Imaging of Prostate Cancer With Positron Emission Tomography

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Abstract Prostate cancer is most commonly imaged through a combination of magnetic resonance imaging, x-ray computed tomography, and ^{99m}Tc-methylene diphosphonate bone scan. These conventional imaging modalities, however, suffer from limited sensitivity and specificity for the detection of disease. This can lead to disease understaging and the improper selection of treatment. To address this problem, a variety of novel radiotracers for positron emission tomography (PET) imaging have been developed. This includes agents that accumulate on the basis of alterations in cellular metabolism (eg, ^{11}C-choline and ^{18}F-FACBC) as well as those that bind to specific proteins (eg, ^{68}Ga-PSMA-11, ^{18}F-DCFPyL, ^{68}Ga-RM2, and ^{18}F-DHT). In this review, we examine the performance characteristics of these new PET radiotracers for imaging prostate cancer and discuss ways in which PET imaging can offer more precise clinical information to patients and providers.

Introduction

Prostate cancer is the most common noncutaneous malignancy in men, with more than 160,000 new cases diagnosed each year in the United States.[1] Although the number of available treatment options has increased markedly in recent years, an estimated 29,000 men die each year of prostate cancer, making it the second most common cause of death from cancer among American men. Imaging remains one of the most important tools for the detection and localization of sites of disease. Unfortunately, the most commonly used imaging modalities have limited sensitivity, increasing the risk of understaging a patient's disease burden and undertreating their disease.[2]

Currently recommended studies for staging prostate cancer include abdominal and pelvic imaging with either magnetic resonance imaging (MRI) or x-ray computed tomography (CT), and bone imaging with ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scintigraphy.[3] This combination of tests, however, offers limited sensitivity and specificity for detection of distant sites of prostate cancer. For instance, cross-sectional imaging is limited in detecting lymph node metastases, with one meta-analysis finding

that CT and MRI have pooled sensitivities of 42% (95% CI, 26%-56%) and 39% (95% CI, 22%-56%), respectively.[4] For skeletal lesions, standard ^{99m}Tc-MDP bone scan has been found to have a sensitivity of only 64.6%.[5] Furthermore, the specificity of ^{99m}Tc-MDP bone scan is limited in that a number of benign conditions, such as infection and trauma, can show uptake of the radiotracer, which nonspecifically homes to areas of bone remodeling, regardless of the presence of cancer.[6,7] For these reasons, conventional imaging modalities often underestimate the volume of disease in patients with metastatic prostate cancer.[8,9]

Given the limitations of traditional imaging, the use of molecular imaging with positron emission tomography (PET) has been explored to better identify sites of disease. Although molecular imaging in oncology is most commonly performed with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT, this test has not shown clinical utility in prostate cancer imaging, with reported sensitivities as low as 37% for detection of organ-confined disease.[10] Thus, a number of new PET radiotracers have been developed for prostate cancer imaging. In this review, we outline the imaging and performance characteristics of the most important of these novel radiotracers (Figure 1).

PET Imaging of Prostate Cancer

^{18}F-Sodium Fluoride

As early as the 1960s, researchers began evaluating ^{18}F-sodium fluoride (Na^{18}F) for bone imaging.[11] With the advent of widespread PET scanner availability and improvements in fluorine-18 radiopharmaceutical delivery logistics, the use of this imaging agent has become more common.[12] Studies comparing the diagnostic utility of Na^{18}F PET with ^{99m}Tc-MDP single-photon imaging have consistently found that Na^{18}F offers significantly better sensitivity and specificity in the detection of bone metastases.[12-14] Na^{18}F has a number of additional advantages, including high and rapid bone uptake along with fast blood clearance, resulting in high-quality skeletal images within a relatively short time frame.[15] However, this radiotracer is associated with a number of limitations. Na^{18}F is not tumor-specific, and thus can lead to higher false-positive rates in areas of benign bone remodeling or stress.[16] Thus, differentiation between lesions requires further validation of structural morphology by CT or MRI. Furthermore, the Na^{18}F radiotracer is of limited utility in the detection of soft-tissue malignancies, including the primary tumor, lymph node disease, and visceral metastases.[17]

Several other practical considerations limit the widespread use of Na^{18}F. Though few studies on overall cost-effectiveness are known to exist, at least one comparative study confirmed it to be significantly more costly than standard ^{99m}Tc-MDP.[18] Also, in a decision memo from 2010, the Centers for Medicare & Medicaid Services (CMS) announced that the evidence that Na^{18}F imaging improves health outcomes in people with cancer is insufficient, and thus the technique is nonreimbursable.[19] In the same document, CMS did allow for an exception for its use as part of qualifying for a prospective clinical trial.[19]

Choline-Based Radiotracers

Although a number of solid cancers show increased glycolytic activity, allowing for detection with ^{18}F-FDG PET, prostate cancer cellular metabolism is unique in that prostate cancer cells typically do not undergo increased aerobic glycolysis. These cells do, however, display upregulated de novo lipid synthesis and activity of lipogenic enzymes.[20] It is this increase that enables lipid precursors such as acetate and choline to function as radiotracers for PET imaging. In 2012, the US Food and Drug Administration (FDA) approved ^{11}C-choline for PET imaging in patients with suspected prostate cancer recurrence and noninformative CT, MRI, or bone scintigraphy.[21]

A number of meta-analyses assessing the diagnostic performance of ^{11}C-choline PET/CT have been carried out. One such recent meta-analysis found values of sensitivity and specificity of 87% (95% CI, 74%-94%) and 98% (95% CI, 96%-99%).[22] Another study compared MRI, ^{11}C-choline PET, and ^{11}C-choline PET/CT in nodal staging of prostate cancer patients.[23] The sensitivity for these 3 methods was found to be 18.5%, 40.7%, and 51.9%, respectively. The specificity was 98.7%, 98.4%, and 98.4%, respectively.

^{11}C-choline PET/CT has been shown to be useful in a number of clinical scenarios. In one study, post-prostatectomy patients with suspected biochemical recurrence underwent ^{11}C-choline PET/CT after standard imaging.[24] PET/CT findings altered the treatment approach in 55% of the patients, impacting decisions concerning radiation therapy and androgen deprivation therapy (ADT). Another recent study found similarly significant impact, with changes in therapeutic management in 66.1% of patients who participated.[25] Furthermore, evidence suggests that ^{11}C-choline PET/CT can be used to aid in the selection of patients who may benefit from aggressive salvage radiation therapy.[26]

Although a number of studies have demonstrated the benefits of ^{11}C-choline PET/CT relative to CT, MRI, and ^{99m}Tc-MDP bone scan in the detection of prostate cancer metastases, several limitations exist governing its use. Serum levels of prostate-specific antigen (PSA) have been found to be positively correlated with the sensitivity of ^{11}C-choline PET/CT, with most studies suggesting

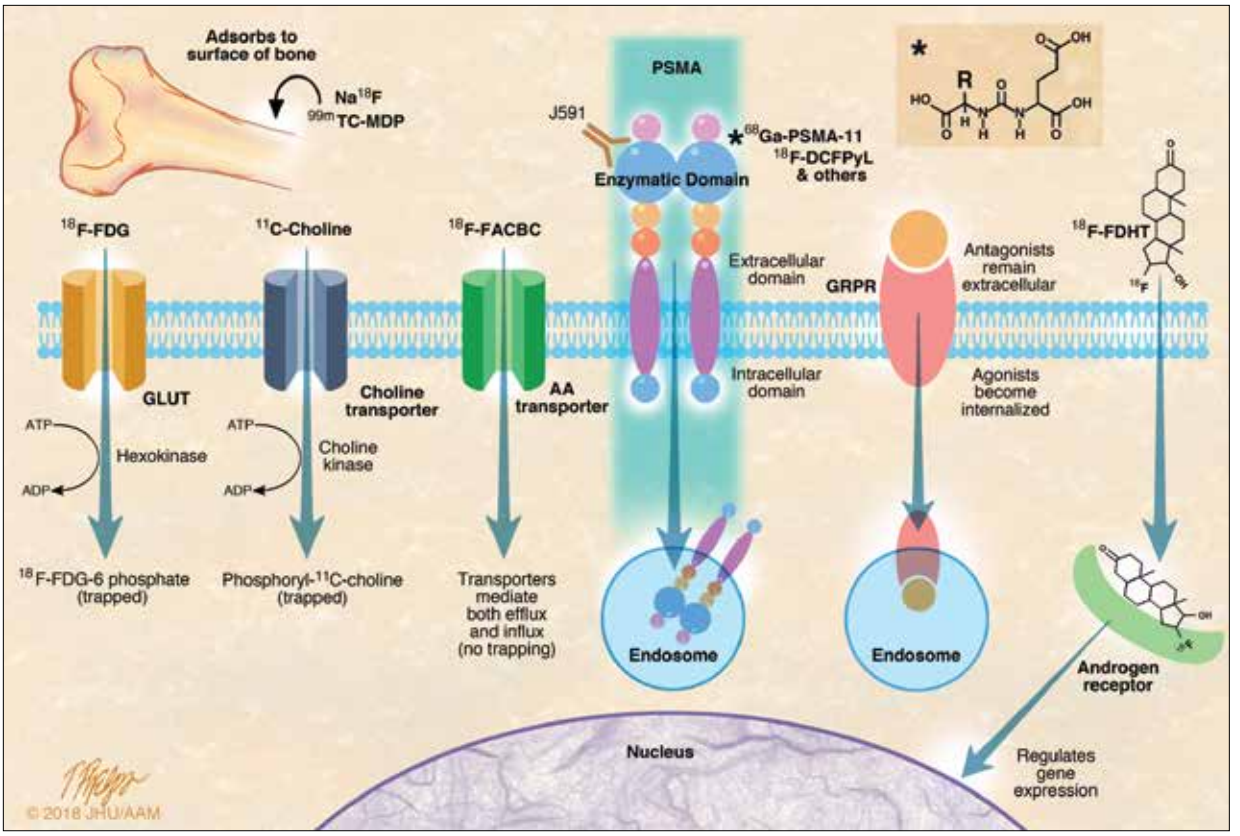

Figure 1. Schematic diagram demonstrating the mechanism of uptake of each radiotracer discussed in this review. Blue arrows show the uptake of each compound. ^{99m}Tc-MDP and Na^{18}F home to areas of bone remodeling. ^{18}F-FDG, ^{11}C-choline, and ^{18}F-FACBC are metabolic radiotracers that are taken up through specific membrane transporters in response to alterations in cellular metabolism. Urea-based small molecules targeting PSMA (*) are internalized via endocytosis. A number of these molecules have been described, including ^{18}F-DCFPyL and ^{68}Ga-PSMA-11. These compounds are based on a common urea scaffold, but differ by their specific chemical linker and radionuclide (R group). The J591 antibody has also been developed for molecular imaging of prostate cancer and binds to the extracellular domain PSMA. GRPR is another transmembrane protein that has been targeted for molecular imaging of prostate cancer. Bombesin analogues targeting GRPR can act as either agonists or antagonists. ^{18}F-FDHT diffuses across the phospholipid bilayer and binds to the androgen receptor.

AA, amino acid transporter; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-FDHT, 16-beta-^{18}F-fluoro-5-alpha-dihydrotestosterone; GLUT, glucose transporter; GRPR, gastrin-releasing peptide receptor; PSMA, prostate-specific membrane antigen; ^{99m}Tc-MDP, ^{99m}Tc-methylene diphosphonate.

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that these scans have decreased sensitivity for patients with PSA values that fall below the range of 1 to 2 ng/mL.[26-28] Additionally, choline-based radiotracers are not cancer-specific, and can be taken up in other tissues or areas of benign inflammation.[29] For instance, high levels of ^{11}C-choline uptake have been observed in cases of benign prostatic hyperplasia.[30] Additionally, ADT might significantly reduce ^{11}C-choline uptake in androgen-sensitive prostate cancer.[31] Furthermore, ^{11}C-choline has a short physical half-life of approximately 20 minutes, requiring the use of an on-site cyclotron and local radiopharmacy capabilities.[32]

^{18}F-fluorocholine is a mechanistically similar radiotracer that addresses some of the limitations of ^{11}C-choline. ^{18}F-fluorocholine has a physical half-life of 110 minutes. Thus, it can be prepared commercially and distributed for clinical use in smaller facilities.[33] Of note, the diagnostic performance of ^{18}F-fluorocholine has been found to be uninfluenced by ADT.[34] However, this radiotracer also has high levels of urinary excretion, which can interfere with imaging the pelvic region.[7,33]

Much like ^{11}C-choline, PET/CT imaging with ^{18}F-fluorocholine offers superior efficiency relative to conventional imaging in detecting bone involvement of

prostate cancer.[35,36] Additionally, in a study comparing ^{18}F-fluorocholine PET/CT with conventional imaging modalities, ^{18}F-fluorocholine was found to be superior to diagnostic CT scans in detecting lymph node involvement, with a sensitivity of 69.2% (vs 46.2%), and identical specificities of 92.3%, leading to a change in cancer staging in 33.3% of patients.[36] Furthermore, this study compared the performance of ^{18}F-fluorocholine relative to conventional bone scan and found it to have both better sensitivity (100% vs 90%) and specificity (86.4% vs 77.2%). At present, the use of ^{18}F-fluorocholine has not been approved by the FDA for use in prostate cancer imaging.[37]

^{18}F-fluciclovine

^{18}F-fluciclovine (Axumin, Blue Earth Diagnostics), also known as ^{18}F-FACBC, was approved by the FDA in 2016 as an alternative PET radiotracer for prostate cancer imaging.[38,39] This radiotracer is a synthetic amino acid that is largely taken into cells via sodium-dependent amino acid transporters, which are upregulated in prostate cancer.[40] Unlike ^{11}C-choline, which requires on-site radiotracer production, ^{18}F-fluciclovine has a physical half-life of 110 minutes and can be centrally produced and shipped to distant imaging sites. Additionally, this agent shows relatively little renal excretion and bladder activity, leading to a greater accuracy than choline-based radiotracers for detecting pelvic lymph node metastases.[41-43] Moreover, a multisite study found that ^{18}F-fluciclovine is well tolerated and able to detect local and distant prostate cancer recurrences across a wide range of PSA values.[44]

A large meta-analysis found that ^{18}F-fluciclovine has a sensitivity of 79.7% (95% CI, 51.9%-93.4%) and a specificity of 61.9% (95% CI, 41.1%-79.0%) for all sites of disease compared with reference standards such as pathology or follow-up imaging.[45] ^{18}F-fluciclovine uptake can be seen in both primary and metastatic sites of prostate cancer and has shown superiority to ^{11}C-choline.[46] One study found that the target-to-background ratio was greater with ^{18}F-fluciclovine than with ^{11}C-choline in 15 of 18 lesions imaged, meaning that the fluorinated radiotracer produced better image quality.[47] In the same study, the total detection rate of ^{18}F-fluciclovine was also greater, capturing approximately 60% more lesions than ^{11}C-choline and identifying disease in 20% more patients studied. In another study of patients with biochemical recurrence after definitive treatment for prostate cancer, ^{18}F-fluciclovine was found to be superior to ^{11}C-choline in detecting both local and distant sites of disease relapse.[48] Additionally, imaging with ^{18}F-fluciclovine has been shown to aid in treatment planning.[49-52] In one such study, the use of ^{18}F-fluciclovine in post-prostatectomy radiation therapy planning led to a change in target planning volume in 83% of lesions.[52] Additional studies have corroborated this finding and shown other significant impacts on radiotherapy decision management.[49-51] However, as with the other agents discussed, ^{18}F-fluciclovine has a nonspecific mechanism of uptake by other metabolically active cells. Thus, ^{18}F-fluciclovine is not cancer-specific, and uptake has been related to infection, areas of inflammation, benign bone lesions, and benign prostatic hyperplasia.[41] Like choline, ^{18}F-fluciclovine shows decreased sensitivity at PSA levels below 2 ng/mL.[37] Figure 2 includes representative images of a patient with biochemically recurrent prostate cancer that was imaged with ^{18}F-fluciclovine PET/CT.

PSMA-Targeted Radiotracers

PSMA is a type 2 transmembrane glycoprotein that is nearly universally expressed by prostate cancer cells.[53,54] PSMA expression is 100 to 1000 times greater in prostate cancer than in other tissues, including benign prostate cells.[41] Additionally, PSMA expression positively correlates with increasing tumor grade and stage.[55] Although PSMA has been studied extensively as an imaging target, no FDA-approved PET radiotracer targeting PSMA is currently available for routine clinical use.[2] It is worth noting that the ^{111}In-labeled PSMA-targeted antibody capromab pendetide (ProstaScint, Cytogen) is approved by the FDA for use with single-photon emission computed tomography (SPECT)/CT scanning; however, owing to poor image quality, this single-photon imaging agent is uncommonly used.[56,57]

A number of PSMA-targeted PET radiotracers have been developed for prostate cancer imaging, including both antibody- and small molecule–based agents.[54] The class of agents that have been most extensively explored are the urea-based small molecule inhibitors of PSMA. Examples of these agents include ^{68}Ga-PSMA-11, ^{68}Ga-PSMA imaging and therapy (I&T), ^{18}F-PSMA-1007, and ^{18}F-DCFPyL.[37] The majority of the world literature on PSMA-targeted imaging has involved ^{68}Ga-PSMA-11.[41] However, an increasing body of data now exists for ^{18}F-PSMA-1007 and ^{18}F-DCFPyL.[58,59] There are a number of advantages of fluorine-18 over gallium-68. Fluorine-18 has greater ease of production and distribution, as well as superior radiophysical properties.[60,61] In addition, ^{18}F-labeled small-molecule PSMA imaging performs at least comparably to ^{68}Ga-labeled agents in image quality and lesion detection ability. Furthermore, because of slower urinary excretion, it is less likely to accumulate rapidly in the bladder and obscure the prostate during imaging.[62] Applications also exist for antibody targeting of PSMA.[63] One of the most widely studied antibodies is J591, a monoclonal antibody that targets the extracellular domain of PSMA and has demonstrated safety in numerous human studies.[64] In addition to offering promise as an

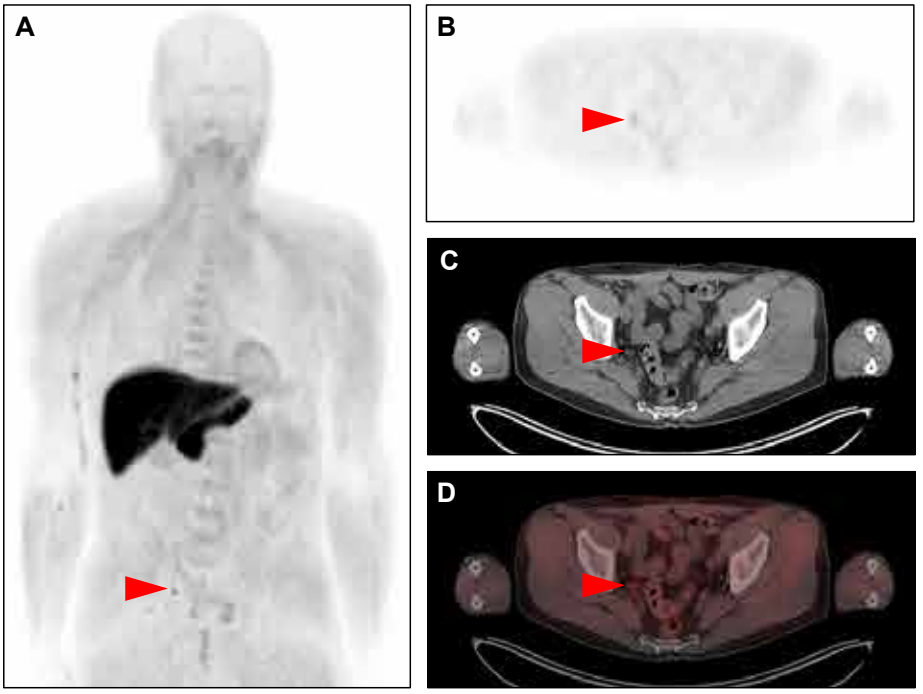

Figure 2. Representative images of a patient with biochemically recurrent prostate cancer and negative conventional imaging findings who was found on ^{18}F-fluciclovine PET/CT to have a lymph node metastasis.

A, Whole-body maximum intensity projection image from the ^{18}F-fluciclovine PET demonstrating normal uptake in the liver, pancreas, skeletal muscles, and bone marrow, as well as focal uptake in the right side of the pelvis. **B**, Axial PET. **C**, Axial attenuation-correction CT. **D**, Axial fused PET/CT images from the same study show that the uptake in the right pelvis corresponds to a 7-mm short-axis right internal iliac lymph node, likely representing a site of recurrent disease.

CT, computed tomography; PET, positron emission tomography.

imaging agent, J591 is being studied as a means to deliver radiotherapy with effective antitumor activity.[65,66]

The performance of PSMA-targeted ligands has been studied in the setting of biochemical recurrence. A retrospective study of 319 patients evaluated the diagnostic value of ^{68}Ga-PSMA-11 PET/CT during biochemical recurrence and found a sensitivity of 76.6% and a specificity of 100%.[67] The utility of ^{68}Ga-PSMA-11 PET/CT in this setting was further demonstrated in an Australian study evaluating its impact on management.[68] In 431 patients with biochemical recurrence, the radiotracer revealed disease in the prostate bed in 27% of patients, locoregional lymph nodes in 39%, and distant metastatic disease in 16%. Further, this analysis found that this additional scan changed the management plan in 51% of patients. When compared with other molecular imaging agents, PSMA-targeted imaging appears to offer higher sensitivity than that afforded by ^{11}C-choline or ^{18}F-fluciclovine PET/CT imaging, along with higher levels of specificity. In a head-to-head comparison of ^{68}Ga-PSMA-11 and ^{18}F-fluoromethylcholine (an ^{18}F-labeled choline derivative) in patients with biochemically recurrent prostate cancer, the PSMA-targeted ligand showed superior overall performance.[69] More specifically, of the 37 patients included in this analysis, ^{68}Ga-PSMA-11 PET/CT found 78 lesions in 32 patients (86%), whereas ^{18}F-fluoromethylcholine detected 56 lesions in 26 patients (70%). Notably, each lesion detected by ^{18}F-fluoromethylcholine was also detected by ^{68}Ga-PSMA-11. Further, the tumor-to-background ratio for the PSMA-targeted tracer compared with ^{18}F-fluoromethylcholine was more than 10% higher in 94.9% of lesions. This study also found that the PSMA-11 radiotracer performed relatively well at low PSA levels. More specifically, ^{68}Ga-PSMA-11 PET/CT detected prostate cancer lesions in 68.8% of patients with PSA levels less than 2.82 ng/mL, whereas ^{18}F-fluoromethylcholine detected lesions in only 43.8% of these patients. As with ^{11}C-choline and ^{18}F-fluciclovine, however, the sensitivity of PSMA-targeted radiotracers correlates directly with serum PSA levels.[37] In another comparative study of 38 patients with biochemical recurrence, 26 scans in total were positive for disease; of these, 14 were positive with

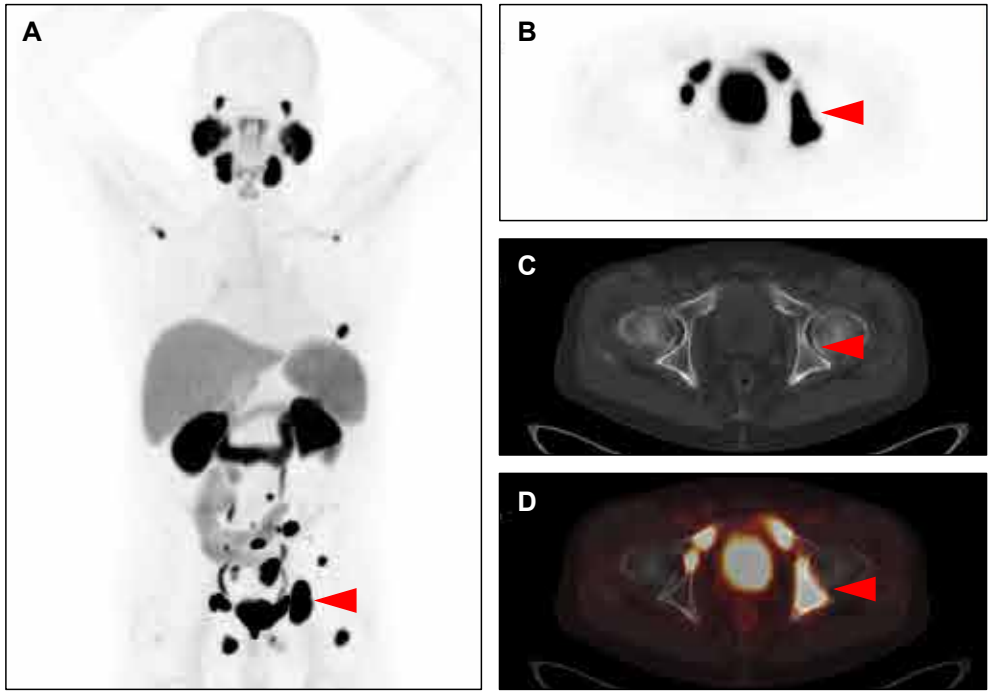

Figure 3. Representative images of a patient with metastatic prostate cancer imaged with PSMA-targeted ^{18}F-DCFPyL PET/CT. **A**, Whole body maximum intensity projection image from the ^{18}F-DCFPyL PET demonstrating numerous skeletal metastases, with the largest lesion in the left pelvis. **B**, Axial PET. **C**, Axial attenuation-correction CT. **D**, Axial fused PET/CT images from the same study indicate extensive pelvic involvement, although the lesions are not well appreciated on CT.

CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

^{68}Ga-PSMA-11 PET alone, 11 were positive with both ^{68}Ga-PSMA-11 and ^{18}F-fluoromethylcholine, and only 1 was positive with ^{18}F-fluoromethylcholine alone.[70] Furthermore, at PSA levels less than 0.5 ng/mL, the detection rate was 50% for ^{68}Ga-PSMA-11 PET, but only 12.5% for the choline-based tracer. Additional studies have corroborated this result, finding relatively higher detection rates for PSMA-targeted ligands than for choline-targeted ligands at lower PSA levels.[71-74]

In the setting of lymph node metastases, studies of PSMA-targeted PET imaging have generally demonstrated very high specificity combined with moderate sensitivity.[61,75-77] For example, in a study comparing the use of conventional CT and bone scan with PSMA-targeted ^{18}F-DCFPyL PET/CT, 139 sites of PET-positive metastatic disease were detected vs 45 lesions using conventional methods.[78] This study also found that 72% of negative or equivocal lesions identified using conventional methods were found to be positive using PET, and only 3% of negative or equivocal PET lesions were positive on conventional imaging. Similar results were found in a study comparing ^{68}Ga-PSMA-11 PET/CT with ^{99m}Tc-MDP bone scintigraphy.[79] In this study, 126 patients were imaged with both methods and PSMA-targeted imaging greatly outperformed bone scan, with sensitivities of 98.7% to 100% for ^{68}Ga-PSMA-11 PET/CT compared with 86.7% to 89.3% for ^{99m}Tc-MDP bone scintigraphy, and specificity was 88.2% to 100% for ^{68}Ga-PSMA-11 PET/CT and 60.8% to 96.1% for the conventional bone scan. Figure 3 includes representative images of a patient with metastatic prostate cancer imaged with the PSMA-targeted radiotracer ^{18}F-DCFPyL.

Although the majority of research with PSMA-targeted radiotracers has been in the setting of recurrent and/or metastatic disease, recent studies have evaluated their efficacy in primary staging.[80-83] In one study evaluating ^{68}Ga-PSMA-11 PET/CT prior to radical prostatectomy, significant correlations were seen between peak radiotracer uptake and Gleason score as well as tumor volume.[84] Sensitivity and specificity were 94.7% and 75.0%, respectively, with regard to tumor infiltration of individual prostate lobes. In another study of 50 treatment-naive patients with prostate cancer prior to radiation therapy, ^{68}Ga-PSMA-11 PET/CT was used in addition to conventional imaging to determine its impact on therapeutic management.[85] In this cohort, PSMA-targeted PET/CT imaging changed the tumor, node, metastasis (TNM) stage and the radiotherapeutic plan in 26% and 44% of patients, respectively. Another study of preoperative staging, this time evaluating ^{18}F-DCFPyL PET/CT, found a patient-

level sensitivity of 71.4% (95% CI, 29.0%-96.3%) and specificity of 88.9% (95% CI, 65.3%-98.6%) for detecting one or more pelvic uptake sites among men with negative conventional imaging findings and clinically localized high-risk prostate cancer.[86]

Other promising clinical applications of PSMA imaging are on the horizon. For instance, intraprocedural detection of sites of radiotracer uptake can potentially aid in performing biopsies or surgery.[87] It has already been shown that use of ^{111}In-labeled PSMA-I&T and an intraoperative gamma probe can improve the detection of small subcentimeter pelvic lymph nodes.[88] In addition, ^{111}In-PSMA-I&T has been successfully applied to preoperative SPECT/CT visualization and radioguided resection of PSMA-positive lesions.[89] With further study, in situ visualization of this sort holds great potential for better guidance of surgical treatment of prostate cancer.

Other Experimental Agents

Another class of PET radiotracers under investigation for prostate cancer imaging that is worthy of mention is the bombesin analogues that bind with high affinity to gastrin-releasing peptide receptor (GRPR)–expressing cells.[90] The first study in humans of a ^{68}Ga-labelled bombesin antagonist that evaluated safety, tolerability, pharmacokinetics, biodistribution, and dosimetry was published in 2013.[91] This study found the radiotracer to be safe, with rapid metabolism in circulation. It also found that it would be feasible from a radiation safety perspective to perform the scan in a single person multiple times per year. Another study of a different bombesin analogue in 14 men scheduled for radical prostatectomy or with biochemical recurrence found a sensitivity and specificity of 88% and 81%, respectively.[92] These and other early clinical studies of GRPR-targeting bombesin analogues show promise.[93,94]

PET-visible radiotracers linked to androgen analogues are another group of imaging agents currently under investigation.[95] An early study of the feasibility of one such metabolite, 16-beta-^{18}F-fluoro-5-alpha-dihydrotestosterone (^{18}F-FDHT), found that it localized to tumor sites in patients with metastatic prostate cancer, and may be a promising agent for the determination of androgen receptor status.[96] Another study of 19 men using the same molecule found that ^{18}F-FDHT PET had a patient-level sensitivity of 63% for all sites of disease, and detected an additional 17 unsuspected lesions compared with conventional imaging.[97] Relatively few other clinical data are available at present concerning the sensitivity and specificity of this class of radiotracer.[98] One study did, however, find that high FDHT uptake is potentially a useful biomarker in men with castration-resistant prostate cancer, with uptake being associated with shorter overall survival.[99]

Conclusion

It is crucial when managing men with prostate cancer to have the best available information about the location and extent of disease. New molecular imaging agents have been developed that show considerable promise in addressing the limitations of conventional imaging modalities. Prostate-specific PET radiotracers, such as PSMA-targeted agents, offer the potential to provide more-reliable imaging throughout the progression of the disease and represent a significant step forward in the care of men with prostate cancer.

Disclosures

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