Image acquisition and interpretation of 18F-DCFPyL (piflufolastat F 18) PET/CT: How we do it

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Prostate-specific membrane antigen (PSMA)-targeted positron emission tomography (PET) is rapidly becoming widely accepted as the standard-of-care for imaging of men with prostate cancer. Labeled indications for regulatoryapproved agents include primary staging and recurrent disease in men at risk of metastases. The first commercial PSMA PET agent to become available was 18F-DCFPyL (piflufolastat F 18), a radiofluorinated small molecule with high-affinity for PSMA. The regulatory approval of 18F-DCFPyL hinged upon two key, multi-center, registration trials, OSPREY (patient population: highrisk primary staging) and CONDOR (patient population: biochemical recurrence). In this manuscript, we will (1) review key findings from the OSPREY and CONDOR trials, (2) discuss the clinical acquisition protocol we use for 18F-DCFPyL PET scanning, (3) present information on important pearls and pitfalls, (4) provide an overview of the PSMA reporting and data system (PSMA-RADS) interpretive framework, and (5) posit important future directions for research in PSMA PET. Our overall goal is to provide a brief introduction for practices and academic groups that are adopting 18F-DCFPyL PET scans for use in their patients with prostate cancer.

Key Words: prostate-specific membrane antigen, PSMA, prostate cancer, OSPREY, CONDOR

Introduction

Prostate cancer is the second most common malignancy in men with more than one million new cases diagnosed worldwide each year.[1] Accurate diagnostic imaging for staging and re-staging of men with prostate cancer is paramount and this need has recently been at least partly addressed by the widespread adoption of radiotracers for positron emission tomography (PET) that target the prostate-specific membrane antigen (PSMA).[2] PET is the premier molecular imaging modality in a number of solid and hematologic malignancies, with high sensitivity and specificity based on its ability to interrogate both biochemical/metabolic processes and specific target expression.[3]

The first commercial PSMA PET agent to receive regulatory approval was ^{18}F-DCFPyL (piflufolastat F 18, PYLARIFY), a radiofluorinated small molecule with high affinity for PSMA.[4] Fluorine-18 is a radionuclide with that is produced on a cyclotron, has a 2-hour half-life, and undergoes near-universal decay by emission of low-energy positrons. This set of characteristics makes it the ideal PET radionuclide.[5] ^{18}F-DCFPyL can be manufactured in large batches at centralized

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cyclotron facilities and widely distributed, even in a geographically dispersed country such as the United States, Canada, or Australia. As such, PSMA PET imaging is becoming increasingly accessible for men in many parts of the world.

There have been two key, multi-center, United States Food and Drug Administration (FDA) registration trials with ^{18}F-DCFPyL, each of which has answered a different clinical question regarding the performance of the agent. The first was the OSPREY trial, which evaluated two cohorts of men with prostate cancer: 252 with newly diagnosed, high-risk prostate cancer planned to undergo radical prostatectomy with an extended pelvic lymph node dissection (Cohort A), and 93 patients with evidence of recurrent or metastatic prostate cancer on conventional imaging (Cohort B).[6] For Cohort A, ^{18}F-DCFPyL PET/CT was found to have moderate sensitivity (median 40.3% among three central readers) but very high specificity (median 97.9% among three readers) for the detection of pelvic nodal disease against a histopathologic gold standard.[6] As regards Cohort A, OSPREY missed the sensitivity co-primary endpoint but met the specificity co-primary endpoint. However, in a post hoc analysis in which very small lymph nodes (≤ 0.5 cm) were not included, both co-primary endpoints would have been met. In regards to Cohort B, the median sensitivity was 95.8%, with a median positive predictive value of 81.9% for extraprostatic lesions across the three central readers.[6] Of note, only Cohort A contributed to the FDA approval of ^{18}F-DCFPyL and, as regards OSPREY, only primary staging data are included in the PYLARIFY prescribing information.

The second registration trial was CONDOR.[7] CONDOR enrolled 208 men with biochemical recurrence of prostate cancer and uninformative conventional imaging with a median prostate-specific antigen (PSA) level of 0.8 ng/mL.[7] The pre-specified primary endpoint of CONDOR was a correct localization rate (CLR) of at least 20%; CLR is similar to positive predictive value but with the added requirement of correct anatomic colocalization.[7] There was a hierarchical composite standard of truth to determine if a lesion had been correctly localized: (1) histopathology, if feasible, (2) confirmatory standard imaging, or (3) focal radiation to visible lesions with a corresponding ≥ 50% decrease in PSA.[7] The three central readers identified sites of putative disease in 59%-66% of patients and arrived at a CLR of 84.8%-87.0%, meeting the primary endpoint of the study.[7]

In the remainder of this article, we will discuss our current practice for the acquisition protocol for ^{18}F-DCFPyL PET/CT, highlight aspects of image interpretation, and touch on future directions for PSMA PET imaging.

Method and technique

No specific preparation is required of the patient prior to arriving at the PET center for imaging. The following description of the image acquisition protocol is based on the Johns Hopkins Hospital experience; at the institutions of other authors, there may be slight variations related to scanner capabilities and established workflows.

Upon arrival, the patients have a peripheral IV catheter placed and the recommended dose of 333 MBq (9 mCi, with an acceptable range of 296 to 370 MBq [8-10 mCi]) of ^{18}F-DCFPyL are injected via IV.[8] At 60 to 90 minutes following radiotracer injection, the patients are positioned on the scanner and the acquisition protocol is started. We acquire an initial low-dose CT for anatomic localization and attenuation correction. Our patients are typically imaged on a Siemens Biograph mCT 128-slice scanner (Siemens Healthineers, Erlangen, Germany). We use 3:30 minutes per bed position, with a typical patient requiring 6-8 bed positions to cover a mid-thigh-to-skull-base field-of-view. The field-of-view is acquired beginning with the pelvis. Images are reconstructed utilizing the vendor-supplied algorithm.

Our current practice is based on a number of considerations. Although a higher detection efficiency has been described for patients with biochemical recurrence at 120 minutes versus 60 minutes,[9] 120-minute uptake times can be difficult to accommodate at busy PET centers because of a set number of dosing rooms. 120 minutes is also outside of the range described in the prescribing information for PYLARIFY. As such, we typically acquire images at 60 minutes. We ask patients to void immediately prior to getting on the scanner table, both to increase patient comfort and to minimize the amount of excreted radioactivity in the bladder.

It is highly important for radiologists and nuclear medicine physicians who are interpreting ^{18}F-DCFPyL PET/CT to be familiar with the interpretive pitfalls inherent to PSMA PET. Such pitfalls can include a number of non-prostate malignancies,[10] many non-malignant conditions,[11,12] and uptake within normal-variant biodistribution of the agent. An imaging specialist who calls all sites of abnormal uptake runs the risk of over-staging patients and precluding them from potential curative therapies. The typical patterns of spread of prostate cancer should be well-known to the imaging interpreter so that atypical patterns (such as isolated involvement of the chest or a visceral organ) can be potentially attributed to

another malignancy[10] and further work up, which may include histopathologic diagnosis, can be decided upon. Non-malignant structures and conditions that can have uptake include peripheral ganglia, Paget's disease, fibrous dysplasia, and sarcoidosis.[11,12]

One of the most important pitfalls in the interpretation of PSMA PET scans is excreted radiotracer in the ureters, which can appear to mimic pelvic adenopathy. While some centers administer Lasix and/or utilize late imaging in order to dilute/flush-out radioactivity from the urinary tract prior to imaging,[13] we do not use these approaches in our practice due to concerns with giving patients, who may have significant lower urinary tract symptoms, forced diuresis, as well as difficulties in managing the scheduling of patients that may need additional late imaging.

Nearly all patients in our population scanned with ^{18}F-DCFPyL since regulatory approval have been evaluated in one of two labeled indications, either primary staging of patients at risk for metastasis or elevated PSA suggestive of recurrent disease. For those men who are being primarily staged and are at risk for harboring either locoregional pelvic nodal or distant metastatic disease, ^{18}F-DCFPyL PET provides sensitive whole-body staging that can effectively replace conventional staging with computed tomography (CT) of the abdomen and pelvis/MRI of the pelvis combined with ^{99m}Tc- bone scan. In brief, evidence of uptake within pelvic lymph nodes, particularly along the proximal external iliac, obturator, and internal iliac chains, should be read with high sensitivity given the very high specificity described in OSPREY.[6] Indeed, even in a post hoc analysis of the OSPREY data that were confined only to those lymph nodes that were at least 5 mm in short axis, the sensitivity improved substantially with no loss of specificity.[6] As such, those lymph nodes within the expected distribution of prostate cancer involvement can be called as "positive" even with marginal (i.e. slightly above background) levels of radiotracer uptake. Regarding the prostate gland itself, focal radiotracer uptake is often indicative of a site of clinically significant prostate cancer, Figure 1,

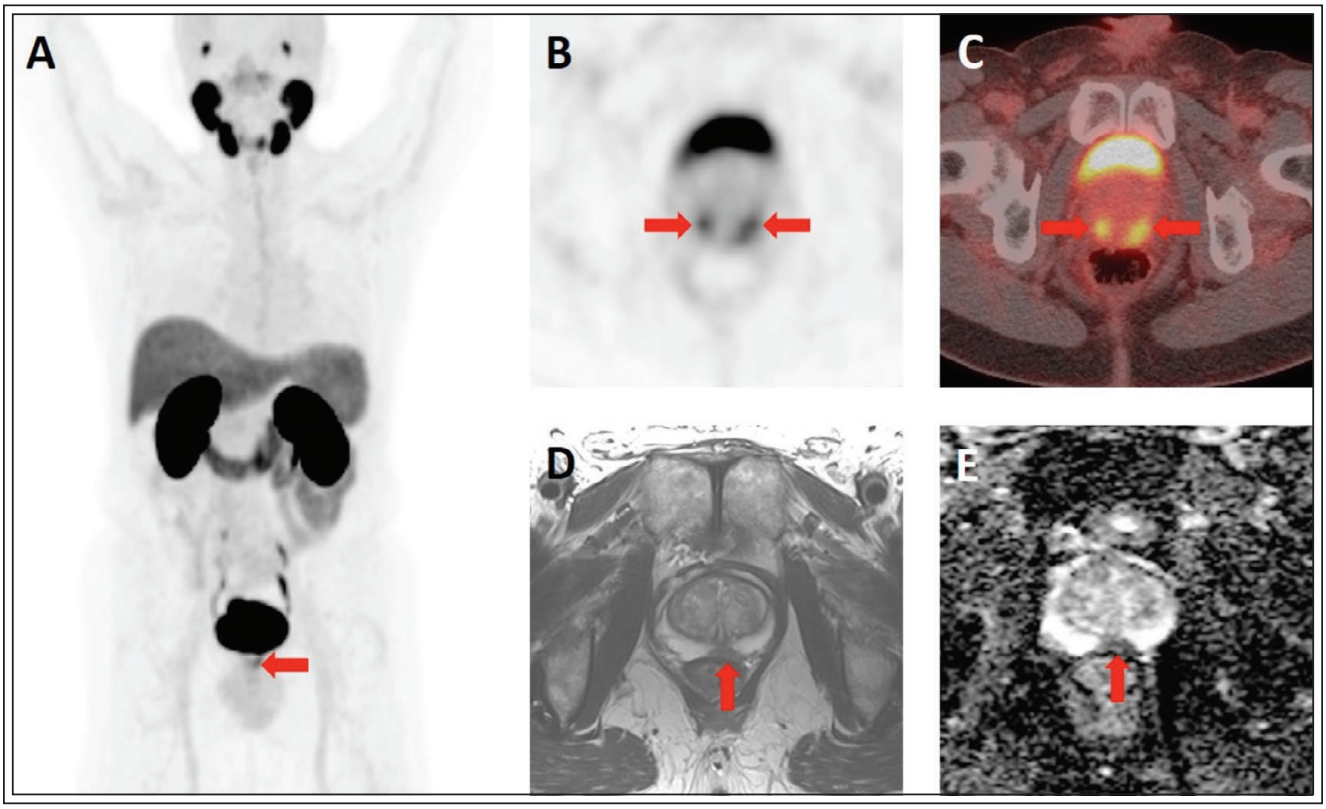

Figure 1. 72-year-old man with high-risk prostate cancer. **(A)** Maximum intensity projection (MIP) 18F-DCFPyL PET image with corresponding **(B)** axial PET and **(C)** PET/CT images demonstrating bilateral abnormal uptake in the base-to-mid peripheral zone of the prostate (arrows). On contemporaneous **(D)** T2-weighted and **(E)** apparent diffusion coefficient map magnetic resonance images, the left sided lesion is identifiable as low signal on both sequences (arrows). On surgical pathology, the patient had bilateral disease.

although uptake can occur in benign prostatic hyperplasia.

For both primary staging and recurrent disease, uptake outside of the pelvis should be interpreted with caution. Although OSPREY found high sensitivity and positive predictive value for ^{18}F-DCFPyL uptake at distant sites,[6] false positives may occur,[11,12] with implications for scan interpretation. First, in patients who are candidates for curative local therapy, but who have abnormal uptake at a distant site, additional diagnostic tests (e.g. tumor protocol MRI for a bone lesion) or histopathologic confirmation should be sought before consigning the patient to palliative treatment. Second, for patients with recurrence, if a finding is out-of-proportion to the PSA level (e.g. one or more bone metastases in a patient with a PSA < 0.5), it will also be important to perform further imaging or histologic work up. Third, for patients who may be candidates for metastasis-directed therapy, both the patient and the treatment team should be cognizant that false-positive lesions may be treated in an attempt to eradicate visible sites of disease.

Due to those and other considerations, there have been multiple attempts to provide structured reporting approaches to the interpretation of PSMA PET including the PSMA reporting and data system (PSMA-RADS[14]) and the prostate cancer molecular imaging standardized evaluation (PROMISE[15]) criteria. Each of these systems has its advantages and disadvantages, and efforts are underway to create a consensus approach. At Johns Hopkins Hospital, we provide clinical reads based on PSMA-RADS. PSMA-RADS is much like other RADS templates in that it is a 5-point Likert scale based on the likelihood of prostate cancer in both individual lesions and at the scan level.[14] The primary advantage of PSMA-RADS is that it is focused on lesion-level characterization. For patients with biochemical recurrence or limited metastatic disease, such characterizations can help guide the appropriate selection of therapy. For patients with more widespread metastatic disease, individual lesions are of less importance and the advantages of PSMA-RADS are less pronounced. In a variety of clinical contexts, PROMISE provides a template approach to reports that is based on a molecular imaging tumor, node, metastasis (miTNM) paradigm,[15] which may be particularly useful for clinical trial data collection and artificial intelligence applications.

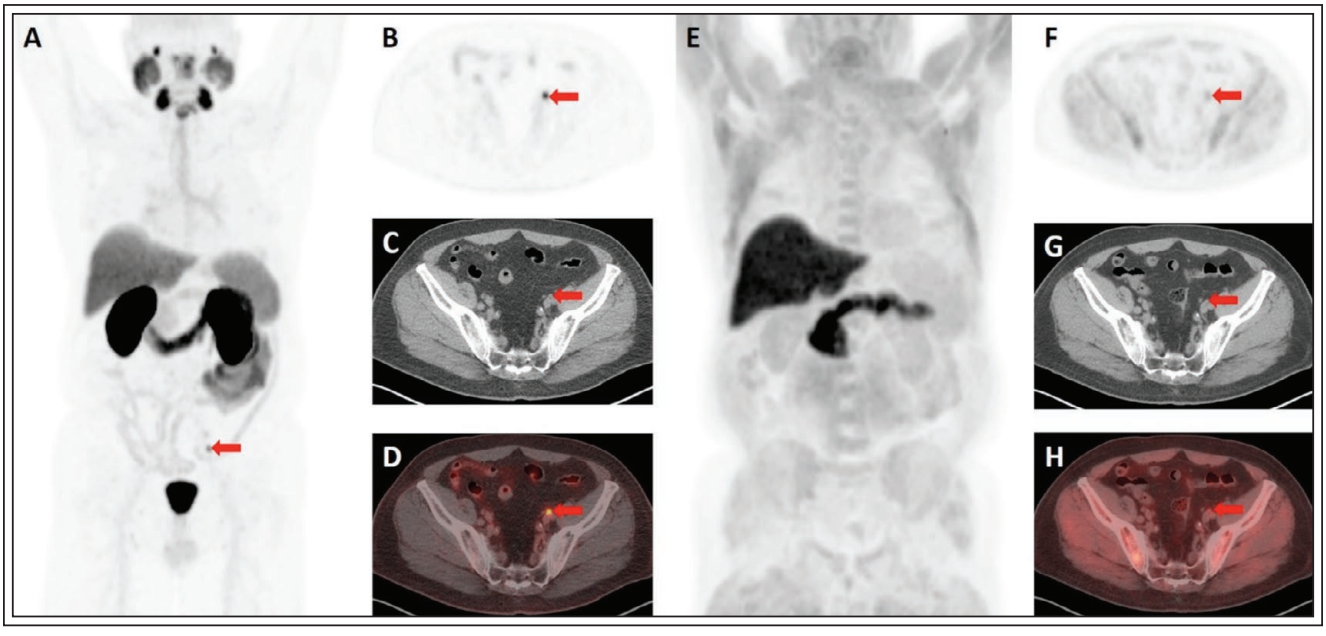

Figure 2. 59-year-old man with biochemical recurrence of prostate cancer **(A)** Maximum intensity projection (MIP) and corresponding **(B)** PET, **(C)** CT, and **(D)** PET/CT images from a 18F-DCFPyL scan demonstrates a 4 mm external iliac lymph node with intense uptake (arrows), consistent with a site of recurrent disease. This patient was imaged as part of the CONDOR trial, in which confirmatory imaging was part of the composite truth standard; this patient was imaged shortly after his 18F-DCFPyL PET with 18F-fluciclovine PET. **(E)** MIP and corresponding **(F)** PET, **(G)** CT, and **(H)** PET/CT images from the 18F-fluciclovine PET corroborate the findings from the 18F-DCFPyL PET scan with uptake above blood-pool in the external iliac node (arrows; the finding is not easily discernable on the MIP).

Example images for both of the labeled indications of ^{18}F-DCFPyL are shown in Figure 1 and Figure 2. The normal biodistribution of ^{18}F-DCFPyL includes intense uptake within the lacrimal and salivary glands, intense uptake in the kidneys, moderate to intense uptake in the proximal small bowel, moderate uptake in the liver, and variable (but generally moderate) uptake in the spleen. Figure 1 is from a 72-year-old patient who presented with an elevated PSA (7.3 ng/mL) and was found to have high-risk disease (Gleason 4+3=7, grade group 3, pT3bN0, with seminal vesicle invasion and extraprostatic extension). The scan demonstrates the normal biodistribution of ^{18}F-DCFPyL as well as the appearance of primary disease within the prostate. Figure 2 is from a 59-year-old man with prior prostatectomy for Gleason 4+3=7, grade group 3 prostate cancer who subsequently developed a rising PSA (0.6 ng/mL at the time of the scan) with negative conventional staging with CT and bone scan. The patient had a small external iliac lymph node with intense uptake, consistent with a site of recurrent prostate cancer (PSMA-RADS-4.[15]). The patient was scanned as part of the CONDOR trial and had confirmatory imaging with ^{18}F-fluciclovine.

Figure 3 demonstrates the appearance of bone lesions on ^{18}F-DCFPyL PET in a patient with widespread metastatic castration-resistant prostate cancer who was being considered for treatment with PSMA-targeted radioligand therapy. Bone lesions from prostate cancer can be seen with this imaging modality regardless of effects on the surrounding bone such as are needed for detection by bone scan or CT.

Brief discussion of the results

PSMA PET is changing the way that men with prostate cancer are staged and re-staged. Evidence from the OSPREY[6] and CONDOR[7] trials has shown that ^{18}F-DCFPyL PET is a superior imaging modality compared to CT/MRI and bone scan across the spectrum of prostate cancer.

The downstream consequences of the incorporation of PSMA PET into the clinical care of patients with prostate cancer are only starting to become apparent but include a greater use of metastasis-directed therapy, incorporation of PSMA PET findings into primary and salvage radiotherapy planning, avoidance of futile initial and salvage therapies, and selection of

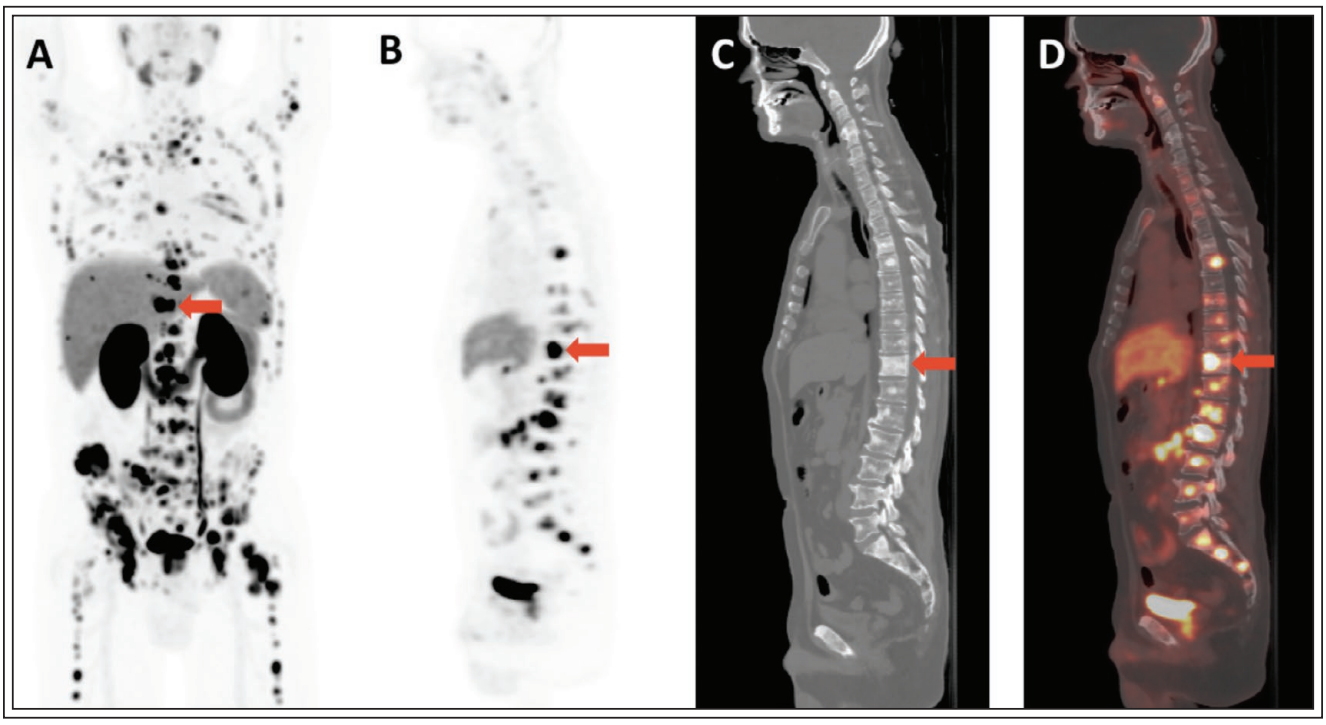

Figure 3. 59-year-old man with widespread metastatic castration-resistant prostate cancer and PSA of 57 who presented for evaluation for treatment with PSMA-targeted radioligand therapy. **(A)** Maximum intensity projection (MIP) from 18F-DCFPyL PET and corresponding **(B)** sagittal PET, **(C)** CT, and **(D)** PET/CT images show extensive bone metastatic disease (example lesion indicated by arrow).

men for treatment with PSMA-targeted radioligand therapy. Although outcomes data are needed and will be forthcoming, it seems highly likely that they will be supportive given the improved sensitivity for detecting subtle sites of disease relative to conventional imaging.

There are important questions that remain. The first regards how PSMA PET should be incorporated into clinical trials. With improved sensitivity of imaging comes earlier detection of different disease states (the so-called "Will Rogers Phenomenon"), upstaging of a proportion of patients, and the potential for earlier identification of progression on therapy. Many landmark clinical trial results based on conventional imaging may no longer be valid in the PSMA PET era, and this will need to be addressed in future clinical trial design.

Furthermore, we are at the intersection of emerging advanced imaging techniques with burgeoning artificial intelligence. These two revolutions in medical diagnosis will play complementary roles, with the added information from new radiotracers, such as ^{18}F-DCFPyL, creating a feedback loop with more advanced neural networks that will be able to derive unprecedented information from scans by extracting key imaging biomarkers. We can expect artificial intelligence algorithms to improve patient risk stratification, prognostication, and choice of therapy in the relatively near-term.

Conclusions

The regulatory approval of ^{18}F-DCFPyL indicated a major -change in how men with prostate cancer will be imaged as it marked the first commercial availability of a PSMA PET agent. PSMA PET, such as with ^{18}F-DCFPyL, is quickly becoming the unequivocal standard-of-care for imaging men with primary or recurrent prostate cancer at risk of metastatic disease, as was shown in the OSPREY and CONDOR trials, respectively and reflected in the recent updates of both the NCCN guidelines as well as the SNMMI Appropriate Use Criteria. The incorporation of PSMA PET into future therapeutic trials and the role of artificial intelligence in extracting important imaging features should be prioritized in future research. We hope that this overview has provided important practical information about how we perform ^{18}F-DCFPyL PET and can serve as a starting point for both imaging specialists and referrers who plan to incorporate this new imaging modality into their clinical practices.

Disclosure/Conflict of interest

Under a license agreement between Progenics (a wholly-owned subsidiary of Lantheus) and the Johns Hopkins University, MGP and the University are entitled to royalties on an invention described in this article. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. SPR and MAG are consultants for Progenics Pharmaceuticals, Inc. All other authors declare that there is no conflict of interest as well as consent for scientific analysis and publication. □

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