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Invited Perspective

PSMA-based ^{18}F-DCFPyL PET: a better choice than multiparametric MRI for prostate cancer diagnosis?

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Abstract: Owing to the high tissue contrast, multiparametric MRI (mpMRI) has already been the most widely applied imaging method for prostate cancer. Recently, prostate-specific membrane antigen (PSMA) ligands for nuclear imaging are emerging as a promising modality in prostate cancer, especially since the 2 PET/CT agents (^{68}Ga-PSMA-11 and ^{18}F-DCFPy) approved by U.S. Food and Drug Administration (FDA). However, limited studies have performed the comparison of mpMRI versus recently approved ^{18}F-DCFPyL PET/CT. In this issue of AJNMMI, Lu et al. compared the performance of ^{18}F-DCFPyL PET/CT and pelvic mpMRI in intermediate-high risk and biochemical recurrent prostate cancer patients. The results demonstrated the two modalities have a good concordance rate for patient-based analysis, and ^{18}F-DCFPyL PET/CT has a better diagnostic performance in detecting lymph node metastases and bone metastases for lesion-based analysis. The use of ^{18}F-DCFPyL PET/CT provides more diagnostic confidence to better assess prostate cancer lesions.

Keywords: ^{18}F-DCFPyL, multiparametric MRI, ^{68}Ga-PSMA-11, PSMA, PET

Introduction

Prostate cancer is one of the most common solid-organ malignancy in men, accounting for 27% of all new diagnoses [1]. Furthermore, the proportion of prostate cancer diagnosed at a distant stage has increased over the past decade, posing a great threat to patients' lives. Early diagnosis and accurate staging of patients with prostate cancer are critical to select suitable treatment.

For prostate cancer screening, serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE) are commonly used methods. The value of the PSA level is limited by poor specificity and the false positive of test can be caused by inflammation or hyperplasia. In addition, the early stages of the disease may be missed by DRE. Transrectal ultrasound-guided (TRUS) biopsy has proven to be an inadequate diagnostic modality for shortcomings of systematic sampling [2]. The above methods remain controversial in contemporary urology practice. Hence, clinical guidelines recommend the use of both nuclear medicine imaging (positron emission tomography [PET]) and magnetic resonance imaging (MRI) to assess local recurrence and distant metastases of prostate cancer [3].

Multiparametric MRI (mpMRI) is the current valuable tool for primary prostate cancer detection. It gives more accurate visualization and allows guidance for targeted prostate biopsies. However, it has been shown to miss pivotal tumor lesions and underestimates their volume. PSMA is a type II transmembrane protein that is highly expressed in most prostate cancer cells and a variety in normal prostate tissue [6]. Prostate-specific membrane antigen (PSMA)-PET is emerging as a promising modality to improve lesion detection, guiding biopsy, and non-invasive lesion delineation [3-5]. ^{111}In-capromab pendetide is a monoclonal antibody targeting PSMA labeled with indium-111, while limited by low specificity [7]. Based on the basic structure of glutamine-urea-lysine, PSMA

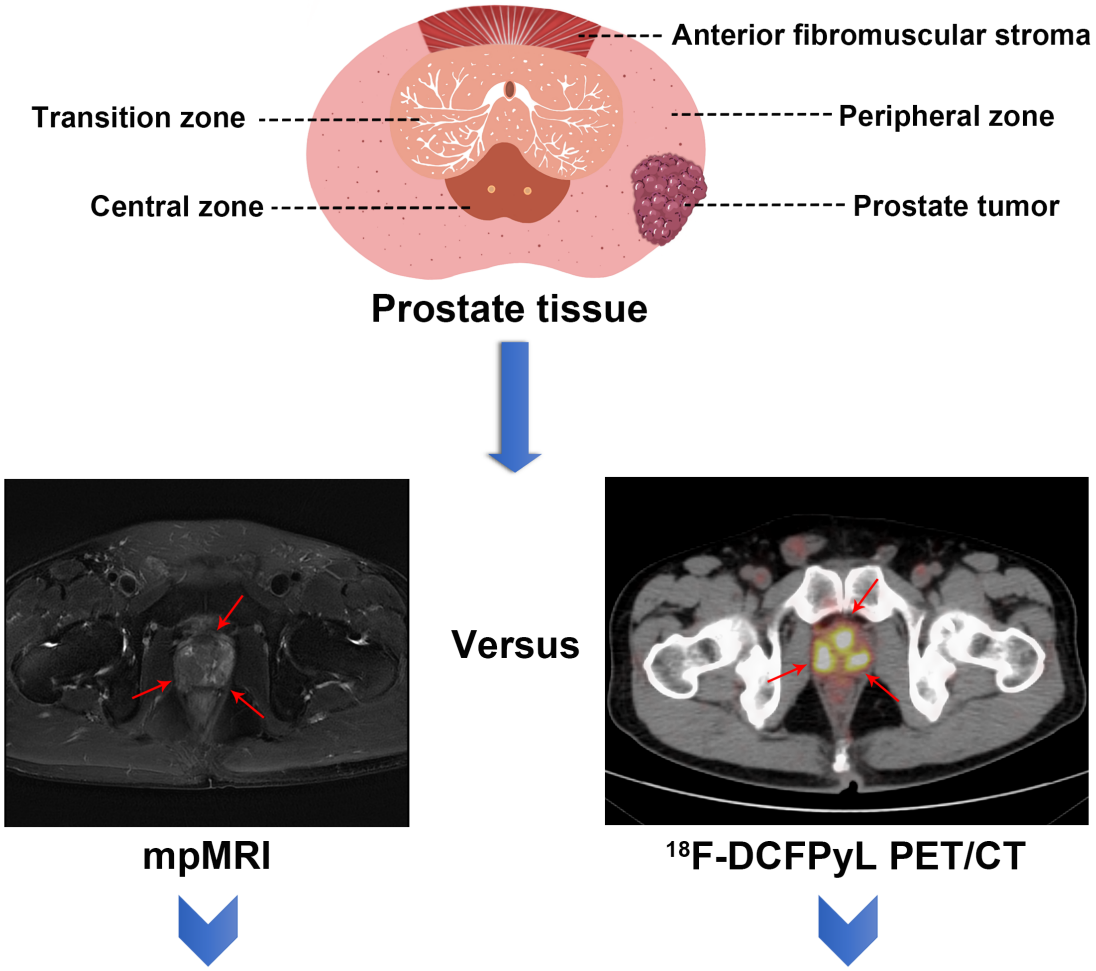
inhibitors with superior binding ability have been radiolabeled (^{68}Ga-PSMA-11, ^{68}Ga-PSMA-617, ^{68}Ga-PSMA-I&T, ^{68}Ga-PSMA-1007, ^{18}F-DCFPyL, ^{18}F-PSMA-1007, ^{18}F- and ^{68}Ga-rhPSMA-7) for wide application in prostate cancer [4, 8]. They demonstrated high sensitivity and specificity for the identification of recurrent detection and initial staging in patients with prostate cancer [9]. The diagnostic performance for regional and distant metastases between these PSMA-PET and mpMRI is expected to differ.

In December 2020, U.S. Food and Drug Administration (FDA) approved ^{68}Ga labeled PSMA targeting PET imaging drug (^{68}Ga-PSMA-11) [10]. The related prospective clinical trials demonstrated that ^{68}Ga-PSMA-11 was useful for accurate staging and recurrence detection in patients with prostate cancer [11, 12]. Sonni's group did a prospective head-to-head comparison of ^{68}Ga-PSMA-11 PET/CT and mpMRI [12]. They found PSMA PET/CT and mpMRI performed similarly in the detection and intraprostatic localization of prostate cancer foci, whereas mpMRI was superior for the definition of T stage (T2c, T3). In Yaxley's study, ^{68}Ga-PSMA-11 PET/CT detected more tumor foci (77.2% vs. 69.3%) and multifocal disease (22% vs. 12.5%) compared with mpMRI [13]. Zamboglou's study included 101 patients and showed that ^{68}Ga-PSMA-11 PET/CT depicts larger tumor volumes (median 4.9 ml vs. 2.8 ml) and more bilateral lesions (71 vs. 57) than mpMRI [14]. It allows the complementary use of ^{68}Ga-PSMA-11 PET/CT for biopsy guidance to improve coverage of intraprostatic tumor lesions. ^{68}Ga-PSMA-11 PET/CT also detected more lesions characteristic for recurrent prostate cancer compared to mMRI [15].

Subsequently, ^{18}F labeled PSMA inhibitor, ^{18}F-DCFPyL, was also approved by FDA in May 2021 [16]. For its longer half-life than ^{68}Ga-PSMA-11, ^{18}F-DCFPyL is preferred for scheduling patients and is easier to commercialize [17]. Besides, F-18 exhibits a lower positron emission energy of 0.6 MeV than Ga-68 (β+-energy = 2.3 MeV), demonstrating a shorter distance to decelerate the positron in human tissue resulting in a much higher image resolution [18]. Thus, ^{18}F-DCFPyL has quickly gained significant popularity in routine clinical scenarios. Though early clinical studies demonstrated promising results, the comparison of the performance of mpMRI versus ^{18}F-DCFPyL PET/CT is still needed to investigate.

Excitedly, in this issue of American Journal of Nuclear Medicine and Molecular Imaging, Lu and colleagues retrospectively analyzed the patients with ^{18}F-DCFPyL PET/CT and pelvic mpMRI within a 3-month interval [19]. They included 57 patients to compare the performance of paired exams. The findings were verified by follow-up pathology or other imaging methods. For patient-based analysis, the two modalities have a good degree of concordance (75.4%). For lesion-based analyses, they further categorized the lesions into prostate bed, pelvic lymph nodes and bone lesions (**Figure 1**). ^{18}F-DCFPyL PET/CT has a slightly higher specificity, positive predictive value (PPV) and negative predictive value (NPV) rate in detection lesions in prostate bed (100%, 100%, 90% vs. 94%, 98%, 89%), but without statistical significance. For pelvic lymph node and bone metastases, ^{18}F-DCFPyL PET/CT and mpMRI were statistically significant in lesion detections (pelvic lymph nodes, $P < 0.0001$; bone lesions, $P = 0.0026$). The study concluded that ^{18}F-DCFPyL display complementary roles in the clinical assessment of prostate bed lesions, with notably superior performance in the detection of small metastatic nodal and skeletal disease. Lindenberg and colleagues also found that ^{18}F-DCFPyL delineated more lymph nodes (128 vs. 23 nodes) and improved PPV and specificity when added to mpMRI [20]. They prospectively recruited 77 patients with biochemically recurrent prostate cancer and obtained the histologic samples for identification. Compared with mMRI, ^{18}F-DCFPyL also improved PPV (81% vs. 66%) and specificity (86% vs. 52%) in the identification of local recurrence.

Despite well designed and significant results, this study by Lu et al. has several limitations [19]. Firstly, it is a retrospective and single-center study, which may be insufficient to evaluate the diagnostic potential of the two imaging technologies. Furthermore, the enrolled patients were intermediate-high risk prostate cancer or those with biochemical recurrence, which lead to the study suffering from different degrees of bias. Yet their findings are of great value for the comparison of ^{18}F-DCFPyL PET/CT and pelvic mpMRI and further promote the clinical use of ^{18}F-DCFPyL PET/CT.



PSMA PET vs. mpMRI	Prostate bed		Lymph nodes		Bones	
	^{18}F-DCFPyL	mpMRI	^{18}F-DCFPyL	mpMRI	^{18}F-DCFPyL	mpMRI
Sensitivity	96%	96%	100%	52%	100%	86%
Specificity	100%	94%	100%	100%	98%	73%
PPV	100%	98%	100%	100%	95%	50%
NPV	90%	89%	100%	55%	100%	94%

Figure 1. MpMRI and ^{18}F-DCFPyL PET/CT imaging of prostate cancer. The table is concluded from Ref. [19]. PSMA-based ^{18}F-DCFPyL PET/CT showed a higher sensitivity and negative predictive value (NPV) rate in lymph nodes, as well as higher sensitivity, specificity, positive predictive value (PPV) and NPV in bones.

The head-to-head comparison of ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL for clinical use has also been carried out. In Dietlein's study, they selected patients with biochemically relapsed prostate cancer and performed both ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL PET/CT [18]. In 3 of 14 patients, ^{18}F-DCFPyL found additional lesions, displayed with a higher sensitivity. It also discovered a significantly higher SUVmax (14.5 vs. 12.2, P = 0.028, n = 15) and tumor to background ratios (using kidney, spleen, or parotid as reference organs; P = 0.006, P = 0.002, P = 0.008) in ^{18}F-DCFPyL PET than the ones in ^{68}Ga-PSMA-11 PET. They concluded that ^{18}F-DCFPyL is a valuable tool to detect relapsed prostate cancer lesions with favorable results.

With integrated PET/MR development, PSMA-PET/MR is gradually adopted in clinics. It combines high soft-tissue contrast resolution with molecular information of PSMA expression, which is conducive to better anatomic localization and biomarker's characterization of prostate lesions. Several comparative studies have also been performed between PSMA-PET/MR and mpMRI [21, 22]. MpMRI is limited by the signal alterations of the treated prostate cancer, especially after interventional therapy. And PSMA-PET is of limited use in a small portion (10%) of the patients, who do not express PSMA [21]. Bodar's group conducted a prospective study to compare the diagnostic accuracy of intermediate- to high-risk prostate cancer within the prostate gland between ^{18}F-DCFPyL PET/MRI and mpMRI imaging, as well as the ability to guide potential targeted prostate biopsies [22]. However, they found that ^{18}F-DCFPyL PET/MRI does not outperform mpMRI with the same detection (90.0%) of the highest Grade Group lesion at patient level. This may cause by the majority of patients being diagnosed using mpMRI targeted biopsy, which might favor results towards mpMRI. Burger et al. investigated ^{68}Ga-PSMA-11 PET/MRI in patients with negative mpMRI after high-intensity focused ultrasound therapy [21]. All tumor lesions with Gleason scores 4 + 3 or higher were detected on PET/MRI, preliminarily indicating the potential to localize the lesions occulted on mpMRI. Further investigation should be conducted to compare the value of PSMA-PET/MR and mpMRI.

Another advantage of PSMA-PET imaging is to select patients who may benefit from systemic targeted radionuclide therapy [23]. During the last 5 years, radioligand therapy with ^{177}Lu-PSMA has rapidly evolved as a highly promising treatment for patients with prostate cancer [24]. And on Jun 16, 2021, FDA granted Breakthrough Therapy designation (BTD) to ^{177}Lu-PSMA-617 (Pluvicto) as an investigational radioligand therapy for the treatment of metastatic castration-resistant prostate cancer (mCRPC) patients with positive PSMA [25]. Phase III studies demonstrated that ^{177}Lu-PSMA-617 significantly improved overall survival and radiographic progression-free survival for men with progressive PSMA-positive mCRPC [26]. On March 23, 2022, the FDA approved ^{177}Lu-PSMA-617 treatment for adult patients with PSMA-positive mCRPC treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. Clinically, ^{68}Ga-PSMA PET/CT imaging or ^{177}Lu-PSMA SPECT/CT imaging could perform first, followed by a therapeutic dose of ^{177}Lu-PSMA-617 for the targeted therapy of prostate cancer and its metastasis [27]. Targeted α-therapy with ^{225}Ac-PSMA-617, although still experimental, obviously has a strong potential to significantly benefit advanced-stage prostate cancer patients [28].

In addition to being highly expressed in prostate cancer cells, PSMA is also highly expressed in tumor-associated angiogenesis. Therefore, PSMA-PET/CT is of certain diagnostic value in tumors with vigorous neovascular growth, including kidney cancer, colorectal cancer, pancreatic cancer, lung cancer, bladder cancer, breast cancer and glioma [29]. High uptake of ^{68}Ga-PSMA can be found in high-grade gliomas with very vigorous neovascular growth, while low-grade gliomas have less neovascular growth, and the lesions have less or no uptake of ^{68}Ga-PSMA, thus contributing to the differentiation of low-grade and high-grade gliomas [30]. In addition, high uptake of ^{68}Ga-PSMA-11 can also be found in hepatocellular carcinoma with abundant blood supply, which can make up for the deficiency of ^{18}F-FDG PET/CT and improve the sensitivity and accuracy of PET/CT diagnosis of hepatocellular carcinoma [31]. Many other diseases are related to neoangiogenesis, including fibrous dysplasia, osteoarthritis, diabetic retinopathy, diabetic kidney disease, sarcoidosis, and cardiac remodeling.

Benefiting from the excellent specificity and sensitivity, PSMA-PET imaging has been applied at an unprecedented increase. Growing studies and trials have been performed on seeking the diagnostic value of ^{18}F-DCFPyL PET. Based on available preliminary data, one might conclude that PSMA-based ^{18}F-DCFPyL PET is of great potential for prostate disease and gives complementary benefits to mpMRI. The large-scale, prospective, and multi-center investigation should be further conducted for comparison by using histologic validation.

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Disclosure of conflict of interest

None.

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