry facilities. These are expensive to maintain and have come under increasing scrutiny by regulatory agencies in recent years. Alternatively, ^{18}F -choline is an agent with a half-life of 110 min so that it can be produced off-site in a central facility

and transported to the imaging center. ^{18}F as an isotope also has favorable positron energies, which tend to improve the quality of imaging. However, ^{18}F -choline is primarily excreted by the urinary tract and therefore has less favorable imaging characteristics in the pelvis due to bladder interference [22,23].

In a meta-analysis by Fanti *et al.*, PET/CT with ^{11}C -choline was assessed in 18 studies in patients with BCR. The pooled detection rate of ^{11}C -choline PET/CT was 62%, and the pooled sensitivity and specificity were both 89% in a combined population of 2686 patients [24]. A limitation of meta-analysis is that the variables in the patient population are difficult to control and thus, it is unclear whether these data are representative of the majority of patients despite the large number of patients. In a smaller, single institution study, Mitchell *et al.* examined ^{11}C -choline PET/CT performance in 176 patients with BCR finding the sensitivity, specificity, positive predictive value and negative predictive value to be 93, 76, 91 and 81%, respectively on a per patient basis. The scan became very reliable for detecting recurrent disease only after the PSA was >2.0 ng/ml, which is a level associated with a poorer prognosis [25]. The ability of ^{11}C -choline PET/CT to specifically highlight the location of recurrence was emphasized in a study by Garcia *et al.* that evaluated patients with BCR and found that it was capable of detecting metastatic lymph nodes in a high percentage. This specifically changed therapy as salvage RT was used to extend the fields to encompass the affected nodes [26]. A separate retrospective study by Incerti *et al.* also demonstrated that ^{11}C -choline was able to detect patients who could benefit from intensity-modulated radiation therapy of recurrent lymph nodes. Results showed that the 2-year overall survival, locoregional relapse-free survival and biochemical relapse-free survival were 87, 91 and 40%, respectively for 68 patients (PSA range: 0.61–27.56 ng/ml) with a median follow-up of 20 months [27]. Another retrospective study by the same group found that ^{11}C -choline PET/CT can predict survival in hormone naïve PCa patients with BCR after RP. A total of 302 hormone-naïve PCa patients with a median PSA of 1.02 ng/ml were included and the 15-year PCa-specific survival probability was 42 and 95.5% in patients with positive and negative ^{11}C -choline PET/CT scans, respectively [28]. Prior to this study, the same group also reported

retrospectively that ^{11}C -choline PET/CT predicts PCa-specific survival in patients with BCR during androgen deprivation therapy, since the androgen receptor (AR) has been shown to contribute to the growth of PCa. This study found that in 195 PCa patients with RP and subsequent BCR, the median PCa-specific survival was 16.4 and 11.2 years in patients with negative and positive ^{11}C -choline PET/CT scans, respectively, with a significance of $p < 0.001$ [29]. Given its convenience compared with ^{11}C -choline, ^{18}F -choline PET/CT has been extensively tested in the BCR setting. A meta-analysis by von Eyben *et al.* compared pooled detection rates for ^{11}C - and ^{18}F -choline and found the latter to have a statistically higher detection rate of positive findings in patients with BCR following RP (60 vs 46%; $p < 0.0005$) [30]. However, ^{18}F -choline is a far from perfect method even in patients at extremely high risk of recurrence. For instance, a study by Colombie *et al.* found that only 137 of 172 (80%) of patients with a mean PSA of 10.7 ± 35.0 ng/ml, were positive on ^{18}F -choline PET/CT. Among the positive PET/CT patients, 30% had intraprostatic recurrence, 42% had pelvic lymph node recurrence, and 28% had distant metastases [31]. In populations with lower PSA levels, ^{18}F -choline performs even worse. For instance, Evangelista *et al.* summarized the results of a three-center study including 1031 patients (PSA range: 0.22–18.13 ng/ml). Only 12.7% (131) of patients showed positive ^{18}F -choline uptake and of these patients, only 57% ($n = 75$) were able to have their ^{18}F -choline scans correlated to MRI and/or histopathology. Among the positive scans, 79% ($n = 59$) were true-positive ^{18}F -choline scans, while 21% were false positive. Additionally, the false-positive rate increased to 50–65% in patients with PSA ≤ 2 ng/ml [32].

Thus, despite its advantages, ^{18}F -choline has significant sensitivity and specificity issues in the evaluation of patients with BCR, problems that intensify at lower PSA values. For instance, Schiavina *et al.* reported that the detection rate of BCR at lower PSA levels (< 5 ng/ml) was only 30–40%. The dependency of performance on PSA (a surrogate for the mass of recurrent disease) was also illustrated by Zaorsky *et al.* who evaluated 46 published studies of ^{18}F -choline PET in the BCR setting. The pooled sensitivity and specificity for ^{11}C -choline PET/CT were 38–98% and 50–100%, respectively, for detecting local recurrence, lymph node and distant

metastases, while ^{18}F -choline had pooled sensitivity and specificity of 47–92% and 33–99%, respectively, in detecting all sites of recurrence. Thus, this study indicated a broad range of sensitivity, which varied with the amount of disease [33].

For patients suspected of harboring metastases, choline PET/CT has shown the ability to detect bone metastases. Schiavina *et al.* reported that the principal advantage of choline PET/CT is in its ability to detect recurrence at lower PSA levels (< 5 ng/ml) with a detection rate between 30 and 40% following radical treatment and that the tracer is able to change therapeutic approaches by finding bone metastases in 15% of patients with a negative bone scan due to its better accuracy than cross-sectional imaging [34]. Similarly, Fuccio *et al.* showed ^{11}C -choline PET/CT could detect bone metastases with a negative bone scan. Interestingly, 15% of patients previously negative on bone scan were positive on PET/CT; however, the study was limited by lack of histologic validation and variable intervals between the bone scan and PET/CT (ranging up to 4 months with a mean of 2.5 months, PSA range: 0.2–25.5 ng/ml) [35]. Thus, choline PET/CT is more sensitive than conventional bone scan and in at-risk populations will detect approximately 15% more patients with metastatic disease.

In summary, choline PET generally performs well at high PSA values and is useful in distinguishing between locoregional recurrence versus distant PCa metastases, thus aiding in salvage and androgen-deprivation therapy treatment options [10]. However, the current body of evidence with choline-based tracers is limited due to possible study population biases and limited availability of histological validation. What emerges is that choline PET may be insufficiently sensitive to detect recurrences at low PSA values (~ 0.5 ng/ml) to be valuable in the decision to perform salvage RT. Moreover, there are country-to-country variations in the availability of choline PET/CT. For instance, in the USA, ^{11}C choline is available at a few centers but ^{18}F -choline is not available, whereas the opposite is true in Europe. Given the success of newer PET agents, the future of this agent is uncertain.

^{11}C -acetate

Fatty acid metabolism increases in PCa cells through upregulation of fatty acid synthase. Acetate is a substrate for fatty acid synthase that is

taken up by cells and converted into acetyl-CoA, which is oxidized in the mitochondria for the production of energy, or further metabolized to be incorporated into the cellular membrane [21,36]. ^{11}C -acetate should therefore be a biomarker of metabolic processes such as cancer. As with any ^{11}C -labeled tracer, it has a relatively short half-life (~20 min) and thus requires an onsite cyclotron and radiochemistry facility. However, it has the favorable characteristic of minimal urinary tract excretion and therefore, little interference from the bladder (Figure 1). ^{11}C -acetate has been well studied in the detection, recurrence, and staging of PCa [21,37–38].

In the setting of BCR, ^{11}C -choline and ^{11}C -acetate are quite similar. For instance, in a meta-analysis of 14 studies, Mohsen *et al.* found the pooled sensitivity for ^{11}C -acetate to be 64%, with a pooled specificity of 93% in distinguishing recurrent disease. The sensitivity was 20% higher in detecting recurrence in postsurgical versus post-RT patients, likely due to background uptake in patients undergoing RT. However, sensitivity was still a problem with 35% lower detection rates in patients with PSA levels <1 ng/ml [39]. The uptake of ^{11}C -acetate appears to correlate with tumor aggressiveness. Leisser *et al.* conducted a retrospective study on 123 PCa patients undergoing ^{11}C -acetate PET/CT and found that the standard uptake value (SUV) correlated with initial Gleason and PSA velocity. However, sensitivity was still low in patients with low PSA indicating that sensitivity was less than ideal. Median PSA value for patients with positive PET scans was significantly higher at 5.9 ng/ml (range: 0.5–99.9) than in patients with negative PET scans (median: 3.2 ng/ml; range: 0.2–116) [40].

Nevertheless, some studies showed slightly improved sensitivity for ^{11}C -acetate compared with ^{11}C -choline. For example, Dusing *et al.* retrospectively analyzed 120 patients with positive ^{11}C -acetate PET/CT scan findings in which the PSA was at least 1.24 ng/ml. The sensitivity and specificity for ^{11}C -acetate were 87 and 66%, respectively, and using a PSA velocity threshold of 1.32 ng/ml/year or greater produced a sensitivity and specificity of 74 and 75%, respectively. These results are better than published results of ^{11}C -choline at a similar distribution of PSA [41]. There are few head-to-head comparisons of ^{11}C -choline and ^{11}C -acetate. One study by Buchegger *et al.* in a group of 23 BCR patients with low PSA values (<5 ng/ml) produced similar results on per patient and per lesion basis suggesting that both tracers perform equally well in recurrent PCa staging [42].

How does ^{11}C -acetate perform in the metastatic setting? Spick *et al.* evaluated the detection of bone metastases using ^{11}C -acetate in 90 patients. ^{11}C -acetate PET detected 90% of lesions with a specificity of 96% on a per patient basis. Spick *et al.* also found that ^{11}C -acetate detected about 7% additional bone metastases over the bone scan [43].

Because of the absence of head-to-head comparisons of ^{11}C -choline and ^{11}C -acetate studies, it is difficult to ascertain which is better. In terms of detecting locoregional recurrences and metastases, there is no evidence that one agent is vastly superior to the other. All ^{11}C -compounds will be limited in their distribution due to their short half-life and the differences in function appear small at this time. Importantly, only a few centers around the world are actively producing ^{11}C -acetate and this fact alone will limit its use.

Figure 1. A 43-year-old man with a serum prostate-specific antigen of 30.4 ng/ml with Gleason 4 + 5 prostate cancer. Axial ^{11}C -acetate PET (A) demonstrates uptake in adenopathy in the left proximal iliac chain (arrows). Computed tomography images (B) show enlarged lymph nodes in the left proximal iliac chain consistent with nodal prostate cancer metastases (arrows).

Anti-1/2/3-¹⁸F-fluorocyclobutane-1-carboxylic acid

Anti-1/2/3-¹⁸F-fluorocyclobutane-1-carboxylic acid (¹⁸F-FACBC) is a PET tracer that has recently been approved by the US FDA for the detection of recurrent PCa. This agent is a radiolabeled synthetic leucine analog and thus targets amino acid transport, which is upregulated in PCa [44,45]. This compound has slow excretion from the urinary tract reducing competing signal in the bladder [34].

In an initial prospective study by Schuster *et al.* of patients with a median PSA of 15 ng/ml, ¹⁸F-FACBC PET/CT showed 100% sensitivity. Median PSA of participants in this small trial was 15.0 ± 18.6 ng/ml (range: 1.9–71 ng/ml); however, this study was limited by its small patient cohort and by the SUV_{max} methodology in using a ratio of SUV_{max} to muscle SUV_{mean} to overcome regions of low uptake [46]. In a second study of patients with a mean PSA of 6.6 ng/ml, the agent showed a sensitivity of 89% and specificity of 67% for recurrence on a per patient basis among 50 patients studied. Outside the prostatectomy bed, ¹⁸F-FACBC had 100% sensitivity (n = 10) and specificity (n = 7), on a per patient basis [47]. More recently Nanni *et al.* compared ¹⁸F-FACBC to ¹¹C-choline PET/CT in 15 patients with BCR (mean PSA: 2.1 ± 2 ng/ml, range: 0.2–8.48) following radical treatment of PCa. All 15 patients were post RP, while five patients received postsurgical RT and seven received postsurgical hormone therapy. This study found ¹⁸F-FACBC to be superior to ¹¹C-choline, almost doubling its detection rate (40 vs 20%) on both per patient and per lesion bases, also finding all positive regions found with ¹¹C-choline. However, this study was limited by its small patient population and there was no statistically significant difference between the two tracers (p = 0.25) [48]. A note should be made of the declining sensitivity as the mean PSA in the study is lower, reflecting a more activist stance on the part of referring physicians in recent years. Odewole *et al.* confirmed the correlation between positive ¹⁸F-FACBC PET/CT scans with PSA in 53 bone scan negative patients. On a per patient basis, 78% of the ¹⁸F-FACBC PET/CT scans were positive compared with 19% on CT alone for all PSA levels. However, for PSA levels <1 ng/ml, ¹⁸F-FACBC was positive in only 37.5%, whereas this rose to 78% for PSA levels between 1 and 2 ng/ml. Additionally, Odewole *et al.* found that ¹⁸F-FACBC was better

in demarcating prostatic and extraprostatic recurrence. However, the CTs were performed for an average of 46 days before the ¹⁸F-FACBC scans and 23 patients did not have intravenous contrast agent added during CT. Though a separate analysis with CT contrast did not change the outcome of the study, these two limitations are important to consider [49]. Assuming equal populations, these results make ¹⁸F-FACBC PET/CT more sensitive than choline and acetate imaging for lower PSA settings but leave the possibility of other agents with better sensitivities at lower PSA values wide open.

Recently, ¹⁸F-FACBC PET/CT has been approved for use in the USA. The trials that form the basis of this approval have not yet been published but clearly were favorable with regard to other existing PET probes. The approval of ¹¹C-choline in 2012 was limited to single institution use so that the current approval ¹⁸F-FACBC is the first, major approval of a PET probe for PCa recurrence that could have broad implications for patient access.

16beta-¹⁸F-fluoro-5alpha-dihydrotestosterone

The AR plays a central role in growth of PCa. The normal AR is activated by dihydrotestosterone (DHT, a derivative of testosterone), in the cytoplasm, which becomes a promoter for a host of growth-directed downstream client genes, including PSA [21,50]. With time the AR can mutate so that DHT no longer is necessary to promote downstream genes and the patient becomes 'androgen independent'. 16beta-¹⁸F-fluoro-5alpha-dihydrotestosterone (¹⁸F-FDHT) PET is a tracer used to delineate expression of AR in metastatic PCa lesions. The ¹⁸F-FDHT PET tracer binds to the AR as it is the natural ligand. This agent has mostly been used in specific drug development. For instance, in the development of the drug enzalutamide, ¹⁸F-FDHT was used to show that the drug blocked the DHT-binding site on the AR, thus showing a pharmacodynamic effect. It has not been used widely outside of this research setting, and has been limited.

In a prospective study, Larson *et al.* performed a feasibility study of ¹⁸F-FDHT versus ¹⁸F-FDG in a small group of PCa patients with advanced metastases and very high PSA values (median PSA: 69 ng/ml; range: 6.3–2637). On a per lesion basis, this study found ¹⁸F-FDHT was able to localize 78% of lesions compared

with ^{18}F -FDG finding 97% of the lesions [51]. Dehdashti *et al.* performed another prospective feasibility study on ^{18}F -FDHT PET/CT in a group of 19 patients with advanced PCa. Mean PSA was 86.9 ng/ml for all patients, and the mean PSA of patients with positive ^{18}F -FDHT PET was significantly higher than in patients with negative ^{18}F -FDHT PET scans ($p = 0.006$). Results indicated that ^{18}F -FDHT showed an overall sensitivity of 63% and a lesion detection rate of 86% [52]. Beattie *et al.* confirmed that ^{18}F -FDHT uptake was related to AR levels in the cancers. This study was conducted in 13 prospectively selected patients with advanced disease (median PSA: 94.65 ng/ml; range: 0.49–885.05) [53]. Vargas *et al.* also compared ^{18}F -FDHT PET/CT and ^{18}F -FDG PET/CT tracers with two readers in 38 castration-resistant PCa patients, retrospectively, with bone metastases and mean PSA of 43.5 ng/ml (range: 0–389.3) at the time of study. Results showed that patients with higher ^{18}F -FDHT uptake had slightly shorter survival (reader 1: HR: 1.078; $p = 0.02$; reader 2: HR: 1.092; $p = 0.02$), but ^{18}F -FDG uptake did not correlate with shorter survival (reader 1: $p = 0.65$; reader 2: $p = 0.38$). Thirty-three patients were followed until death and five patients were followed for an average of 37.5 months until death (range: 6.6–59.1 months) [54]. Thus, ^{18}F -FDHT use has been confined to patients with advanced PCa and has been useful in drug development, but there is no compelling evidence that it could be useful on a broader scale as most agents are positive in this advanced setting from a diagnostic perspective. Additionally, studies on ^{18}F -FDHT are limited with small patient populations. Nevertheless, this agent remains a potentially useful part of the portfolio of PCa imaging agents as it is the only one that informs on the status of the AR which plays such a central role in PCa [21,50,52,55].

^{18}F -NaF

Bone metastases in PCa tend to be osteoblastic. The cancer cells induce bone to be laid down and thus agents that are taken up in the bone-forming process will be positive. This is the theory behind conventional bone scanning agents that do not utilize positron emitters. Sodium fluoride (^{18}F -NaF) is a relatively older tracer used for imaging skeletal disease for bone metastases in several cancer types including PCa. Compared with the traditional bone scan, ^{18}F -NaF PET/CT has

shown improved sensitivity, but lacks specificity as it also can detect nontumor pathologies such as degenerative osteopathy, healing fractures, bone dysplasia or any other process in which bone is laid down [21]. Initially approved by the FDA in 1972, this tracer is an inorganic chemical compound that dissociates into Na^+ and F^- ions. The F^- ions are quickly taken up in the active bone by chemisorption and label areas of increased bone growth [56,57]. ^{18}F -NaF is advantageous due to its rapid bone-specific uptake, lack of blood pool and good axial skeletal visualization due to its integration into the hydroxyapatite–collagen matrix (Figure 2) [10,37]. Thus, ^{18}F -NaF has no role outside of detecting bone metastases.

A prospective evaluation of ^{18}F -NaF was performed by Jadvar *et al.* to compare this tracer with FDG PET/CT in the detection of occult metastatic disease using a combination of conventional imaging and clinical follow-up as the reference standard. A total of 37 men at risk for metastases but not yet diagnosed were studied and showed a 16.2% rate of positivity for ^{18}F -NaF PET/CT but only 8.1% for FDG PET/CT. This study also found a positive trend of ^{18}F -NaF positivity with increasing PSA in men post RP. Median PSA for patients with a positive ^{18}F -NaF PET/CT was 4.1 ng/ml (range: 1.9–5.8) whereas it was 2.9 ng/ml (range: 0.5–40.2 ng/ml) for patients with negative scans, a difference that proved not to be significant ($p = 0.31$) [58]. In a literature review by Wondergem *et al.* of 11 articles pertaining to ^{18}F -NaF PET/CT with varying PSA levels, ^{18}F -NaF in the detection of PCa bone metastases produced pooled sensitivities of 89 and 87%, and specificities of 91 and 80% on a per lesion and per patient basis, respectively [59]. A recent literature review by Azad *et al.* concluded that ^{18}F -NaF and ^{11}C and ^{18}F -choline PET/CT have equivalent sensitivities in finding PCa bone metastases although specificity is higher for the choline-based agents [60]. The role of ^{18}F -NaF in monitoring patients has been unclear. A recent prospective study by Apolo *et al.* analyzed 60 advanced PCa patients, 30 of whom had no known bone metastases at enrollment (median PSA: 10.97 ng/ml [range: 0.01–190]), and 30 of whom had known metastases (median PSA: 9.93 ng/ml [range: 0.1–593]). As expected ^{18}F -NaF PET/CT detected more bone metastases than traditional bone scan on a per patient basis and that there was a correlation between overall survival and the baseline number of malignant

lesions on ^{18}F -NaF PET/CT and changes in SUV on subsequent ^{18}F -NaF PET/CT scans [37].

The advantages of ^{18}F -NaF PET/CT are that it is clearly more sensitive than bone scan for the detection of early bone metastases. It can be performed more rapidly after injection (1 h) than bone scan (3–4 h). Because it is combined with CT, obvious degenerative disease can be seen at one setting without acquiring additional studies. However, once the diagnosis of bone metastasis is established there does not seem to be a compelling advantage to its use. In fact, some investigators dislike its higher sensitivity as it makes the discussion with the patient more complicated. Although this agent was approved for use by the FDA, to date, it has not been approved for reimbursement due to the lack of compelling clinical data. Hopefully, this agent will be made available for patients at risk for metastatic disease in whom the conventional bone scan is equivocal or negative. However, it is also possible that this agent will be supplanted by other agents discussed here.

Prostate-specific membrane antigen-targeted tracers

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein expressed prominently on the surface of PCa cells. PSMA levels correlate well with androgen deprivation, disease progression and metastasis. It is associated with more aggressive forms of the disease [61]. Although its function is obscure, and cancer cells can grow without it being present, it presents an attractive target for imaging and therapy. Therefore, a number of PET agents have been developed to bind to PSMA. PSMA targeting tracers for PET/CT include both low-molecular weight radiopharmaceutical-based imaging tracers and macromolecular antibodies, although we will not focus on the latter here. As a group, PSMA agents have shown high affinity even at low PSA values and have quickly become the ‘lead horse’ in the race for an effective BCR detection agent [62,63].

Even though the field is relatively young, multiple generations of PSMA-targeted small molecules have been developed and tested. The most extensively studied tracer and most widely used is the ^{68}Ga -labeled PSMA HBED-CC (^{68}Ga -PSMA) PET tracer that was developed in Germany. ^{68}Ga -PSMA has been shown to have better detection rates than ^{18}F -choline tracers in the case of recurrent and primary PCa [38,64–68].

Figure 2. A 68-year-old male with a serum prostate-specific antigen of 6.8 ng/ml and Gleason 4 + 5 prostate cancer diagnosis. The (A) anterior and (B) posterior projections of technetium bone scans show metastatic lesions in the axial skeleton, ribs and bilateral femur. Coronal ^{18}F -NaF PET image (C) not only confirms presence of these bony lesions, but also reveals additional widespread bony lesions that appear to be more helpful in estimation of the bony metastases burden compared with technetium bone scan.

A recent systematic review and meta-analysis by Perera *et al.* examined the sensitivity, specificity and predictors of ^{68}Ga -PSMA PET/CT in advanced PCa since current data are somewhat limited due to this tracer's novelty. In this comprehensive review of 16 articles with a total of 1309 patients, the authors found pre-PET PSA to predict positive ^{68}Ga -PSMA PET/CT since the percentage of positive ^{68}Ga -PSMA PET/CT scans increased with increasing PSA. This analysis demonstrates the ability of ^{68}Ga -PSMA PET/CT to detect recurrence even at low PSA values with a pooled positive detection rate of 42% in detecting disease recurrence. Additionally, four studies met the inclusion criteria for reporting histology-proven disease and the summary per patient sensitivity and specificity were both 86%. On a per lesion basis, the summary sensitivity and specificity were 80 and 97%, respectively, from the four included studies [69].

Another study by Afshar-Oromieh *et al.* in 2015 retrospectively evaluated 319 patients with ^{68}Ga -PSMA PET/CT in primary, recurrent and metastatic PCa. The median PSA for the 264 patients with tracer uptake was 6.02 ng/ml (range: 0.01–41,395) and was 1.14 ng/ml for 55 patients with no pathological findings (range: 0.03–15.8). While this statistic is initially disappointing, overall 83% of patients showed ^{68}Ga -PSMA uptake, and the tumor detection was correlated with PSA level. The sensitivity and specificity on a per lesion basis were 76.6 and 100%, respectively. However, there were 30 false negatives among 416 lesions and only 42 patients underwent histological verification [70]. In the case of BCR following RP, a study by Eiber *et al.* retrospectively evaluated 248 patients with BCR following RP (median PSA: 1.99 ng/ml) with ^{68}Ga -PSMA ligand PET/CT. The patient-based detection rates for positive pathological findings were 97, 93, 73 and 58% for PSAs ≥ 2 , 1 to <2 , 0.5 to <1 and 0.2 to <0.5 ng/ml, respectively. The detection rate improved with higher PSA velocities as well. The overall detection rate was 90%. These results are superior to the other agents previously discussed with impressive results even at low PSA levels. This study found ^{68}Ga -PSMA PET/CT to have higher detection rates with smaller PSA values compared with other PET tracers, ultrasonography, CT and MRI; however, a major limitation of this study was that only 37.1% of patients (92/248) had a comprehensive reference standard (histopathology, decrease in PSA after target RT or confirmed by follow-up imaging modalities) in addition to its relatively high false-negative rate [62]. Thus, these results await confirmation in more carefully controlled clinical studies.

Similar results with similar methodologies have been published by other investigators. For instance, van Leeuwen *et al.* prospectively examined 70 patients with BCR with ^{68}Ga -PSMA PET/CT following RP with two readers. Again, the rate of positivity depended on PSA values with an 8% sensitivity for PSA levels between 0.05 and 0.09 ng/ml, 23% for PSA level between 0.1 and 0.19 ng/ml, 58% for PSA level between 0.2 and 0.3 ng/ml, 36% for PSA levels between 0.3 and 0.5 ng/ml and 57% for PSA level between 0.5 and 0.99 ng/ml. These results confirm the first results and extended observations to include utility in restaging of PCa patients with rising PSA levels for metastatic disease; however, this study was also limited by a lack of histologic confirmation [71].

Few comparative studies of PSMA agents have been performed. In one, ^{68}Ga -PSMA was compared with ^{18}F -choline. ^{68}Ga -PSMA had higher detection rates in BCR [72–74]. However, results from these studies include small patient populations with limited histological follow-up. Future directions of ^{68}Ga -PSMA include utilizing it on PET/MRI scanners rather than using PET/CT [75,76].

In addition to ^{68}Ga -PSMA, two alternative PSMA-targeting tracers N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4- ^{18}F -fluorobenzyl-L-cystein (^{18}F -DCFBC) and ^{18}F -DCFPyL have been recently tested. These fluorine-based compounds have theoretical advantages. ^{18}F is a superior positron emitter compared with ^{68}Ga based on energy spectra. Moreover, it has a longer half-life enabling centralized distribution whereas ^{68}Ga must be produced on site via a ‘generator’ which requires considerable upfront expenditure and a radiopharmacy. A study by Rowe *et al.* determined that ^{18}F -DCFBC PET/CT was able to detect more lesions than conventional imaging methods in 17 prospectively enrolled patients (PSA range: 3.5–564.5 ng/ml) on a per lesion basis. Additionally, this study found ^{18}F -DCFBC tended to have higher sensitivity (0.92) than conventional imaging methods (0.71) on follow-up. **Figures 3 & 4** demonstrate two examples of suspected local recurrence and metastasis, respectively. However, ^{18}F -DCFBC PET/CT was found to have significant blood-pool activity, which could potentially obscure evaluation of nodal disease [77]. A second-generation agent, ^{18}F -DCFPyL has just recently been studied in BCR and results in higher tumor to blood uptake ratios due to its higher affinity and lower background signal compared with ^{18}F -DCFBC PET/CT [78,79]. It also compares favorably to ^{68}Ga -PSMA. Dietlein *et al.* reported 14 patients with BCR (PSA range: 0.17–50 ng/ml) who underwent both ^{18}F -DCFPyL PET/CT and ^{68}Ga -PSMA PET/CT. ^{18}F -DCFPyL was able to detect all lesions whereas ^{68}Ga -PSMA PET/CT missed lesions in three patients. Higher mean SUVs were observed in ^{18}F -DCFPyL than in ^{68}Ga -PSMA scans indicating that this tracer is encouraging as an alternative to ^{68}Ga -PSMA PET/CT in the detection of recurrent PCa [80].

Overall, the PSMA agents as a class have a higher detection rate for BCR and metastatic PCa compared with other PET imaging tracers [63]. Though, PSMA-based PET imaging is still considered experimental, the future of this tracer is promising in the detection of biochemical

Figure 3. A 63-year-old male with a serum prostate-specific antigen of 0.61 ng/ml and primary biopsy confirmed Gleason 3 + 4 prostate cancer. The patient is status post-radical prostatectomy. Axial T2-weighted MRI (A) shows a lesion at the right side of the anastomosis (arrows), which also demonstrates early enhancement on dynamic contrast-enhanced MRI (B) (arrows). ^{18}F -DCFBC PET (C) shows specific uptake within this lesion, which suggests residual/recurrent prostate cancer (arrow).

recurrent and metastatic PCa and this, in turn, could have implications for targeted radioguided surgery and other focal therapies. More prospectively, trials with histologic confirmation are necessary to further confirm the use of this tracer [12]. At present, there are several companies pursuing approval for various agents around the world and it should be interesting to see how the outlook changes for prostate-targeted PET agents in the near future.

Bombesin analog agents

New emerging tracers in the detection of early PCa BCR include radiolabeled bombesin analogs. Bombesin is a linear tetradecapeptide and antagonist of the gastrin-releasing peptide receptor (GRP), which interacts to enhance growth of PCa cells. It has been shown that PCa strongly expresses GRP. The radiolabeled bombesin analogs allow the expression of GRP receptors, thereby detecting the location of recurrence.

Few studies have explored the efficacy of this tracer, but most recently, a study by Sah *et al.* performed the first clinical evaluation of ^{18}F -bombesin PET/CT in five men with PSA recurrent PCa and compared results to that of ^{18}F -choline PET/CT. In two out of five patients (40%), ^{18}F -bombesin was positive, but was positive in all patients on ^{18}F -choline [81]. In another first clinical evaluation of a bombesin analog, Kahkonen *et al.* studied the effect of ^{68}Ga -bombesin PET/CT in the detection of metastatic PCa in three BCR patients following RP or hormone therapy (PSA levels: 0.36, 4.7 and 282 ng/ml). This study found the tracer to exhibit fast excretion through the kidneys and 25% of the injected dose still observed in the urinary tract 30 min postinjection. Additionally,

the tracer was positive in the two hormone-naïve patients with BCR (67%). ^{68}Ga -bombesin BCR results were compared with ^{11}C -acetate PET/CT ($n = 2$) and ^{18}F -choline PET/CT ($n = 1$), finding the two patients with ^{11}C -aceta PET/CT to be in accordance, but ^{68}Ga -bombesin was not positive in the evidently positive ^{18}F -choline PET/CT [82]. Though promising, the true potential of this tracer remains unknown as current studies remain with very small patient populations and also due to the relative new nature of this tracer. Future studies with larger patient cohorts are necessary to confirm the significance of bombesin-labeled tracers in recurrent PCa.

A list of all tracers included in this manuscript along with their half-life, cyclotron requirements, action mechanism, excretion characteristics, pooled sensitivities, pooled specificities, advantages and disadvantages for the detection of recurrent and metastatic PCa at all PSA levels is provided in Table 1.

Figure 4. A 63-year-old man with a serum prostate-specific antigen of 2.58 ng/ml, who underwent radical prostatectomy for Gleason 5 + 4 prostate cancer. Axial contrast-enhanced computed tomography (A) shows a subcentimeter lymph node in the right iliac chain (arrow). ^{18}F -DCFBC PET image (B) demonstrates specific radiotracer uptake within this right iliac chain lymph node suggestive of prostate cancer metastases (arrow).

Table 1. Table describing half-life, cyclotron requirements, action mechanism, excretion characteristics, pooled sensitivities, pooled specificities, advantages and disadvantages for the detection of recurrent and metastatic prostate cancer at all prostate-specific antigen levels.

Tracer	Half-life (min)	Cyclotron requirements	Mechanism of action	Excretion	Sensitivity (%)	Specificity (%)	Advantages	Disadvantages	Ref.
¹¹ C-choline	20	On-site	Cell membrane synthesis	Hepatic	38–98	50–100	Minimal bladder excretion, available in the USA	Variable sensitivity and specificity for BCR, especially at lower PSA values, short half-life requiring cyclotron on site	[24–25,30,33]
¹⁸ F-choline	110	Regional	Cell membrane synthesis	Urinary/renal	47–92	33–99	Longer half-life and can be produced off-site	Variable sensitivity and specificity for BCR, especially at lower PSA values, primarily excreted via urinary tract, not readily available in the USA	[30,33]
¹¹ C-acetate	20	On-site	Lipid synthesis	Hepatic	42–90	64–96	Minimal bladder excretion	Short half-life requiring on-site cyclotron, few centers are actively producing this agent	[39,41,43]
¹⁸ F-FACBC	110	Regional	Amino acid transport	Hepatic	89–100	67	Seems more sensitive at lower PSA values than choline and acetate tracers, approved for use in the USA, slow urinary excretion for improved signal	Moderate specificity, only moderate performance at lower PSA values, needs larger study validation	[47]
¹⁸ F-FDHT	110	Regional	AR	Gastrointestinal and urinary	63	N/A	Utilizes AR, which plays an important role in PCa growth, showing potential in this tracer	Mainly used in specific drug development, needs further validation in BCR and metastatic PCa with larger patient cohorts	[52]
¹⁸ F-NaF	110	Regional	Chemisorption within bone matrix	Hepatic	87–89	80–91	Improved sensitivity compared with traditional bone scan, long history and has been validated well, rapid bone-specific uptake, lack of blood pool, good axial skeletal visualization, can perform more rapidly than traditional bone scan	Lower specificity detecting a number of false positives, only useful in detecting bone metastases, not approved for reimbursement, potential to become obsolete to other agents	[10,37,59]
⁶⁸ Ga-PSMA	68	Generator (cyclotron independent)	PSMA analog	Urinary/renal	63–86	95–100	Promising agent with high sensitivity and specificity, even at low PSA values	Relatively newer tracer, still being studied and validated, moderate half-life, requires a generator with considerable upfront expenditure and a radiopharmacy	[69,70]

AR: Androgen receptor; BCR: Biochemical recurrence; N/A: Not applicable; PCa: Prostate cancer; PSA: Prostate-specific antigen.

Table 1. Table describing half-life, cyclotron requirements, action mechanism, excretion characteristics, pooled sensitivities, pooled specificities, advantages and disadvantages for the detection of recurrent and metastatic prostate cancer at all prostate-specific antigen levels (cont.).									
Tracer	Half-life (min)	Cyclotron requirements	Mechanism of action	Excretion	Sensitivity (%)	Specificity (%)	Advantages	Disadvantages	Ref.
¹⁸ F-DCFBC	110	Regional	PSMA inhibitor/antibodies	Renal	92	88	Longer half-life compared with ⁶⁸ Ga, ¹⁸ F is a superior positron emitter compared with ⁶⁸ Ga based on energy spectra	Significant blood-pool activity, newer tracer awaiting further validation in larger studies	[77]
¹⁸ F-DCFPyL	110	Regional	PSMA inhibitor/antibodies	Renal	N/A	N/A	Longer half-life than ⁶⁸ Ga, higher tumor to blood uptake ratios due to its higher affinity and lower background signal compared with ¹⁸ F-DCFBC, may be more sensitive than ⁶⁸ Ga in detection of BCR	Newer tracer awaiting further validation in larger studies	[78–80]
AR: Androgen receptor; BCR: Biochemical recurrence; N/A: Not applicable; PCa: Prostate cancer; PSA: Prostate-specific antigen.									

AR: Androgen receptor; BCR: Biochemical recurrence; N/A: Not applicable; PCa: Prostate cancer; PSA: Prostate-specific antigen.

Conclusion

The ideal imaging agent for PCa would detect only clinically significant disease at first diagnosis, at recurrence and at the first signs of metastasis. It would have few false positives and be convenient to use. It would be capable of detecting recurrent disease at PSA values <0.5 ng/ml. Decisions regarding its use would be based on studies that were well controlled with histologic correlation. Armed with such an agent, the treatment of PCa could be very different. Focal therapies for primary disease and recurrent disease could be developed. Even focal therapies for early metastatic disease could be developed. Patients might not have to undergo long courses of androgen-deprivation therapy. Thus, early detection of recurrent and metastatic PCa is imperative in improving the diagnosis and management of PCa.

Clearly, none of the PET imaging agents discussed here meet all the criteria for the ideal agent. The current portfolio of agents ¹⁸F/¹¹C-choline, ¹¹C-acetate, ¹⁸F-FACBC, ¹⁸F-FDHT, ¹⁸F-NaF and PSMA-targeted tracers have flaws. Yet, it is important to develop these agents further and establish a single agent that could serve as the standard bearer. Whichever of these PET tracers prove most effective, it is clear that they will change our understanding of the disease and facilitate the development of new therapies that maximize survival and minimize the side effects of treatment.

Future perspective

In the case of BCR, early detection and initiation of therapy is a key to better long-term outcomes. Early intervention is associated with a lower rate of metastatic disease. Thus, accurate and early detection of recurrence leading to earlier treatment will aid in hindering the progression of BCR to metastatic disease. Currently, conventional imaging techniques such as CT, bone scan and MRI are commonly used; however, their utility in detecting early BCR is quite limited. PET imaging offers specific imaging in several malignancies, but in the case of PCa BCR, the use of PET imaging is limited. Several tracers exist such as radiolabeled choline, acetate, ¹⁸F-FACBC, ¹⁸F-FDHT, PSMA-targeting agents and several studies have investigated these tracers. Yet, these studies are limited due to potential patient selection bias, limited study designs and gold standard validation. Moreover, these

tracers suffer in sensitivity at lower PSA levels (e.g., PSA <2–5 ng/ml), with the exception of PSMA-targeting tracers that offer relatively higher sensitivity and specificity compared with the others. Further studies with prospective methods and focus on lower PSA values will determine the ideal radiotracer for the detection of PCa BCR in the future.

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EXECUTIVE SUMMARY

- Early detection and initiation of therapy is a key to better long-term outcomes in biochemical recurrence.
- Accurate localization of recurrent prostate cancer at low PSA values is a major challenge as patients with biochemical recurrence are best treated as early as possible.
- Current imaging modalities, aside from PET/computed tomography, are limited in detection of recurrence or metastasis for PSA values <5 ng/ml.
- $^{11}\text{C}/^{18}\text{F}$ -choline, ^{11}C -acetate, anti-1/2/3- ^{18}F -fluorocyclobutane-1-carboxylic acid have reasonable sensitivity at higher PSA levels in the setting of PSA, but these agents suffer in sensitivity at lower PSA levels (<1 ng/ml).
- 16beta- ^{18}F -fluoro-5alpha-dihydrotestosterone targets androgen receptors, and few studies report its utility on androgen receptor status, which may assist to depict castrate-resistant prostate cancer lesions.
- ^{18}F -NaF targets bone-forming processes and detects tumor-associated osteoblastic lesions as well as healing fractures, bone dysplasia, etc.
- Prostate-specific membrane antigen-targeting tracers are current highly studied agents both in the USA and Europe. Recent studies report promising sensitivity and specificity even at lower PSA values; however, more tissue validation-based data are required to better understand this tracer.
- PET imaging with novel tracers will change our understanding of the disease and facilitate the development of new therapies that maximize survival and minimize the side effects of treatment.

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