Role of molecular imaging in the detection of localized prostate cancer

Samuel J. Galgano, Janelle T. West and Soroush Rais-Bahrami

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.

Keywords: cancer staging, fusion biopsy, positron emission tomography (PET), prostatic adenocarcinoma

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. 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 ultrasound-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. 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. 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. Moreover, targeted biopsy specifically addressing lesions deemed suspicious by prebiopsy mpMRI is superior to standard TRUS-biopsy in diagnosing clinically significant prostate cancer.

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]fluorocholine, [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. To date, the majority of PET
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 its 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 \( ^{18} \)F-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 \([^{111}\text{In}]\)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 \( ^{18} \)F and \( ^{68} \)Ga. For \( ^{68} \)Ga-labeled radiotracers, the half-life is 68 min and unlike other PET radiotracers used in prostate cancer, this radionuclide is produced from a \( ^{68} \)Ge\(^{68} \)Ga generator and not a cyclotron. For \( ^{18} \)F-labeled radiotracers, the half-life is 110 min and like other radiotracers tagged with \( ^{18} \)F, 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 \( ^{18} \)F over \( ^{68} \)Ga radiotracers is that the longer half-life of \( ^{18} \)F 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 \([^{18}F]\)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 \([^{11}C]\)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. 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.

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. Additional studies suggest that fluciclovine and $[{\text{11C}}]$ choline have similar sensitivity and specificity for the detection of the primary prostate cancer. 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%. 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%. 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. 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. A head-to-head analysis of 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. However, additional studies demonstrate higher sensitivity for extracapsular extension when compared with mpMRI. 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. 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
within the gland when compared with mpMRI, but some studies suggest that focal mass-like enhancement can correlate with underlying prostate cancer.\(^{35,36}\) Concomitantly, acquired PET imaging data may increase reader confidence and detection of the findings within the prostate gland, but both \(^{11}\)C-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). PSMA-PET/MRI has been shown to demonstrate improved sensitivity for the detection of prostate cancer when compared with mpMRI alone. 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. 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. 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. 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. However, the diagnostic performance of mpMRI is variable between studies and mpMRI can demonstrate both false-positive and false-negative results. 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. Fluciclovine-guided biopsies for recurrent prostate cancer have been studied and the approach is feasible, improving on template biopsy alone. 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. 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.
cancer suspicion within the prostate gland. 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. 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.
diagnosis of prostate cancer. JAMA 2015; 313: 390–397.

4. Klotz L, Chin J, Black PC, et al. Comparison of multiparametric magnetic resonance imaging-targeted biopsy with systematic transrectal ultrasonography biopsy for biopsy-naive men at risk for prostate cancer: a phase 3 randomized clinical trial. JAMA Oncol 2021; 7: 534–542.

5. Siddiqui MM, George AK, Rubin R, et al. Efficiency of prostate cancer diagnosis by MR/ultrasound fusion-guided biopsy vs standard extended–sixtiant biopsy for MR-visible lesions. J Natl Cancer Inst 2016; 108: djw039.

6. Gordetsky JB, Thomas JV, Nix JW, et al. Higher prostate cancer grade groups are detected in patients undergoing multiparametric MRI-targeted biopsy compared with standard biopsy. Am J Surg Pathol 2017; 41: 101–105.

7. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018; 378: 1767–1777.

8. Drost FH, Osses D, Nieboer D, et al. Prostate magnetic resonance imaging, with or without magnetic resonance imaging-targeted biopsy, and systematic biopsy for detecting prostate cancer: a Cochrane systematic review and meta-analysis. Eur Urol 2020; 77: 78–94.

9. Klotz L, Pond G, Loblaw A, et al. Randomized study of systematic biopsy versus magnetic resonance imaging and targeted and systematic biopsy in men on active surveillance (ASIST): 2-year postbiopsy follow-up. Eur Urol 2020; 77: 311–317.

10. Alemozaffar M, Akintayo AA, Abiodun-Ojo OA, et al. [(18)F]fluciclovine positron emission tomography/computerized tomography for preoperative staging in patients with intermediate to high risk primary prostate cancer. J Urol 2020; 204: 734–740.

11. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020; 395: 1208–1216.

12. Zarzour JG, Galgano S, McConathy J, et al. Lymph node imaging in initial staging of prostate cancer: an overview and update. World J Radiol 2017; 9: 389–399.

13. Mena E, Black PC, Rais-Bahrami S, et al. Novel PET imaging methods for prostate cancer. World J Urol 2021; 39: 687–699.

14. Meissner VH, Rauscher I, Schwamborn K, et al. Radical prostatectomy without prior biopsy following multiparametric magnetic resonance imaging and prostate-specific membrane antigen positron emission tomography. Eur Urol. Epub ahead of print 6 December 2021. DOI: 10.1016/j.euro.2021.11.019.

15. Ackerstaff E, Giunde K and Bhuvalla ZM. Choline phospholipid metabolism: a target in cancer cells? J Cell Biochem 2003; 90: 525–533.

16. National Comprehensive Cancer Network. Prostate cancer, version 3.2020, https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf (accessed 2 February 2021).

17. Rais-Bahrami S, Efstathiou JA, Turnbull CM, et al. (18)F-fluciclovine PET/CT performance in biochemical recurrence of prostate cancer: a systematic review. Prostate Cancer Prostatic Dis 2021; 24: 997–1006.

18. Glaser ZA and Rais-Bahrami S. Fluciclovine positron emission tomography in the setting of biochemical recurrence following local therapy of prostate cancer. Transl Androl Urol 2018; 7: 824–830.

19. Segawa A, Nagamori S, Kanai Y, et al. L-type amino acid transporter 1 expression is highly correlated with Gleason score in prostate cancer. Mol Clin Oncol 2013; 1: 274–280.

20. Oka S, Okudaira H, Ono M, et al. Differences in transport mechanisms of trans-1-amino-3-[18F]fluorocyclobutanecarboxylic acid in inflammation, prostate cancer, and glioma cells: comparison with L-[methyl-11C]methionine and 2-deoxy-2-[18F]fluoro-D-glucose. Mol Imaging Biol 2014; 16: 322–329.

21. Hoyle JM, Lenzie A, Galgano SJ, et al. Synchronous malignancies identified by (18)F-fluciclovine positron emission tomography for prostate cancer: case series and mini-review. Clin Genitourin Cancer 2021; 19: e37–e40.

22. Kwee SA, Wei H, Sesterhenn I, et al. Localization of primary prostate cancer with dual-phase 18F-fluorocholine PET. J Nucl Med 2006; 47: 262–269.

23. Martorana G, Schiavina R, Corti B, et al. 11C-choline positron emission tomography/computerized tomography for tumor localization of primary prostate cancer in comparison with 12-core biopsy. J Urol 2006; 176: 954–960; discussion 960.

24. Pier M, Park H, Khan A, et al. Detection of aggressive primary prostate cancer with 11C-choline PET/CT using multimodality fusion techniques. J Nucl Med 2009; 50: 1585–1593.
25. Chen J, Zhao Y, Li X, et al. Imaging primary prostate cancer with 11C-choline PET/CT: relation to tumour stage, Gleason score and biomarkers of biologic aggressiveness. *Radiol Oncol* 2012; 46: 179–188.

26. Suzuki H, Inoue Y, Fujimoto H, et al. Diagnostic performance and safety of NMK36 (trans-1-amino-3-[18F]fluorocyclobutanecarboxylic acid)-PET/CT in primary prostate cancer: multicenter phase IIb clinical trial. *Jpn J Clin Oncol* 2016; 46: 152–162.

27. Sorensen J, Owenius R, Lax M, et al. Regional distribution and kinetics of [18F]fluorocitrate, a tracer of amino acid transport, in subjects with prostate cancer. *Eur J Nucl Mol Imaging* 2013; 40: 394–402.

28. Zanoni L, Mei R, Bianchi L, et al. The role of [(18)F]fluorocitric PET/CT in the characterization of high-risk primary prostate cancer: comparison with [(11)C]choline PET/CT and histopathological analysis. *Cancers* 2021; 13: 1575.

29. Jambor I, Kuisma A, Kahkonen E, et al. Prospective evaluation of (18)F-FACBC PET/CT and PET/MRI versus multiparametric MRI in intermediate- to high-risk prostate cancer patients (FLUCIPRO trial). *Eur J Nucl Med Mol Imaging* 2018; 45: 355–364.

30. Hole KH, Tulipan AJ, Reijnen JS, et al. Localization of primary prostate cancer: FACBC PET/CT compared with multiparametric MRI using histopathology as reference standard. *Am J Nucl Med Mol Imaging* 2021; 11: 387–394.

31. Jena A, Taneja R, Taneja S, et al. Improving diagnosis of primary prostate cancer with combined (68)Ga-prostate-specific membrane antigen-HBED-CC simultaneous PET and multiparametric MRI and clinical parameters. *Am J Roentgenol* 2018; 211: 1246–1253.

32. Zamboglou C, Drendel V, Jilg CA, et al. Comparison of (68)Ga-HBED-CC PSMA-PET/CT and multiparametric MRI for gross tumour volume detection in patients with primary prostate cancer based on slice by slice comparison with histopathology. *Theranostics* 2017; 7: 228–237.

33. Sonni I, Felker ER, Lenis AT, et al. Head-to-head comparison of (68)Ga-PSMA-11 PET/CT and mpMRI with histopathology gold-standard in the detection, intra-prostatic localization and local extension of primary prostate cancer: results from a prospective single-center imaging trial. *J Nucl Med* 2022; 63: 847–854.

34. Chen M, Zhang Q, Zhang C, et al. Comparison of (68)Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) and multiparametric magnetic resonance imaging (MRI) in the evaluation of tumor extension of primary prostate cancer. *Transl Androl Urol* 2020; 9: 382–390.

35. Spohn S, Jaegle C, Fassbender TF, et al. Intraindividual comparison between (68)Ga-PSMA-PET/CT and mpMRI for intraprostatic tumor delineation in patients with primary prostate cancer: a retrospective analysis in 101 patients. *Eur J Nucl Med Mol Imaging* 2020; 47: 2796–2803.

36. Jia JB, Houshyar R, Verma S, et al. Prostate cancer on computed tomography: a direct comparison with multi-parametric magnetic resonance imaging and tissue pathology. *Eur J Radiol* 2016; 85: 261–267.

37. Huang G, Lebovic G and Vlachou PA. Diagnostic accuracy of (68)Ga-PSMA-PET/CT in primary prostate cancer: multicenter PET/CT and mpMRI for intraprostatic tumor delineation in patients with primary prostate cancer: a retrospective analysis in 101 patients. *Eur J Nucl Med Mol Imaging* 2020; 47: 2796–2803.

38. Souvatzoglou M, Weirich G, Schwarzenboeck S, et al. The sensitivity of [11C]choline PET/CT to localize prostate cancer depends on the tumor configuration. *Clin Cancer Res* 2011; 17: 3751–3759.

39. Yoshida S, Nakagomi K, Goto S, et al. 11C-choline positron emission tomography in prostate cancer: primary staging and recurrent site staging. *Urol Int* 2005; 74: 214–220.

40. Lapidus RG, Tiffany CW, Isaacs JT, et al. Prostate-specific membrane antigen (PSMA) enzyme activity is elevated in prostate cancer cells. *Prostate* 2000; 45: 350–354.

41. Wright GL Jr, Haley C, Beckett ML, et al. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. *Urol Oncol* 1995; 1: 18–28.

42. Galgano SJ, McDonald AM, Rais-Bahrami S, et al. Utility of (18)F-fluciclovine PET/MRI for staging newly diagnosed high-risk prostate cancer and evaluating response to initial androgen deprivation therapy: a prospective single-arm pilot study. *Am J Roentgenol* 2021; 217: 720–729.

43. Elschot M, Selnaes KM, Sandmark E, et al. Combined (18)F-fluciclovine PET/MRI shows potential for detection and characterization of high-risk prostate cancer. *J Nucl Med* 2018; 59: 762–768.

44. Hicks RM, Simko JP, Westphalen AC, et al. Diagnostic accuracy of (68)Ga-PSMA-11 PET/
MRI compared with multiparametric MRI in the detection of prostate cancer. *Radiology* 2018; 289: 730–737.

45. Arslan A, Karaarslan E, Güner AL, *et al.* Comparison of MRI, PSMA PET/CT, and fusion PSMA PET/MRI for detection of clinically significant prostate cancer. *J Comput Assist Tomogr* 2021; 45: 210–217.

46. Margel D, Bernstine H, Groshar D, *et al.* Diagnostic performance of (68)Ga prostate-specific membrane antigen PET/MRI compared with multiparametric MRI for detecting clinically significant prostate cancer. *Radiology* 2021; 301: 379–386.

47. Barnett CL, Davenport MS, Montgomery JS, *et al.* (18)F-choline PET/mpMRI for detection of clinically significant prostate cancer: part 2. Cost-effectiveness analysis. *J Nucl Med* 2019; 60: 1705–1712.

48. Elschot M, Selnaes KM, Sandsmark E, *et al.* A PET/MRI study towards finding the optimal [(18)F]Fluciclovine PET protocol for detection and characterisation of primary prostate cancer. *Eur J Nucl Med Mol Imaging* 2017; 44: 695–703.

49. Hoffmann MA, Miederer M, Wieler HJ, *et al.* Diagnostic performance of (68)Gallium-PSMA-11 PET/CT to detect significant prostate cancer and comparison with (18)FEC PET/CT. *Oncotarget* 2017; 8: 111073–111083.

50. Jain H, Sood R, Faridi MS, *et al.* Role of 68Ga-PSMA-PET/CT for the detection of primary prostate cancer prior to biopsy: a prospective study. *Cent European J Urol* 2021; 74: 315–320.

51. Lopci E, Lughezzani G, Castello A, *et al.* Prospective evaluation of (68)Ga-labeled prostate-specific membrane antigen ligand positron emission tomography/computed tomography in primary prostate cancer diagnosis. *Eur Urol Focus* 2021; 7: 764–771.

52. Abiodun-Ojo OA, Akintayo AA, Akin-Akintayo OO, *et al.* (18)F-fluciclovine parameters on targeted prostate biopsy associated with true positivity in recurrent prostate cancer. *J Nucl Med* 2019; 60: 1531–1536.

53. Fei B, Abiodun-Ojo OA, Akintayo AA, *et al.* Feasibility and initial results: fluciclovine positron emission tomography/ultrasound fusion targeted biopsy of recurrent prostate cancer. *J Urol* 2019; 202: 413–421.

54. Emmett L, Buteau J, Papa N, *et al.* The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. *Eur Urol* 2021; 80: 682–689.

55. Piert M, Montgomery J, Kunju LP, *et al.* 18F-choline PET/MRI: the additional value of PET for MRI-guided transrectal prostate biopsies. *J Nucl Med* 2016; 57: 1065–1070.

56. Simopoulos DN, Natarajan S, Jones TA, *et al.* Targeted prostate biopsy using (68)gallium PSMA-PET/CT for image guidance. *Urol Case Rep* 2017; 14: 11–14.

57. Lazzeri M, Lopci E, Lughezzani G, *et al.* Targeted 11C-choline PET-CT/TRUS software fusion-guided prostate biopsy in men with persistently elevated PSA and negative mpMRI after previous negative biopsy. *Eur J Hybrid Imaging* 2017; 1: 9.

58. Fei B, Nieh PT, Master VA, *et al.* Molecular imaging and fusion targeted biopsy of the prostate. *Clin Transl Imaging* 2017; 5: 29–43.

59. Liu Y, Yu H, Liu J, *et al.* A pilot study of (18)F-DCFPyL PET/CT or PET/MRI and ultrasound fusion targeted prostate biopsy for infra-prostatic PET-positive lesions. *Front Oncol* 2021; 11: 612157.

60. Logan JK, Rais-Bahrami S, Turkbey B, *et al.* Current status of magnetic resonance imaging (MRI) and ultrasonography fusion software platforms for guidance of prostate biopsies. *BJU Int* 2014; 114: 641–652.