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Molecular Imaging of Prostate Cancer

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Abstract

Purpose of review—Prostate cancer is a complex and biologically heterogeneous disease that is not adequately assessed with conventional imaging alone. Molecular imaging with positron emission tomography (PET) is poised to fill this unmet need through noninvasive probing of the multiple molecular and cellular processes that are active in prostate cancer patients.

Recent findings—Several PET tracers are active in early and late stage prostate cancer in humans. F18-FDG, C11/F18-choline and F18-sodium fluoride (NaF) have been studied most extensively. There is a growing body of literature supporting to the utility of choline in early stage prostate cancer. FDG and NaF are more valuable in advanced disease, especially for assessing bone metastases, the prevalent form of metastases in this patient population. F18-Fluoro-dihydrotestosterone is active in castrate disease and is emerging as a valuable pharmacodynamic marker in the development of novel AR-targeted therapies. Anti-PSMA PET tracers are in the early stages of clinical development.

Summary—Multiple PET tracers are currently available to aid in the detection and management of prostate cancer across the clinical spectrum of the disease. Prospective, rigorously controlled, clinical imaging trials are needed to establish the optimal role of PET in prostate cancer.

Keywords

Prostate cancer; PET; FDG; Choline; FDHT

Introduction

Prostate cancer is a biologically heterogeneous disease across the spectrum of its clinical states¹, and is thus challenging to treat. Successful management is further confounded by the disease-specific limitations of conventional imaging². Positron emission tomography (PET) carries a distinct advantage over conventional imaging in its unique ability to non-invasively interrogate metabolic and molecular processes in-vivo. These processes include alterations in glucose, amino acid and fatty acid metabolism, receptor status, cellular proliferation, tumor hypoxia and blood flow. Several PET tracers are active in early and late stage prostate cancer (see Table 1). Among these, F18-FDG, Choline (C11 and F18 labeled) and sodium

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Conflicts of Interest: None

F18-fluoride (NaF) have been studied most extensively. Choline is emerging from the vast cloud of data (quite heterogeneous, akin to the disease itself) as a valuable tool for assessment of early prostate cancer, while FDG and NaF appear to have greater utility in advanced disease.

C11 and F18 Choline

The two radiolabeled forms of choline are generally considered to provide similar information, with the advantage of C11 labeled choline being minimal urinary excretion, while the F18 compound is better fit for commercial use, owing to its longer half life (110 minutes vs 20 minutes for C11). Choline PET is increasingly utilized in the Eastern Hemisphere for evaluation of prostate cancer; however, in many studies the patient populations and states of disease are quite heterogeneous. A recent systematic review³ of 37 studies noted several sources of variation affecting the reported performance of F18-choline PET, underscoring the need for rigorously standardized prospective imaging trials. Nonetheless, it is apparent that choline PET is a rational and viable modality for evaluating prostate cancer, particularly in its early stages.

A major challenge for PET imaging of localized prostate cancer is the difficulty in detecting small lesions and in discriminating between benign and malignant processes. This is a well-known challenge for FDG, but also exists for other tracers including choline-PET. In an elegant study, Souvatzoglou and colleagues recently evaluated 43 patients who underwent radical prostatectomy within 31 days after C11-choline PET/CT⁴. Transaxial images and histologic specimens were analyzed by comparing the respective slices. Not surprisingly, the authors found that small focal tumors (< 5 mm) and ring-like tumors were poorly detected on PET, while larger well-defined tumors were evident on PET (figure 1). In addition, SUVmax failed to distinguish between cancer (median SUVmax 4.9), benign prostatic hypertrophy (median SUVmax 4.5) and prostatitis (median SUVmax 3.9), $P = 0.102$ and $P = 0.054$, respectively.

The greatest value of the choline agents seems to be in the setting of rising PSA following definitive local therapy. By definition, patients with “biochemical relapse” have a rising PSA level as the only manifestation of their disease⁵. The goal of molecular imaging with PET in this setting is to localize foci of recurrent disease that are unrecognized clinically or on conventional imaging (e.g., small lymph nodes that do not meet size criteria on standard CT or MRI, or disease in bone marrow that is not recognizable on CT). The main purpose here is to distinguish between local, regional or distant disease recurrence, because the treatment will vary (e.g., irradiation to prostate bed versus hormonal or chemotherapy). Choline uptake in prostate cancer is presumed to correlate with tumor volume as reflected by PSA levels. In a report on 63 patients categorized in biochemical recurrence, 35 (56%) patients had abnormal scans⁶. Recurrent disease could be localized in 36% of patients with PSA-value <1 ng/ml, 43% with PSA-value 1 to <2 ng/ml, 62% with PSA-value 2 to <3 ng/ml and 73% with PSA-value ≥ 3 ng/ml. The detection rate was not influenced by concurrent anti-androgen therapy. Other investigators have demonstrated a strong link between PSA kinetics - including PSA doubling time (PSADT) and velocity (PSAV) - and abnormal choline PET/CT findings. Shorter doubling time and higher PSA velocity reflect

the rate of tumor cell proliferation. Giovacchini and colleagues⁷ studied 170 patients with biochemical relapse following radical prostatectomy, C11-choline PET/CT was positive in 75 of 170 patients (44%). The percentage of patients with positive C11-choline PET/CT was 27% for PSADT >6 months, 61% for PSADT between 3 and 6 months and 81% for PSADT <3 months. Pathologic uptake in the skeleton was seen in 52% of patients with PSADT <3 months and only in 3% of patients with PSADT >6 months. More recently, the same group showed a positive correlation with PSAV in the same patient population⁸. Patients with positive C11-choline PET/CT (n = 75) had significantly ($p < 0.05$) higher PSAV than patients with negative scans (n = 95) (6.93 ± 13.08 vs. 1.23 ± 2.03 ng/mL/y). The percent of patients with positive C11-choline PET/CT was 21% for PSAV <1 ng/mL/y, 56% for PSAV between 1 and 2 ng/mL/y, and 76% for PSAV >2 ng/mL/y. These and other studies^{9,10} clearly demonstrate a relationship between choline uptake and PSA kinetics; however, it is worth noting that the patient populations studied do not strictly qualify for “biochemical relapse”, as many of the PET-positive lesions were also present on conventional imaging.

F18-Sodium Fluoride (NaF)

Bone metastases are the primary cause of morbidity and mortality in progressive prostate cancer, eventually developing in 80–90% of patients with metastatic disease, either alone or in conjunction with less frequent visceral metastases¹¹. Bone disease is notoriously difficult to assess by conventional radiography and computed tomography. In fact, the osteoblastic variety, most commonly found in prostate cancer patients, is considered non-measurable disease according to RECIST¹². Scintigraphic techniques have long been the mainstay for assessing bone disease. Tc99m-methylene diphosphonate (MDP) and similar single-photon radiolabeled phosphate analogues are incorporated into the hydroxyapatite crystalline lattice and collagen matrix¹³. Uptake of MDP is a function of blood supply, rate of bone turnover or osteoblastic activity, quantity of mineralized bone, capillary permeability, fluid pressure and local acid/base balance. Bone scintigraphy is highly sensitive for osteogenic activity and allows for quick assessment of the entire skeleton. There are several limitations: bone scan findings depict derivative changes rather than the tumor itself; regression of disease is difficult to discern due to lingering radiotracer uptake in healing bone; and response assessment is confounded by the flare phenomenon, a major obstacle that can occur up to 12 weeks post effective treatment¹⁴.

In recent years, F18-sodium fluoride (NaF) has re-emerged in the form of PET as a radiotracer for imaging bone metastases¹⁵. It was originally used for bone imaging with conventional gamma cameras applying a high energy collimator, yielding to poor resolution, and was then largely replaced by Tc99m-labeled bone tracers, which were more suitable for imaging with a conventional gamma camera¹⁶. The mechanism of NaF uptake is similar to that of the phosphonates. Advantages of NaF over MDP include its higher affinity for bone¹⁷, allowing for earlier imaging time with better image quality, which is also a product of the superior imaging characteristics of PET (figure 2). Several studies to date have suggested that NaF performs better than MDP for the assessment of osteoblastic metastases, particularly when combined with the anatomic information derived from CT. Notably, Even-Sapir and colleagues compared planar bone scintigraphy, bone SPECT, NaF-PET, and NaF-PET/CT in patients with localized, high-risk or metastatic prostate cancer¹⁸. The reported

sensitivity and specificity for detection of bone lesions was higher for NaF-PET/CT (100% and 100%, respectively) than for planar bone scanning (70% and 57%), SPECT (92% and 82%) or NaF-PET alone (100% and 62%). These results appear to favor NaF-PET/CT over conventional bone scintigraphy; however, limitations of the study include the mixed patient population and lack of a true standard of reference.

Although NaF-PET is widely considered superior to MDP, no prospective studies have yet demonstrated an incremental benefit in staging or patient management; it is unclear if NaF will provide more meaningful information (possibly based on quantitative assessment) regarding treatment response and disease progression than the conventional bone scan. Additionally, it is uncertain whether quantitation of NaF uptake in bone lesions, using standardized uptake values (SUV), confers prognostic information. The information derived from a conventional planar bone scan can be reduced to a single quantitative parameter, termed the bone scan index (BSI)¹⁹, a measure of the fractional volume of skeletal tumor burden. BSI derived from conventional bone scans is prognostic of survival^{20,21,22}, and its value as an indicator of response or progression is under investigation²³. Manual BSI measurements are relatively reproducible, but are tedious to perform. An automated platform for BSI calculation that generates reproducible results within seconds was recently shown to correlate well with manually derived BSI scores^{24,25}. With the increasing availability of NaF-PET it remains to be seen whether the BSI can be optimized even further by the three-dimensional and quantitative properties of PET imaging.

Further experience with NaF-PET is needed before it is able to supplant conventional single photon bone scans, which are less expensive and more widely available. With the recent decision of the Centers for Medicare & Medicaid Services to reimburse sites participating in the National Oncologic PET Registry (NOPR) for NaF-PET scans, a wealth of data is expected to surface in the coming months and years.

F18-FDG

In 2008, the National Oncologic PET Registry (NOPR) published results on the clinical impact of FDG-PET^{26,27}. The registry found that FDG-PET influenced management of prostate cancer patients in 35–45% of cases across clinical indications, similar to other cancers, despite the widely held notion that FDG is of limited value in prostate cancer. It is true that FDG-PET is of not the optimal modality for assessing organ-confined prostate cancer, owing to the low glycolytic activity of many tumors, and due to technical factors such as interference by physiologic, hyperplastic or inflammatory-type FDG uptake in the prostate, and high excreted activity in the adjacent urinary bladder. However, FDG-PET does play an important role in more advanced disease states²⁸.

Schoder and colleagues compared the performance of FDG-PET/CT and conventional imaging in 91 patients with PSA relapse following prostatectomy²⁹. The standard of reference included biopsy or clinical and imaging follow-up. PET was true positive in 28 of 91 (31%) patients, showing isolated disease in the prostate bed ($n = 3$) or metastatic disease with ($n = 2$) or without ($n = 23$) simultaneous disease in the prostate bed. Mean PSA was higher in FDG-positive than in FDG-negative patients (9.5 ± 2.2 versus 2.1 ± 3.3 ng/mL).

PSA of 2.4 ng/mL and PSA velocity of 1.3 ng/mL/y provided the best tradeoff between sensitivity (80%; 71%) and specificity (73%; 77%) of PET in a receiver operating curve analysis. Combination with other clinical parameters in a multivariate analysis did not improve disease prediction. In this study, there were only two patients in whom other imaging studies showed isolated local recurrence or metastatic disease.

Bone scanning, whether with NaF-PET or conventional Tc99m MDP agents, remains an indirect method of imaging bone metastases. Many sclerotic lesions detected on bone scan, including NaF-PET, are in reality dormant or treated. Furthermore, lytic or marrow-based lesions are not readily detectable on bone scan due to lack of bone turnover. FDG-PET, on the other hand, directly assesses tumor metabolism in bone. The value of FDG for assessment of bone metastases in castration resistant prostate cancer (CRPC) was specifically addressed by our group³⁰. In this study, 43 patients underwent FDG-PET and bone scan prior to investigational therapies. Of 105 FDG-positive and MDP-negative lesions, 84 (80%) eventually turned positive on followup bone scan. Survival correlated inversely with FDG-PET SUVmax (median survival 14.4 vs. 32.8 months if SUVmax > 6.10 vs. ≤ 6.10, $p=0.002$), as well as with the BSI (14.7 vs. 28.2 months if BSI >1.27 vs. ≤ 1.27; $p=0.004$). Only SUVmax was an independent factor in multivariate analysis. A combination of SUVmax and a nomogram for progressive prostate cancer dichotomized patients into a high versus low risk group (median survival 14.4 vs. 34.6 months, $p=.015$) that was more prognostic than either alone.

Clinical experience shows that FDG-PET can be applied for response assessment in patients with metastatic disease undergoing hormonal therapy or chemotherapy^{31,32}. Preliminary data suggest that this is also possible with the choline tracers, however, larger prospective studies are lacking.

Future Directions

Molecular imaging probes that target antigens and receptors specifically expressed by prostate cancer cells may eventually be transformative biomarkers for disease management and drug development. Such PET agents are particularly relevant for navigating the biologic heterogeneity of advanced disease.

Androgen Receptor (AR) Probes

The AR signaling axis is implicated as a driving force in the development and progression of CRPC, justifying the need for novel antiandrogen therapies³³. AR expression and binding capacity can be assessed non-invasively with F18-FDHT, an analog of dihydrotestosterone (DHT)³⁴. Since endogenous DHT (the primary AR ligand) competes with FDHT for AR binding, the tracer is most suitably applied in patients with castrate disease, which is characterized by low circulating testosterone levels (<50 ng/dL)^{35,36}. In our experience with total-lesion analyses³⁷ of paired FDG and FDHT-PET scans in metastatic CRPC, we have seen diverse patterns of uptake, including FDG/FDHT concordance, FDG predominance and FDHT predominance (figure 3). These unique phenotypes may have implications for risk stratification and personalization of therapeutic strategies. The potential role of FDHT-PET as a pharmacodynamic marker was recently demonstrated in the context of a therapeutic trial

for a next-generation AR targeted therapy. In this phase 1–2 study of MDV3100, a competitive AR inhibitor, a clear-cut reduction in uptake (~20–100%) was seen in all 22 patients evaluated with FDHT-PET during therapy, with a suggestion of dose dependence and a saturation point prior to reaching the maximum tolerated dose³⁸. Of note, these FDHT “responses” did not necessarily correlate with clinical response. At this time, it remains unclear if therapy-related modulation of FDHT uptake can predict clinical outcomes.

Prostate Specific Membrane Antigen (PSMA) Probes

FDHT uptake reflects AR ligand-receptor interaction, but the dynamics of downstream AR signaling are perhaps better captured by other molecular imaging probes. In particular, J591 is an antibody to an epitope on the extracellular domain of prostate specific membrane antigen (PSMA) that is promising for both imaging and radioimmunotherapy purposes³⁹. PET imaging with J591 is proposed to reflect the downstream effects of AR inhibition, given that PSMA expression is downregulated by androgen administration and upregulated by androgen deprivation^{40,41}. An in-human imaging trial of Zr89-labeled J591 (Zr89-DFO-huJ591⁴²) is currently underway at our institution, and a Cu64-labeled version of the antibody is in preclinical development⁴³. Other PSMA targeted tracers are currently being developed by the group at John’s Hopkins University⁴⁴. Together, AR-axis imaging agents promise to increase our understanding of the biology and escape mechanisms of prostate cancer, hopefully with implications for novel therapies.

Conclusion

Multiple PET tracers are now available to aid in the detection and management of prostate cancer across the clinical spectrum of the disease. Prospective clinical imaging trials using various PET tracers, individually or in combination, rigorously controlled for clinical-state, therapy and well-defined clinical endpoints are needed to establish the optimal role of PET in prostate cancer, just as they are crucial in drug development⁴⁵.

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Key Points

- C11-choline and F18-choline PET are useful for restaging of prostate cancer; uptake appears to be correlated with PSA kinetics in patients with recurrent disease.
- FDG-PET and NaF-PET are valuable in advanced disease, especially for assessing bone metastases.
- FDHT-PET non-invasively assesses the status of the androgen receptor (AR) expression in the setting of castrate disease.
- Prostate specific membrane antigen (PSMA) targeted PET tracers are proposed to reflect the effects of AR inhibition on downstream signaling, and are in the early stages of clinical development.
- Prospective, rigorously controlled, clinical imaging trials are needed to establish the optimal role of PET in prostate cancer.

Figure 1. The sensitivity of C11-Choline PET/CT for localizing prostate cancer (PCa) depends on tumor configuration

Histology specimen (A), PET/CT fused image (B), and PET image (C) of the respective slices in the 4 (I–IV) different tumor configuration forms observed. The tumor is outlined in the histologic specimen. In the first and in the second row unifocal (form I) and multifocal (form II) PCa are shown exhibiting intense C11-choline uptake (SUVmax = 5.6 in I; SUVmax = 7.1 in II). In the third and the fourth row PCa with a rind-like shaped growth pattern (form III) and a small sized focus of cancer (form IV) are shown that are not visualized in the corresponding PET images (SUVmax = 5.7 located in BPH in III and SUVmax = 3.5 located in normal prostate tissue in IV). Reproduced with permission from Souvatzoglou M et al. Clin Cancer Res 2011;17:3751-3759

Figure 2. Enhanced depiction of bone metastases with NaF-PET in a 64-year-old male with CRPC

A. Tc99m-MDP whole body images and lateral spot views of the head demonstrate multiple osseous metastases in the axial and appendicular skeleton. B. NaF-PET/CT MIP, axial CT and fused axial PET/CT images in the same patient show superior detection of numerous metastatic lesions with exquisite demonstration of skull base metastases that are poorly visualized on MDP scan.

Figure 3.

A: FDHT-predominant nodal disease in a 67-year-old male with CRPC and PSA of 789 ng/ml. FDHT (top) and FDG (bottom) MIP, fused axial, CT axial and PET axial images

demonstrate marked discordance in avidity of extensive retroperitoneal nodal metastases. MIP images also demonstrate multiple discordantly FDHT-positive bone lesions.

B: FDHT-predominant bone disease in a 69-year-old male with CRPC and PSA of 213 ng/ml. FDHT (top) and FDG (bottom) MIP, fused sagittal, CT sagittal and PET sagittal images demonstrate marked discordance in avidity of bone metastases.

Table 1**PET Tracers for Clinical Imaging of Prostate Cancer**

Tracer	Isotope Half-Life	Mechanism
F18-FDG	110 min	Analog of glucose; reflects the increased glycolytic activity of tumors (Warburg effect); FDG is trapped in cells via GLUT transport and irreversible HK phosphorylation
C11 -Choline	20 min	Substrate for phospholipid synthesis in cell membranes, transmembrane signaling, lipid and cholesterol transport and metabolism; choline kinase is upregulated in tumors
F18-Choline	110 min	Same as for C11-choline
C11-Methionine	20 min	Naturally occurring amino acid; reflects increased amino acid transport, to a lesser degree also protein synthesis related to tumor cell proliferation and turnover
C11-Acetate	20 min	Naturally occurring metabolite; converted to acetyl-CoA and incorporated into cholesterol and fatty acids ; fatty acid synthetase and acetyl-CoA carboxylase are oncogenic enzymes upregulated in prostate cancer
F18-FACBC	110 min	Synthetic l-leucine analog; reflects increased amino acid transport as prerequisite for protein synthesis
Sodium F18-Fluoride	110 min	Reflects increased osteoblastic activity by slow exchange of fluoride ions with hydroxyapatite crystals, forming fluoroapatite
F18-FDHT	110 min	Androgen receptor expression and binding capacity; AR is upregulated in castrate resistant disease
Zr89-DFO-huJ591	78.4 hr	Monoclonal antibody to epitope on external domain of PSMA

FDG = 2-[18F]fluoro-2-deoxyglucose; GLUT = Glucose Transporter; HK = Hexokinase; FACBC = Anti-1-Amino-3-[18F]fluorocyclobutane-1-carboxylic acid; FDHT = 16 β -[18F]-Fluoro-5 α -dihydrotestosterone; PSMA = Prostate Specific Membrane Antigen