^{18}F-DCFPyL PET Acquisition, Interpretation, and Reporting: Suggestions After Food and Drug Administration Approval

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Recently, ^{18}F-DCFPyL was approved by the Food and Drug Administration for evaluation before definitive therapy and for biochemical recurrence. Here, we focus on the key data that justify the clinical use of ^{18}F-DCFPyL, as well as those aspects of protocol implementation and image interpretation that are important to the nuclear medicine physicians and radiologists who will interpret ^{18}F-DCFPyL PET/CT and PET/MRI scans.

^{18}F-DCFPYL

^{18}F-DCFPyL is a urea-based small-molecule inhibitor of prostate-specific membrane antigen (PSMA) that was developed at Johns Hopkins University in the wake of promising results with a first-generation PSMA PET tracer, ^{18}F-DCFBC (*1,2*). Although the idea for urea-based agents for prostate cancer PET can be traced back to the 1990s, the field began to take off in earnest with the preclinical evaluation of the first PSMA PET agent, ^{11}C-DCMC (also known as ^{11}C-MCG), in 2002 (*3*), followed by its evaluation in an experimental model of prostate cancer, alongside the radiohalogen, ^{125}I-DCIT, in 2005 (*4*). Radiometal agents targeting PSMA were initially described a few years later (*5*).

Initial clinical evaluation of ^{18}F-DCFPyL demonstrated high tumor uptake, comparable to that of ^{68}Ga-PSMA-11 and improved relative to ^{18}F-DCFBC, as well as favorable clearance, with normal-tissue distribution resulting in a radiation dose within the limits required by the Food and Drug Administration (*6*). Semiquantitative and quantitative studies have confirmed the consistency and repeatability of ^{18}F-DCFPyL uptake in normal organs and in metastatic prostate cancer, with the distribution being only minimally altered by variability in tumor burden (*7*).

In newly diagnosed, high-risk prostate cancer, accurate staging is crucial to guide appropriate treatment decisions. The phase II/III prospective, multicenter OSPREY trial, which accrued 252 patients with high-risk prostate cancer into a cohort undergoing radical prostatectomy with extended pelvic lymph node dissection, reported very similar performance for ^{18}F-DCFPyL, with median specificity of 97.9% and sensitivity of 40.3% among 3 central reviewers (*8*). Compared with conventional imaging modalities, ^{18}F-DCFPyL PET/CT has shown improved diagnostic performance, with similar sensitivity (40%) but a 3-fold higher positive predictive value for detecting pelvic nodal metastasis. Those findings were comparable to observations for ^{68}Ga-PSMA-11 PET (*9*). In brief, for initial staging of prostate cancer, both imaging specialists and clinicians should be aware that any finding of focal uptake in a pelvic lymph node is almost certainly representative of true-positive disease but that a subset of patients with small-volume pelvic nodal involvement will have a false-negative scan result.

In the setting of biochemical recurrence, ^{18}F-DCFPyL PET has a high rate of lesion detection after primary definitive therapy. In a cohort of the phase II/III OSPREY study, ^{18}F-DCFPyL PET/CT had a sensitivity of 95.8% and a positive predictive value of 81.9% for extraprostatic lesions in 93 patients with radiologic evidence of recurrent or metastatic prostate cancer on conventional imaging (*8*).The phase III CONDOR study further established the utility of ^{18}F-DCFPyL for prostate cancer biochemical recurrence (*10*), by leveraging a novel composite truth standard referred to as correct localization rate. In 208 men with uninformative conventional imaging results and a median prostate-specific antigen level of 0.8 ng/mL, the detection efficiency among 3 central reviewers was 59%–66%, with a correct localization rate of 84.8%–87.0%. Most importantly, 63.9% of the patients had changes in management after ^{18}F-DCFPyL PET. In several separate prospective studies evaluating ^{18}F-DCFPyL-PET in biochemical recurrence, the overall detection rate was found to be 80.2% and increased with rising prostate-specific antigen (*11–15*). Biochemical recurrence is likely to be the most common indication for ^{18}F-DCFPyL PET, and most scans will have positive findings if they are read with the appropriate level of sensitivity.

An indication of increasing interest among many clinicians is the identification of oligometastatic disease to guide metastasis-directed therapy. A post hoc analysis of the prospective ORIOLE trial found that those men who had all ^{18}F-DCFPyL–avid lesions treated by stereotactic body radiation therapy had improved progression-free survival and distant-metastasis–free survival relative to those men who had only a subset of avid lesions treated (*16*). Careful communication between the interpreting radiologist or nuclear medicine physician and the oncology team will be necessary to ensure that maximum value for detecting and treating oligometastatic disease is realized.

^{18}F-DCFPYL PET VERSUS OTHER PSMA-TARGETING PET RADIOPHARMACEUTICALS

PSMA-targeted PET imaging can be performed with multiple compounds. Overall, for prostate cancer biochemical recurrence,

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PSMA-targeted PET imaging demonstrated a detection rate and positive predictive value higher than those of any other imaging modality (CT, bone scanning, MRI, ^{11}C-choline PET, ^{18}F-fluciclovine PET) (*17–20*). ^{68}Ga-PSMA-11 is the most widely studied PSMA agent. Clinical trials of ^{68}Ga-PSMA-11 (*21–23*) or ^{18}F-DCFPyL (*8,10*) with large cohorts have shown excellent and comparable detection rates in both prostate cancer staging and biochemical recurrence. Few studies directly compared ^{18}F-DCFPyL and ^{68}Ga-PSMA-11. Hammes et al. found no differences in uptake between ^{18}F-DCFPyL and ^{68}Ga-PSMA-11 in bone tissue not affected by osseous metastasis in 21 patients with biochemical recurrence, suggestive of similar negative predictive value (*24*). In a small cohort of 14 patients with biochemical recurrence, ^{18}F-DCFPyL PET detected more lesions than ^{68}Ga-PSMA-11 did, with a significantly higher mean SUV_{max} and tumor-to-background ratio (*25*). The higher SUV_{max} of detected lesions on ^{18}F-DCFPyL PET could be clinically relevant in detecting small lesions such as lymph nodes. One advantage of ^{18}F-DCFPyL over ^{68}Ga-PSMA-11 is that ^{18}F-DCFPyL can be commercially produced and distributed, making it widely available to prostate cancer patients, potentially leading to a paradigm change in clinical management of prostate cancer. However, cyclotron-produced ^{68}Ga will allow for wider availability of ^{68}Ga-PSMA-11 as well. An in-depth review of other ^{18}F-labeled PSMA targeting agents was previously published (*26*).

IMAGING PROTOCOLS

Both PET/CT and PET/MRI systems have been used for ^{18}F-DCFPyL PET imaging. For prostate cancer patients, the same protocol has been used for both primary staging and biochemical recurrence. Patients do not need to fast before ^{18}F-DCFPyL injection. They are instructed to drink water (1–2 glasses) to ensure adequate hydration before receiving the ^{18}F-DCFPyL, and they are encouraged to void frequently for the first few hours after ^{18}F-DCFPyL administration to reduce radiation exposure. No diuresis is necessary, although for some patients it may be helpful to clear radioactive urine out of the ureters to decrease equivocal findings.

A fixed ^{18}F-DCFPyL dose of 333 MBq has been used. Images are typically acquired from the mid thighs to vertex. For PET/CT, either low-dose CT or diagnostic CT with intravenous or oral contrast medium is performed for attenuation correction and anatomic correlation at the start of the ^{18}F-DCFPyL acquisition. For PET/MRI, pelvic multiparametric MRI is performed after ^{18}F-DCFPyL administration, with simultaneous pelvic PET acquired between 45 and 60 min. Fast whole-body MRI is then performed, followed by a whole-body PET acquisition between 60 and 120 min.

No differences in lesion uptake were observed between patients who fasted at least 6 h before ^{18}F-DCFPyL injection and patients who did not fast, although fasting resulted in higher uptake in the submandibular gland, liver, and spleen (*27*). Forced diuresis with furosemide reduced the intensity of ^{18}F-DCFPyL uptake in the ureters, kidneys, and bladder, especially at 120 min after injection with late diuresis at 85 min (*28*). However, forced diuresis could interrupt the PET acquisition or require catherization in patients with incontinence, leading to a risk of infection and urinary discomfort and slowing the technologist workflow. Wondergem et al. found that ^{18}F-DCFPyL PET/CT detected more lesions with significantly higher lesion uptake at 120 min than at 60 min after ^{18}F-DCFPyL administration in 65 prostate cancer patients (*29*). The choice between 60 and 120 min for the interval between injection and imaging will have to be a nuanced decision based on logistical considerations (e.g., number of available dosing rooms or PET center workflow limitations) versus the apparent improved yield for subtle lesions at a more delayed time point, especially for pelvic lymph node and prostate bed detection.

IMAGE INTERPRETATION

^{18}F-DCFPyL has intense physiologic uptake in normal tissues such as the salivary glands, lacrimal glands, kidneys, ureters, and bladder, as well as moderate uptake in the liver, spleen, and proximal bowel. Knowledge of normal-tissue distribution and uptake is important since aggressive windowing may be required to detect small lesions within and adjacent to normal tissues with high uptake. Because of ^{18}F-DCFPyL excretion through the urinary system, lesion detection in the prostate bed and pelvis may be limited, especially in primary staging, and readers will need to be diligent in appropriately windowing and using multiplanar reformatted images to maximize sensitivity for subtle local tumors or recurrences.

Typical patterns of local recurrence and metastatic spread of prostate cancer include the prostate bed; the regional lymph nodes, with extension to the retroperitoneal and extrapelvic lymph nodes; osseous metastases; and other soft-tissue metastases such as the lungs, adrenal glands, liver, or dura when widespread metastatic disease has occurred. Mild uptake in atypical locations for prostate cancer metastases should be interpreted with caution. In addition, caution is needed when interpreting ^{18}F-DCFPyL uptake in bone lesions, especially solitary bone lesions, since PSMA uptake has been shown in both posttraumatic foci and many benign bone lesions. Generally, ^{18}F-DCFPyL is considered superior to bone scanning for lesion detection (*18*), and ^{18}F-DCFPyL has sensitivity nearly identical to that of ^{18}F-NaF, although the specificity of these findings was not assessed (*30*).

PEARLS AND PITFALLS

Although PSMA-based PET imaging has high positive predictive values, PSMA is known to be expressed in normal tissues at physiologic levels, in benign processes, and in some other malignancies. Interpretation of ^{18}F-DCFPyL PET finding should therefore be done with consideration of patient history, findings on other imaging modalities, and common pitfalls. Although a complete discussion of potential interpretive pitfalls is beyond the scope of this text, the reader is encouraged to review more extensive discussions (*31,32*). An in-depth discussion of PSMA PET in nonprostate malignancies has been previously published (*33*).

The peripheral ganglia are one of the most common sites for ^{18}F-DCFPyL accumulation; up to 97% of patients can have uptake in at least one peripheral ganglion, often in the lumbar and cervical dorsal root ganglia, the cervicothoracic and stellate ganglia, or the celiac ganglia. Most peripheral ganglia are located at anatomic sites clearly separated from common nodal stations, except the celiac ganglia, which can be misinterpreted as retroperitoneal lymph nodes. The celiac ganglia are near the celiac trunk origin and are typically linear, with mild ^{18}F-DCFPyL uptake, whereas metastatic lymph nodes are usually round with high ^{18}F-DCFPyL uptake.

Another common pitfall for PSMA PET is uptake in healing fractures or benign bone lesions. In fact, Chen et al. showed that most solitary rib lesions with PSMA uptake on ^{68}Ga-PSMA-11 PET have mild uptake and are benign (*34*). Other commonly encountered benign bone lesions such as Paget disease, fibrous dysplasia, hemangioma, and avascular necrosis have been reported

to have uptake with ^{18}F-DCFPyL or ^{68}Ga-PSMA-11. Correlation with findings on other imaging modalities such as radiography, CT, or MRI using bone marrow sequences is crucial for correctly identifying these benign lesions.

Pulmonary metastases in prostate cancer can occur, often with late metastatic disease, although there is a cohort of men with an underlying genetic profile that predisposes to recurrence in the lung. Several case reports have shown PSMA uptake in a selection of benign pulmonary pathologies, such as granulomatous disease and sarcoidosis, bronchiectasis, tuberculosis, and pneumoconiosis. PSMA uptake in isolated, symmetric pulmonary lesions without other typical sites of prostate cancer metastasis needs to be interpreted with caution and correlated with patient history, the results of other imaging modalities, and histologic sampling in select cases.

The fact that PSMA PET radiopharmaceuticals have no increased uptake in the central nervous system may facilitate the detection of brain metastases. However, ^{68}Ga-PSMA-11 uptake in subacute stroke may mimic brain metastasis. Other benign neurogenic tumors with PSMA uptake include meningioma, schwannoma, paraganglioma, and neurofibroma.

Benign soft-tissue pathologies were also reported to have increased ^{18}F-DCFPyL uptake, such as splenic hemangioma, adrenal adenoma, cylindroma, and elastofibroma dorsi.

Besides benign pathologies, PSMA uptake is increased in other malignancies, often related to accumulation of PSMA in neovascular endothelial cells, as opposed to tumor epithelial cells. Several case reports and case series have described ^{18}F-DCFPyL uptake in renal cell carcinoma, follicular lymphoma, differentiated thyroid cancer, and primary peripheral primitive neuroectodermal tumors. Knowing the patient history and the metastatic pattern of different malignancies can help establish the differential diagnosis of these lesions.

STRUCTURED REPORTING FOR ^{18}F-DCFPYL PET

Structured reports with standardized formats, categorization of findings, and interpretations are essential to improve communication with referring clinicians and promote consistency. The report should be clear, concise, complete, and clinically relevant. The final report should identify the patient and indicate the reason for the study, such as primary staging, evaluation of biochemical recurrence, or evaluation of treatment response. Relevant clinical history should be noted, including whether the patient has other malignancies or recent treatment with antihormonal therapy and whether imaging studies are available for comparison; if such studies are available, the procedure should be noted, including the radiopharmaceutical activity, whether intravenous or oral contrast medium was used, if applicable, and the imaging acquisition protocol. The findings should include the anatomic location, size, and intensity of PET uptake, preferably in SUV_{max} relevant to a normal-tissue reference such as blood pool, liver, or parotid gland uptake, as well as associated CT or MRI findings such as bone sclerosis. The final impression should have reasonable and clinically relevant conclusions and appropriate recommendations.

Several guidelines and interpretation standards have been proposed for PSMA-based PET reporting to improve accuracy and reproducibility among readers. The European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging issued joint procedure guidelines and standardized interpretation criteria for prostate cancer imaging (*35,36*) proposing that all areas of increased radiotracer uptake higher than adjacent background uptake, in sites not expected to show physiologic uptake, are to be reported as anomalous. Anomalous sites of uptake are categorized as pathologic, anomalous, uncertain, nonpathologic, or normal on the basis of anatomic location, degree of uptake, and relevant clinical information. The final summary should identify the study results as normal or abnormal, and the question asked in the study indication should be addressed directly.

The Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria (*37*) proposed that lesions with an SUV_{mean} higher than that of liver are considered typical of prostate cancer. Each lesion is classified as positive, negative, or equivocal, and then a molecular imaging TNM classification is provided with consideration of clinical information and other imaging findings. The final diagnosis is positive, equivocal, or negative, with a 5-point-scale diagnostic level of certainty. The Food and Drug Administration recently approved aPROMISE, a machine learning tool developed to assist with image classification and reporting.

The PSMA Reporting and Data System (RADS) (*38*) proposed that lesions be classified into a 5-point scale, with higher numbers representing increasing likelihood of prostate cancer. The classification is based on the level of PSMA uptake, lesion sites that are typical or atypical of metastatic prostate cancer, and findings on corresponding anatomic imaging. The overall scan score is derived from the corresponding highest PSMA-RADS score assigned to individual detected lesions. This approach is likely most useful for patients with a limited number of lesions, such as in biochemical recurrence or oligometastatic disease.

Toriihara et al. compared these 3 proposed criteria in terms of interreader, intrareader, and intercriteria agreement and found good reproducibility of the 3 criteria in evaluating ^{68}Ga-PSMA-11 PET. However, there are interreader disagreements that suggest the need for further work to harmonize or improve the criteria (*39*). More recently, the European Association of Nuclear Medicine proposed standardized reporting guidelines, E-PSMA (*40*), based on a modified Delphi consensus process. Individual findings are classified as benign, probably benign, or equivocal; probable prostate cancer; or definite evidence of prostate cancer on the basis of PSMA uptake and an anatomic site of disease typical or atypical of prostate cancer. In addition, PSMA PET findings are classified as prostate and prostate bed, regional lymph nodes, or distant metastases on the basis of the molecular imaging TNM regional classification.

FUTURE DEVELOPMENTS

Recently, the phase III VISION trial showed that ^{177}Lu-PSMA-617 significantly improved radiographic progression-free survival in patients with metastatic castration-resistant prostate cancer (*41*). ^{68}Ga-PSMA-11 PET was used in the trial to screen PSMA-positive patients dependent on uptake relative to liver. Screening ^{18}F-DCFPyL PET for ^{177}Lu-PSMA-617 treatment is expected to provide similar sensitivity and specificity on the basis of prior clinical trials of these 2 agents, though additional clinical confirmation may be needed. Future use will likely include ^{18}F-DCFPyL biopsy guidance in men with suspected prostate cancer. ^{18}F-DCFPyL PET may be used to identify or better contour small tumors than does standard-of-care MRI and guide nonconventional focal therapies such as high-intensity focused ultrasound and cryosurgery in local recurrence after radiotherapy in the absence of metastatic disease (*42*). In the setting of castration-resistant prostate cancer, Fendler et al. showed that PSMA PET was able to detect distant metastases in 54.5% of

patients whose disease was classified as nonmetastatic by conventional imaging (*43*). Other indications for ^{18}F-DCFPyL PET may potentially include assessing treatment response after systemic therapy (*44*).

CONCLUSION

PSMA-targeted PET with ^{18}F-DCFPyL will be transformative within the prostate cancer imaging domain, as it is the first widely commercially available PSMA PET agent with approval from a major regulatory body. Radiologists and nuclear medicine physicians who will interpret ^{18}F-DCFPyL PET scans should be aware of the clinical data that have driven approval, as well as the potential interpretive pitfalls associated with this novel type of PET scan. Important points for interpreting physicians and referring clinicians to be aware of include, first, that ^{18}F-DCFPyL has moderate sensitivity but very high specificity for the identification of involved pelvic lymph nodes in patients undergoing primary staging; second, that ^{18}F-DCFPyL has excellent detection efficiency in patients with biochemical recurrence, even at low prostate-specific antigen values; and third, that ^{18}F-DCFPyL PET may be helpful in guiding therapy for patients with oligometastatic disease. Uptake of ^{18}F-DCFPyL in benign lesions, as well as in the neovasculature of nonprostate malignancies, should be understood, and all sites of uptake on a ^{18}F-DCFPyL PET scan should be interpreted in the context of the clinical scenario and known routes of spread of metastatic disease. Structured reporting frameworks are valuable in improving interpretive reliability and consistency.

DISCLOSURE

Progenics Pharmaceuticals provided ^{18}F-DCFPyL to Stanford University as part of a Research Access Program. Under a license agreement between Progenics (a wholly owned subsidiary of Lantheus) and the Johns Hopkins University, the University is 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. Steven Rowe is a consultant for, and has received research funding from, Progenics. Andrei Iagaru is an unpaid consultant for Progenics. No other potential conflict of interest relevant to this article was reported.

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