

**<sup>18</sup>F DCFPyL PET Acquisition, Interpretation and Reporting: Suggestions Post  
Food and Drug Administration Approval**

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**Running title:**  $^{18}\text{F}$  DCFPyL PET Post Approval

$^{18}\text{F}$ -DCFPyL was recently approved by the Food and Drug Administration for evaluation prior to definitive therapy and for biochemical recurrence. Here we focus on the key data that justify the clinical use of  $^{18}\text{F}$ -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  $^{18}\text{F}$ -DCFPyL PET/CT and PET/MR scans.

### **$^{18}\text{F}$ -DCFPyL**

$^{18}\text{F}$ -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,  $^{18}\text{F}$ -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,  $^{11}\text{C}$ -DCMC (also known as  $^{11}\text{C}$ -MCG) in 2002 (3), followed by its evaluation in an experimental model of prostate cancer, alongside the radiohalogen,  $^{125}\text{I}$ -DCIT, in 2005 (4). Radiometal agents targeting PSMA were initially described a few years later (5).

Initial clinical evaluation of  $^{18}\text{F}$ -DCFPyL demonstrated high tumor uptake, comparable to that of  $^{68}\text{Ga}$ -PSMA-11 and improved relative to  $^{18}\text{F}$ -DCFBC, as well as favorable clearance with normal tissue distribution resulting in radiation dose within the limits required by the FDA (6). Semiquantitative and quantitative studies have confirmed consistency and repeatability of  $^{18}\text{F}$ -DCFPyL uptake in normal organs and in metastatic

prostate cancer, the distribution of which is 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, multi-center 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  $^{18}\text{F}$ -DCFPyL, with median specificity of 97.9% and sensitivity of 40.3% among three central reviewers (8). Compared to conventional imaging modalities,  $^{18}\text{F}$ -DCFPyL PET/CT has shown improved diagnostic performance with similar sensitivity (40%), but threefold higher PPV for detecting pelvic nodal metastasis. Those findings were comparable to observations with  $^{68}\text{Ga}$ -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.

In the setting of biochemical recurrence,  $^{18}\text{F}$ -DCFPyL PET has a high rate of lesion detection after primary definitive therapy. In a cohort of the phase II/III OSPREY study,  $^{18}\text{F}$ -DCFPyL PET/CT had sensitivity of 95.8% and positive predictive value of 81.9% for extra-prostate lesions in 93 patients with radiological evidence of recurrent or metastatic prostate cancer on conventional imaging (8). The phase III CONDOR study further established the utility of  $^{18}\text{F}$ -DCFPyL for prostate cancer biochemical recurrence (10), by leveraging a novel composite truth standard referred to as correct localization rate (CLR). In 208 men with uninformative conventional imaging and median prostate

specific antigen (PSA) of 0.8 ng/mL, the detection efficiency among three central reviewers was 59 – 66%, with CLR of 84.8 – 87.0%. Most importantly, 63.9% of the patients had changes in management after <sup>18</sup>F-DCFPyL PET. In several separate prospective studies evaluating <sup>18</sup>F-DCFPyL-PET in biochemical recurrence, overall detection rate was found to be 80.2% and increases with rising PSA (11-15).

Biochemical recurrence is likely to be the most common indication for <sup>18</sup>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 <sup>18</sup>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 the maximum value for detecting and treating oligometastatic disease is realized.

## **<sup>18</sup>F DCFPyL PET VS. OTHER PSMA TARGETING PET RADIOPHARMACEUTICALS**

PSMA-targeted PET imaging can be performed with multiple compounds. Overall, PSMA-targeted PET imaging demonstrated higher detection rate and positive predictive value in prostate cancer biochemical recurrence compared to all other imaging modalities (CT, bone scan, MRI, choline PET, fluciclovine PET) (17-20). <sup>68</sup>Ga-PSMA-11 is the most widely studied PSMA agent. Clinical trials of <sup>68</sup>Ga-PSMA-11 (21-

23) or  $^{18}\text{F}$ -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  $^{18}\text{F}$ -DCFPyL and  $^{68}\text{Ga}$ -PSMA-11. Hammes et al. found no differences in uptake of  $^{18}\text{F}$ -DCFPyL and  $^{68}\text{Ga}$ -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 14 patients with biochemical recurrence,  $^{18}\text{F}$ -DCFPyL PET has been shown to detect more lesions with significantly higher mean SUVmax and tumor-to-background ratios compared to  $^{68}\text{Ga}$ -PSMA-11 (25). The higher SUVmax of detected lesions on  $^{18}\text{F}$ -DCFPyL PET could be clinically relevant in detecting small lesions such as lymph nodes. One advantage of  $^{18}\text{F}$ -DCFPyL over  $^{68}\text{Ga}$ -PSMA-11 is that  $^{18}\text{F}$ -DCFPyL can be commercially produced and distributed making it widely available to prostate cancer patients, potentially leading to paradigm change in clinical management of prostate cancer. However, cyclotron-produced  $^{68}\text{Ga}$  will allow for wider availability of  $^{68}\text{Ga}$ -PSMA-11 as well. For in-depth review of other  $^{18}\text{F}$ -labeled PSMA targeting agents, readers are directed to reference (26).

## **IMAGING PROTOCOLS**

Both PET/CT and PET/MR systems have been employed for  $^{18}\text{F}$ -DCFPyL PET imaging. The same protocol has been used for prostate cancer patients at primary staging or biochemical recurrence. For patient preparation, no fasting is required prior to  $^{18}\text{F}$ -DCFPyL injection. Patients are instructed to drink water (1 to 2 glasses) to ensure adequate hydration prior to  $^{18}\text{F}$ -DCFPyL administration. Patients are encouraged to void frequently for the first few hours following  $^{18}\text{F}$ -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  $^{18}\text{F}$ -DCFPyL dosage of 333 mBq has been used. Images are typically acquired from mid-thighs to vertex. For PET/CT, either a low-dose CT or a diagnostic CT with intravenous and/or oral contrast is performed for attenuation correction and anatomic correlation at the start of the  $^{18}\text{F}$ -DCFPyL acquisition. For PET/MR, pelvic mpMRI is performed after  $^{18}\text{F}$ -DCFPyL administration with simultaneous pelvic PET acquired between 45 mins to 60 mins. A fast whole-body MRI is then performed followed by whole body PET acquisition between 60 and 120 mins.

No differences in lesion uptake were observed between patients who fasted at least 6 hours before  $^{18}\text{F}$ -DCFPyL injection and patients who did not fast, while fasting resulted in higher uptake in the submandibular gland, liver, and spleen (27). Forced diuresis with furosemide was found to reduce intensity of  $^{18}\text{F}$ -DCFPyL uptake in the ureters, kidneys, and bladder, especially at 120 mins after injection with late diuresis at 85 mins (28). However, forced diuresis could interrupt PET acquisition or require catheterization in patients with incontinence that leads to risk of infection, urinary discomfort and slows down technologist workflows. Wondergem et al. found that  $^{18}\text{F}$ -DCFPyL PET/CT detected more lesions with significantly higher lesion uptake at 120 minutes compared to 60 mins after  $^{18}\text{F}$ -DCFPyL administration in 65 prostate cancer patients (29). The choice between 60 minutes and 120 minutes 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, PET center work-flow

limitations, etc.) 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**

$^{18}\text{F}$ -DCFPyL has intense physiologic uptake in normal tissues such as 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 it may require aggressive windowing to detect small lesions within and adjacent to normal tissues with high uptake. Due to  $^{18}\text{F}$ -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 very diligent in appropriately windowing and using multi-planar reformatted images to maximize sensitivity for subtle local tumors or recurrences.

Typical patterns of local recurrence and metastatic spread of prostate cancer include prostate bed, regional lymph nodes with extension to retroperitoneal and extra-pelvic lymph nodes, osseous metastases, and other soft tissue metastases such as lungs, adrenal glands, liver, or dura when wide-spread 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  $^{18}\text{F}$ -DCFPyL uptake in bone lesions, especially solitary bone lesions, since PSMA uptake has been shown in both post-traumatic foci and many benign bone lesions. Generally,  $^{18}\text{F}$ -DCFPyL is considered superior to bone scan for lesion detection (18) and  $^{18}\text{F}$ -DCFPyL has nearly

identical sensitivities compared to  $^{18}\text{F}$ -NaF, although 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 some other malignancies. Interpretation of  $^{18}\text{F}$ -DCFPyL PET should therefore consider patient history, findings on other imaging modalities, and with knowledge of 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, such as references (31) and (32). For an in-depth discussion of PSMA PET in non-prostate malignancies, please see (33).

Peripheral ganglia are one of the most common sites for  $^{18}\text{F}$ -DCFPyL accumulation, and it has been observed that 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/stellate ganglia, or the celiac ganglia. Most peripheral ganglia are located at anatomic sites clearly separated from common nodal stations, except 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  $^{18}\text{F}$ -DCFPyL uptake, while metastatic lymph nodes are usually round with high  $^{18}\text{F}$ -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  $^{68}\text{Ga}$ -PSMA-11 PET have mild uptake and are benign (34). Other commonly

encountered benign bone lesions such as Paget's disease, fibrous dysplasia, hemangioma, and avascular necrosis have been reported to have uptake with  $^{18}\text{F}$ -DCFPyL or  $^{68}\text{Ga}$ -PSMA-11. Correlation with findings on other imaging modalities such as radiography, CT or MRI using bone marrow sequences are 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, TB, 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, other imaging modalities, and histologic sampling in select cases.

PSMA PET radiopharmaceuticals have no increased uptake in the central nervous system, which may facilitate the detection of brain metastases. However,  $^{68}\text{Ga}$ -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  $^{18}\text{F}$ -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  $^{18}\text{F}$ -DCFPyL uptake in renal cell carcinoma, follicular lymphoma, differentiated thyroid cancer, as well as primary peripheral primitive neuroectodermal tumors. Knowing patient history and metastatic pattern of different malignancies can help establish the differential diagnosis of these lesions.

### **STRUCTURED REPORTING FOR $^{18}\text{F}$ -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 include identification of the patient, indication of the study such as primary staging, biochemical recurrence, or evaluation of treatment response. Relevant clinical history should be noted, including other malignancies or recent treatment with anti-hormonal therapy, available imaging studies for comparison, imaging procedure including radiopharmaceutical activity, intravenous or oral contrast, if applicable, and imaging acquisition protocol. Findings should include anatomical location, size, and intensity of PET uptake, preferably in maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ) relevant to normal tissue reference such as blood pool, liver, or parotid gland uptake, as well as associated CT or MR findings such as bone sclerosis. 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, which aim to improve accuracy and reproducibility among

readers. The Joint EANM and SNMMI procedure guideline and standardized interpretation for prostate cancer imaging (35,36) proposed that all areas of increased radiotracer uptake, higher than adjacent background uptake, in sites not expected to show physiological uptake, are to be reported as anomalous. All anomalous sites of uptake are categorized as pathologic, anomalous, uncertain, non-pathologic, or normal based on anatomic location, degree of uptake, and relevant clinical information. Final summary should identify the study as normal or abnormal and the question asked in the study indication should be addressed directly.

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

PSMA-RADS (38) proposed that lesions are classified into a 5-point scale where the higher number represents increasing likelihood of prostate cancer. The classification is based on level of PSMA uptake, lesion sites that are typical or atypical for 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 three proposed criteria in terms of interreader, intrareader, and intercriteria agreement and found good reproducibility of the three criteria in evaluating  $^{68}\text{Ga}$ -PSMA-11 PET. However, there are interreader disagreements that suggest that further work may be needed to harmonize or improve the criteria (39). More recently, the EANM standardized reporting guidelines E-PSMA (40) has been proposed based on a modified Delphi consensus process. Individual findings are classified into benign, probably benign, equivocal findings, probably prostate cancer and definite evidence of prostate cancer based on PSMA uptake and anatomic site of disease typical or atypical for prostate cancer. In addition, PSMA PET findings are classified into prostate and prostate bed, regional lymph nodes or distant metastases based on miTNM regional classification.

## **FUTURE DEVELOPMENTS**

Recently, the phase III VISION trial showed that  $^{177}\text{Lu}$ -PSMA-617 significantly improved radiographic progression free survival in patients with metastatic castration-resistant prostate cancer (41).  $^{68}\text{Ga}$ -PSMA-11 PET was used in the trial to screen PSMA positive patients dependent on uptake relative to liver. Screening  $^{18}\text{F}$ -DCFPyL PET for  $^{177}\text{Lu}$ -PSMA-617 treatment is expected to provide similar sensitivity and specificity based on prior clinical trials of these two agents, though additional clinical confirmation may be needed. Future use will likely include  $^{18}\text{F}$ -DCFPyL biopsy guidance in men with suspected prostate cancer.  $^{18}\text{F}$ -DCFPyL PET may be used to identify or better contour small tumors than standard-of-care MR and guide non-conventional 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 who were classified as non-metastatic by conventional imaging (43). Other indications for  $^{18}\text{F}$ -DCFPyL PET may potentially include assessing treatment response after systemic therapy (44). Lastly, PSMA PET has not yet been integrated into major clinical guidelines for prostate cancer at staging or biochemical recurrence (42,45).

## **CONCLUSIONS**

PSMA-targeted PET with  $^{18}\text{F}$ -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  $^{18}\text{F}$ -DCFPyL PET scans should be aware of the clinical data that has 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 (1) that  $^{18}\text{F}$ -DCFPyL has moderate sensitivity but very high specificity for the identification of involved pelvic lymph nodes in patients undergoing primary staging; (2) that  $^{18}\text{F}$ -DCFPyL has excellent detection efficiency in patients with biochemical recurrence, even at low PSA values; and (3) that  $^{18}\text{F}$ -DCFPyL PET may be helpful in guiding therapy for patients with oligometastatic disease. Uptake of  $^{18}\text{F}$ -DCFPyL in benign lesions, as well as in the neovasculature of non-prostate malignancies, should be understood, and all sites of uptake on a  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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. SPR is a consultant for, and has received research funding from, Progenics. AI is an unpaid consultant for Progenics. No other potential conflicts of interest relevant to this article exist.

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