Role of molecular imaging in the detection of localized prostate cancer

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Abstract: Molecular imaging of prostate cancer continues to grow, with recent inclusion of several positron emission tomography (PET) radiotracers into the recent National Comprehensive Cancer Network guidelines and the US Food and Drug Administration approval of prostate-specific membrane antigen (PSMA)-targeted radiotracers. While much of the work for many of these radiotracers is focused on systemic staging and restaging in both newly diagnosed high-risk prostate cancer and biochemically recurrent disease patients, the potential role of molecular imaging for the detection of localized prostate cancer has not yet been fully established. The primary aim of this article will be to present the potential role for molecular imaging in the detection of localized prostate cancer and discuss potential advantages and disadvantages to utilization of both PET/computed tomography (CT) and PET/magnetic resonance imaging (MRI) for this clinical indication of use.

Introduction

Prostate cancer remains the most common non-cutaneous malignancy in men, with an estimated 248,530 new cases and 34,130 deaths in the United States during the year 2021.[1] A commonly utilized screening method for the detection of prostate cancer is serum prostate-specific antigen (PSA) assessment. This serum test evaluates for elevated levels of the biomarker, which is elevated in patients with prostate cancer. However, PSA levels can also be elevated in cases of benign prostatic hyperplasia (BPH) and prostatitis. Obtaining 10–12 tissue cores using a systematic, template-based approach during transrectal ultrasonography-guided biopsy (TRUS-biopsy) of the prostate has historically been the standard-of-care approach to sampling tissue for pathologic detection of prostate cancer in patients with elevated serum PSA levels. However, this method often fails to detect clinically significant prostate cancer while overdiagnosing clinically insignificant cancers.[2,3] The use of multiparametric magnetic resonance imaging (mpMRI) to identify suspicious lesions within the prostate gland before biopsy has the potential to reduce unnecessary biopsy in

men given its high negative predictive value in addition to reducing the overall detection of clinically insignificant cancer.[2–5] In addition, mpMRI boosts a higher sensitivity than TRUS-biopsy alone for identifying clinically significant prostate cancer that is most commonly defined as Gleason Grade Group 2 or greater adenocarcinoma.[2,4,6] Moreover, targeted biopsy specifically addressing lesions deemed suspicious by prebiopsy mpMRI is superior to standard TRUS-biopsy in diagnosing clinically significant prostate cancer.[7–9]

Historically, molecular imaging has long played a role in the imaging of patients with known prostate cancer, from the earliest planar imaging with [111In]capromab pendetide (ProstaScint) to recent advances in positron emission tomography (PET)/computed tomography (CT), including [18F]fluciclovine, [11C]choline, and a variety of different prostate-specific membrane antigen (PSMA) radiotracers. These radiotracers offer substantial improvements in detection of localized and metastatic disease when compared with conventional anatomic imaging with CT and mpMRI.[10–13] To date, the majority of PET

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imaging for prostate cancer has been embraced in the setting of biochemically recurrent disease following a prior therapeutic intervention and primary staging in patients with clinically higher risk disease states already diagnosed. However, the role of molecular imaging to aid in the primary detection of localized prostate cancer has yet to be fully explored and early reports of PET and MRI image-guided, biopsy-free treatment algorithms suggest this approach is potentially feasible.[14] The primary focus of this article will be to review the nuclear medicine radiotracers used in imaging prostate cancer and their potential role as both PET/CT and PET/MRI to guide diagnosis of localized primary prostate cancer.

PET radiotracers used for prostate cancer imaging

[11C]choline

[11C]choline was one of the earliest PET radiotracers approved for use in imaging of patients with prostate cancer. This radiotracer utilizes choline, a substrate for cell membrane synthesis, which is upregulated in prostate cancer cells.[15] Currently, [11C]choline is approved by the US Food and Drug Administration (FDA) for use in detection of biochemically recurrent prostate cancer and has been incorporated into the National Comprehensive Cancer Network (NCCN) guidelines.[16] The radionuclide is produced in a cyclotron and has a half-life of 20 min, which limits it potential geographic distribution and utilization.

[18F]fluciclovine

[18F]fluciclovine is a synthetic amino acid PET radiotracer that was FDA-approved in 2016 for use in biochemically recurrent prostate cancer.[17,18] Subsequently, it was incorporated into the NCCN guidelines for imaging patients with biochemically recurrent prostate cancer.[16] The molecular target for fluciclovine is the LAT1 and ACST2 transmembrane transporters, both of which are upregulated in prostate cancer cells but can also be found in other neoplastic tissues.[19–21] Unlike other PET radiotracers used in imaging of prostate cancer, a known advantage of fluciclovine is little urinary excretion, which can be helpful in evaluating findings in the pelvis. As with other 18F-labeled radiotracers, the half-life of fluciclovine is 110 min allowing for a wider geographic distribution and potential for off-site production.

PSMA-PET radiotracers

Considerable work has been done in recent years evaluating the potential use of PSMA-targeted radiotracers in patients with prostate cancer. PSMA is a transmembrane protein that is overexpressed by prostate cancer cells and was the original molecular target of [111In]capromab pendetide. The initial PSMA-targeted radiotracer was limited due to targeting of the intracellular domain of the protein, but newer PSMA-PET radiotracers target the extracellular domain and allow for improved diagnostic performance.[13]PSMA-PET radionuclides have been develop that utilize both 18F and 68Ga. For 68Ga-labeled radiotracers, the half-life is 68 min and unlike other PET radiotracers used in prostate cancer, this radionuclide is produced from a 68Ge/68Ga generator and not a cyclotron. For 18F-labeled radiotracers, the half-life is 110 min and like other radiotracers tagged with 18F, the radioisotope is produced in a cyclotron. In addition, while other PET radiotracers used in prostate cancer have only been approved for use in biochemically recurrent prostate cancer, PSMA radiotracers have been FDA-approved for use in both initial staging of high-risk disease and biochemically recurrent prostate cancer with inclusion into recent NCCN guidelines.[16] Data are currently limited in regards to diagnostic performance between different PSMA radiotracers, but a practical advantage of 18F over 68Ga radiotracers is that the longer half-life of 18F allows for easier distribution due to slower radioactive decay and may enable remote sites separate from urban areas and/or academic medical centers to perform these exams.

PET/CT for detection of localized prostate cancer

In current clinical practice, PET/CT is seldom utilized for detection of localized or suspected prostate cancer. This is likely due to many factors, including cost and poor soft tissue characterization when compared with mpMRI. However, there is potential value of PET/CT for the detection of primary localized prostate cancer. An initial study evaluating the potential use of [18F]choline-PET/CT found that dual phase PET (7 min after injection and 1-h delayed images) demonstrated persistent PET radiotracer uptake in areas of cancer while areas of benign prostatic hypertrophy demonstrated washout of radiotracer over time.[22] In a study comparing the potential use of [11C]choline-PET/CT for tumor localization to systematic 12-core biopsy found

that choline-PET/CT demonstrated 83% sensitivity for localization of nodules 5 mm or greater in size and that choline-PET/CT demonstrated similar sensitivity for detection of any cancer focus.[23] Additional research has also demonstrated the potential for choline-PET/CT to characterize aggressiveness of the primary prostate cancer, with higher tumor-to-benign prostate background ratios in aggressive lesions.[24,25]

Fluciclovine has also been evaluated for potential use in the detection of primary prostate cancer (Figure 1). Early studies suggested that fluciclovine played a role for detection of primary prostate cancer with a reported sensitivity and specificity of 92.5% and 90.1%, respectively.[26,27] Additional studies suggest that fluciclovine and [^{11}C]choline have similar sensitivity and specificity for the detection of the primary prostate cancer.[28] The most rigorous study evaluating the potential use of fluciclovine PET/CT for detection of primary prostate cancer was the FLUCIPRO trial, a prospective clinical trial which demonstrated a PET/CT sensitivity of 87% with a specificity of 56%.[29] A quantitative analysis of the findings of this study found that the maximum standardized uptake value (SUV_{max}) was significantly higher for those with clinically significant prostate cancer when compared with those with Gleason $3 + 3 = 6$ prostate cancer. An additional recent study evaluating the use of fluciclovine-PET/CT for localization of primary prostate cancer prior to prostatectomy found that fluciclovine-PET had a sensitivity of 40% and a specificity of 99%.[30] While the diagnostic performance of studies utilizing fluciclovine for this application vary, the reason is not totally clear. However, fluciclovine PET/CT is somewhat challenging to read and the interpretation criteria have evolved since its inception. Thus, as different studies utilize different thresholds and/or variations of the interpretation criteria, it would be expected that diagnostic performance would vary over time.

Several studies have evaluated the use of PSMA radiotracers for the detection of prostate cancer. An early study combining the use of PSMA-PET/CT and mpMRI found that the combination of both modalities lead to improved diagnostic accuracy *versus* either alone.[31] Additional studies have confirmed that the combination of findings on PSMA-PET/CT and mpMRI improve the diagnostic performance for detection of primary prostate cancer.[32] A head-to-head analysis of

Figure 1. Male in his mid-60s with newly diagnosed Gleason $4 + 4 = 8$ prostate cancer undergoes fluciclovine-PET/CT for initial staging of high-risk disease. PET/CT images demonstrate intense focal activity in the right midgland peripheral zone (arrow), corresponding to the location of the patient's biopsy-proven prostate cancer.

PSMA-PET/CT and mpMRI found that the modalities had similar accuracy for detection of prostate cancer, with mpMRI outperforming PET/CT for diagnosis of extraprostatic extension and seminal vesicle invasion likely due to superior spatial resolution.[33] However, additional studies demonstrate higher sensitivity for extracapsular extension when compared with mpMRI.[34] A retrospective analysis of patients who underwent PSMA-PET and mpMRI prior to treatment found that while mpMRI detected a similar number of prostate cancer when compared with PSMA-PET, the gross tumor volume detected by PSMA-PET was approximately twice that of mpMRI.[35] Thus, of the PET radiotracers available for routine clinical use, PSMA radiotracers offer the most potential for the diagnosis of localized prostate cancer.

Potential disadvantages of PET/CT for detection of localized prostate cancer

A major limitation in the use of PET/CT for detection of localized prostate cancer is the ability to accurately differentiate benign prostatic tissue and prostate cancer. In addition, while PET/CT remains a widely utilized tool in oncologic molecular imaging, the CT component of the exam (even if performed with administration of intravenous contrast) is primarily utilized for anatomic co-localization. Contrast-enhanced CT is less sensitive for the detection of prostate cancer
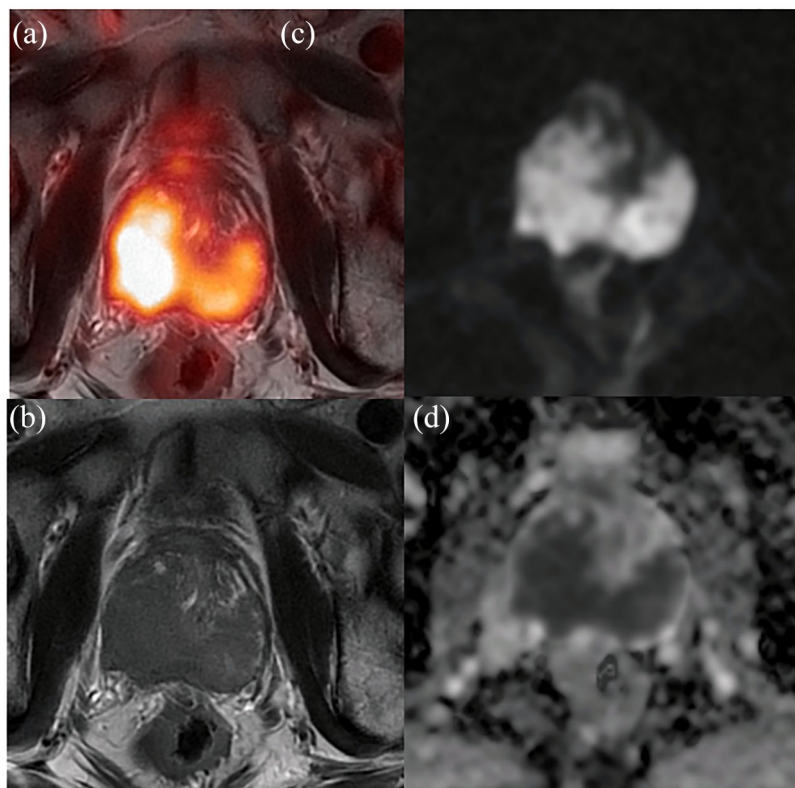
Figure 2. Male in his early 50s with newly diagnosed Gleason 5 + 4 = 9 prostate cancer undergoes PSMA-PET/MRI for initial staging of high-risk disease. (a) Fused PSMA-PET/MRI, (b) axial T2-weighted, (c) b2000 diffusion-weighted, and (d) absolute diffusion coefficient images demonstrate focal T2 hypointensity throughout the bilateral peripheral zone with corresponding marked diffusion restriction and increased tracer activity, consistent with the patient's biopsy-proven prostate cancer.

within the gland when compared with mpMRI, but some studies suggest that focal mass-like enhancement can correlate with underlying prostate cancer.[36,37] Concomitantly, acquired PET imaging data may increase reader confidence and detection of the findings within the prostate gland, but both [11C]choline and fluciclovine demonstrate increased activity within both BPH and prostate cancer.[29,30,38,39] Practically, many centers choose to perform most if not all oncologic PET/CT as noncontrast CT examinations, which render the CT component inadequate for characterization of uptake in the prostate gland.

PSMA radiotracers offer the potential to improve characterization of findings within the prostate gland with improved discrimination between benign and malignant prostate tissues due to differential PSMA expression.[40] However, it is known that approximately 10% of prostate cancers do not overexpress PSMA and would not be best imaged by PSMA radiotracers.[41] Also, given the nonsimultaneous acquisition of the PET and CT images, potential misregistration errors may occur when fusing the images. Excreted radiotracer within the urinary bladder may obscure portions of the prostate gland, a problem more notable with some PSMA radiotracers *versus* fluciclovine. Finally, while PET/CT is a widely utilized tool in oncologic imaging, it is an expensive modality and has less widespread availability when compared with CT or mpMRI. Thus, given the frequency in which prostate cancer is diagnosed and/or suspected, it is simply not currently possible that all patients undergo PET/CT for detection of their prostate cancer.

Potential applications of PET/MRI for detection of localized prostate cancer

PET/MRI is a novel imaging modality that combines the superior soft tissue characterization offered by MRI with the molecular imaging information obtained by PET. In addition, unlike PET/CT, PET/MRI images are acquired simultaneously and offer substantial improvement with potential issues with image fusion misregistration. Given the increasing utilization of mpMRI for the diagnosis and staging of prostate cancer, there is considerable interest in utilizing PET/MRI for prostate cancer (Figure 2). Given the aforementioned limitations of PET radiotracer uptake in both benign and malignant prostatic lesions, and suboptimal performance of mpMRI, it is sensible that combining the strengths of both imaging modalities may provide a superior exam to either alone. In addition, while not the focus of this article, it is well known that PET radiotracers can detect smaller lymph node metastases than either CT or MRI, which is advantageous in staging. However, mpMRI remains the best imaging modality available for evaluation of extracapsular extension and seminal vesicle invasion and remains the imaging gold standard for local primary T-staging.[33]

Multiple studies have evaluated the use of PET/MRI in the evaluation and detection of prostate cancer. A recent study of 14 patients with known prostate cancer, who underwent fluciclovine-PET/MRI prior to any treatment found a high correlation between PET and MRI findings.[42] As stated previously, while fluciclovine uptake

can be seen in both BPH nodules and malignant lesions, these two entities are often easily distinguishable on PET/MRI and can lead to superior characterization of intraprostatic findings (Figure 3).[43] PSMA-PET/MRI has been shown to demonstrate improved sensitivity for the detection of prostate cancer when compared with mpMRI alone.[44] In addition, PET/MRI compared with PET/CT imaging has shown to provide a better volumetric assessment of tumor burden when compared with radical prostatectomy pathology.[45] Another area of interest is the potential use of PET to further characterize lesions classified as PI-RADS 3 (indeterminate for clinically significant prostate cancer). This was confirmed in a recent study of 99 men who underwent PSMA-PET/MRI, where little benefit was seen in patients with PI-RADS 4 and 5 lesions, but the most benefit was gained in patients with indeterminate PI-RADS 3 lesions.[46] Finally, while not yet studied extensively, some research suggests that utilization of PET/MRI for detection of clinically significant prostate cancer may be cost-effective in relation to standard-of-care.[47] However, these systems are extremely limited and only available at select medical centers, limited potential use as a first-line imaging modality.

Use of PET for targeted biopsy guidance

A potential niche use for PET/CT in the detection of localized prostate cancer is for targeted biopsy guidance. While systematic templated nontargeted biopsies remain the mainstay of diagnosis, there is considerable increasing utilization of mpMRI to guide targeted biopsies.[4,7,9] However, the diagnostic performance of mpMRI is variable between studies and mpMRI can demonstrate both false-positive and false-negative results.[2,4,7] A commonly encountered clinical scenario is a patient with an elevated PSA with multiple negative prior biopsies, often including mpMRI-targeted biopsies and/or saturation biopsies. In these patients, potential biopsy guidance from molecular imaging may prove useful in establishing a diagnosis.

Both fluciclovine and PSMA radiotracers have been studied in detection and staging of treatment-naïve prostate cancer and show potential.[10,29,48–51] Fluciclovine-guided biopsies for recurrent prostate cancer have been studied and the approach is feasible, improving on template
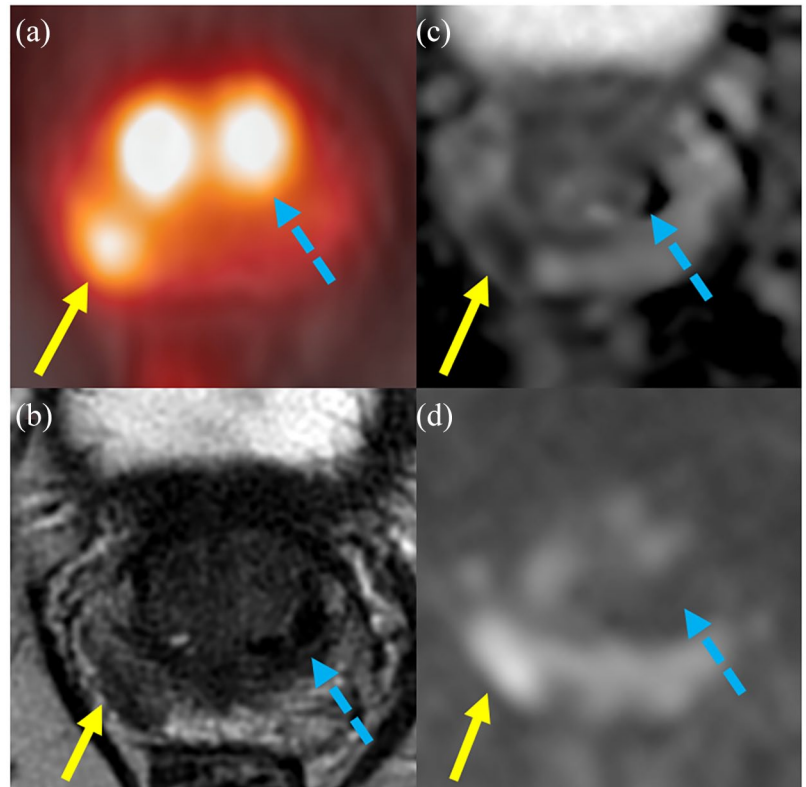

Figure 3. Male in his late 70s with newly diagnosed Gleason 4 + 3 = 7 prostate cancer undergoes fluciclovine-PET/MRI for initial staging of his high-risk disease. (a) Fused fluciclovine PET/MRI, (b) axial T2-weighted, (c) b2000 diffusion-weighted, and (d) absolute diffusion coefficient images demonstrate focal tracer activity in the right peripheral zone with a corresponding PI-RADS 5 lesion (solid arrow), consistent with the patient's known prostate cancer. Of note, symmetric increased tracer activity in the transition zone without corresponding suspicious lesion on MR images (dotted arrow) was consistent with benign prostatic hyperplasia.

biopsy alone.[52,53] Similar work has been done with PSMA radiotracers, including the PRIMARY trial, which demonstrated that inclusion of PSMA-PET in biopsy guidance led to improved negative predictive value compared with mpMRI alone.[54] Thus, while not currently a cost-effective approach, the combination of PET- and mpMRI-guided biopsy can be considered in select patients to adequately rule in or rule out the presence of clinically significant prostate cancer.

In addition, prostate cancer directed PET imaging has been used for guidance of targeted biopsy by means of cognitive and software-based image fusion. Reports from multiple groups have demonstrated the successful use of PET avid lesion co-localization with real-time TRUS for a directed sampling biopsy of the PET imaging areas of

cancer suspicion within the prostate gland.[51,55–59] The basic tenets of using an imaging area of suspicion for targeting mimics the well-established methods of using image overlay, or fusion, to co-localize at the time of targeted biopsy sampling when done with mpMRI and TRUS, only now using PET avid lesions of suspicion as the targetable region of interest.[60] The areas of suspicion can be co-localized between the diagnostic PET imaging with its associated CT or mpMRI to draw the region of interest on any of the diagnostic scans performed. This region of interest is then displayed for cases of cognitive fusion or integrated into the image processing software for software-based fusion, to co-localize with the live TRUS imaging used at time of the targeted biopsy procedure.

Conclusion

The role of molecular imaging for patients with prostate cancer continues to evolve and grow. Given the recent approval of PSMA radiotracers, there is considerable work and many ongoing clinical trials being done in the field to assess how molecular imaging can help advance treatments for patients with prostate cancer. While not as common as initial staging and biochemical recurrence, there is a potential niche role for molecular imaging for detection of localized prostate cancer. This is especially true in particularly challenging clinical scenarios where initial mpMRI or additional imaging may demonstrate equivocal findings, but the increasing utilization of PET/MRI offers significant potential benefits and advantages over both mpMRI and PET/CT alone. However, at this time, it is unclear which patient population would benefit most from integration of molecular imaging into the initial diagnostic algorithm. It is possible that specifically for detection of localized prostate cancer, PET/MRI will be established as the primary imaging modality and research suggests this could potentially be a cost-effective approach. However, this approach may not be practical on a population level given the presence of PET/MRI typically only at larger academic medical centers for which further research and widespread adoption would be needed moving forward. In addition, while an increasing number of prostate cancer-related PET radiotracers continue to be approved for clinical use in various settings, the additional cost of these radiotracers is not insignificant and given how common prostate cancer is, would lead to an increase in related healthcare expenditures for these patients.

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