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Prospective Evaluation of PSMA-Targeted ^{18}F-DCFPyL PET/CT in Men with Biochemical Failure After Radical Prostatectomy for Prostate Cancer

Running Title: ^{18}F-DCFPyL in Biochemical Failure

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Abstract

Purpose: To provide the results of a prospective study evaluating PSMA-targeted ^{18}F-DCFPyL PET/CT in patients with biochemical failure following radical prostatectomy for prostate cancer (PCa).

Procedures: 31 patients with post-prostatectomy serum PSA levels ≥ 0.2 ng/mL and negative conventional imaging were enrolled in this study and imaged with ^{18}F-DCFPyL PET/CT. A consensus central review identified foci of radiotracer uptake consistent with sites of PCa. Descriptive statistics were utilized.

Results: 21/31 (67.7%) patients had at least one finding on ^{18}F-DCFPyL PET/CT consistent with a site of PCa. Imaging was positive in 59.1% of patients with PSA < 1.0 ng/ml and in 88.9% of patients with PSA > 1.0 ng/mL. The median SUV_{max} across all lesions was 11.6 (range 1.5 to 57.6).

Conclusions: In this prospective study utilizing the PSMA-targeted PET agent ^{18}F-DCFPyL, most patients with biochemical failure following radical prostatectomy had foci of suspicious uptake, even at low serum PSA levels.

Main Text

Introduction

Recent years have witnessed the rapid adoption of positron emission tomography (PET) for imaging prostate cancer (PCa) (*1*). Among the available PET radiotracers, those targeting prostate-specific membrane antigen (PSMA) have garnered the widest clinical interest (*2*). One of the most studied indications for PSMA-targeted PET imaging has been biochemical recurrence of PCa following attempted curative local therapy (*3,4*). Although several studies have been prospective in nature (*5,6*), the majority of reports on PSMA-targeted PET imaging of men with recurrent PCa have been retrospective and some have included patients with findings of sites of disease on conventional imaging (e.g. contrast-enhanced computed tomography (CT) and ^{99m}Tc-methylene disphosphonate bone scan). As such, the true added value of PSMA-targeted PET over conventional imaging for identifying sites of disease in men with recurrent PCa detected solely on the basis of an elevated PSA level remains unclear. Furthermore, the vast majority of reports published to date have made use of ^{68}Ga-labeled radiotracers targeting PSMA, although there has recently been a shift towards the more widespread use of ^{18}F-labeled agents (*7*).

Fluorine-18 offers numerous advantages relative to ^{68}Ga as a radionuclide for PET imaging *(8*). These include a longer half-life (110 minutes versus 68 minutes) that facilitates centralized production and distribution, a lower average positron energy, and a higher positron yield. Indeed, early reports have shown improved lesion detection with ^{18}F-DCFPyL as compared to ^{68}Ga-PSMA-11 – two otherwise similar urea-based small molecule inhibitors of PSMA (*9*).

Herein, we present data from a single-center, prospective cohort of patients with biochemical failure following radical prostatectomy who were imaged with the ^{18}F-labeled, PSMA-targeted agent, ^{18}F-DCFPyL.

Materials and Methods

Patient Population

This prospective study was approved by the Johns Hopkins Medicine Institutional Review Board and was carried out under a United States Food and Drug Administration investigational new drug application (IND 121064, Clinicaltrials.gov Identifier NCT02523924). Written, informed consent was obtained from all patients. Inclusion criteria were age ≥ 18 years, history of adenocarcinoma of the prostate post radical prostatectomy, serum prostate specific antigen (PSA) level ≥ 0.2 ng/mL at least 45 days prior to study enrollment, and staging evaluation with CT of the abdomen and pelvis, or magnetic resonance imaging of the pelvis, and bone scan at least 45 days prior to enrollment. Exclusion criteria were history of non-prostate malignancy (other than squamous cell or basal cell carcinoma of the skin) within the three years prior to enrollment and intention to enroll in a blinded therapeutic clinical trial. Patients with definitive findings of recurrent PCa on staging conventional imaging were excluded, as were patients treated with prior systemic therapy. Descriptive statistics were used with medians and ranges or percentages derived as appropriate.

Image Acquisition

Our standard ^{18}F-DCFPyL PET/CT acquisition protocol was followed (*10*). ^{18}F-DCFPyL was synthesized according to current good manufacturing practices as previously described (*11*). Patients were instructed to remain *nil per os* except for water and medications for at least four hours prior to radiotracer injection. Intravenous injection of ≤ 333 MBq (≤ 9 mCi) of ^{18}F-DCFPyL was followed 60 minutes later by PET/CT acquisition on either a Discovery RX 64-slice PET/CT (General Electric, Waukesha, Wisconsin, USA) or a Biograph mCT 128-slice PET/CT (Siemens, Erlangen, Germany). PET/CT scanners were operated in 3D emission mode with CT for attenuation correction. Acquisitions were performed from the mid-thighs to the skull vertex. Image

reconstruction was performed with ordered subset expectation maximization algorithms provided by the manufacturers.

Image Analysis

All attenuation correction CT, ^{18}F-DCFPyL PET, and fusion PET/CT images were reviewed on a SyngoVia Workstation (Siemens Healthineers, Erlangen, Germany). A consensus central review was performed by two nuclear medicine physicians with experience in reading PSMA-targeted PET studies (SPR and ZS). Sites of uptake above background that were consistent with potential sites of recurrent PCa were noted as putative sites of disease. Maximum standardized uptake values corrected for lean body mass (SUV_{max}) were recorded.

Results

31 patients were accrued. The median patient age was 63 years (range 45 – 74 years) and 27 (87.1%) patients were white. Patients had a broad distribution of pathologic stages at the time of radical prostatectomy (11/31 (35.5%) were pT2; 14/31 (45.2%) were pT3a; 6/31 (19.4%) were pT3b; and 8/31 (25.8%) were pN1). Patients were imaged a median of 30 months (range 4 - 152 months) after radical prostatectomy. In total, 20 (64.5%) patients experienced biochemical recurrence after surgery, while 11 (35.5%) had a post-prostatectomy persistently elevated PSA. At the time of ^{18}F-DCFPyL PET/CT, patients had a median PSA level of 0.4 ng/mL (range 0.2 – 28.3 ng/mL) and 21 (67.7%) patients had a PSA level below 0.6 ng/mL. Additional information is provided in Table 1.

In total, 21/31 (67.7%) patients had at least one site of ^{18}F-DCFPyL uptake consistent with PCa (Table 2). Sites of disease included the prostate bed in 8/31 (25.8%) patients, the pelvic lymph nodes in 14/31 (45.1%), non-pelvic lymph nodes in 2/31 (6.5%), and bone in 2/31 (6.5%).

More than one site of disease was found in 5/31 (16.1%) patients. For PSA levels between 0.2 and 1.0 ng/mL, 13/22 (59.1%) patients had findings compatible with sites of PCa. Each of these patients had only one putative site of disease. For those patients with PSA levels > 1.0 ng/mL, the detection efficiency improved to 8/9 (88.9%). Among these patients, 5/9 (55.6%) had more than one suspected site of disease.

The median SUV_{max} for all lesions was 11.6 (range 1.5 to 57.6). For prostate bed lesions, the median SUV_{max} was 3.4 (range 1.9 to 16.3) and for pelvic lymph node lesions the median SUV_{max} was 11.6 (range 1.5 to 55.6). The median SUV_{max} for non-pelvic lymph node lesions was 23.9 (range 1.8 to 57.6). The two visualized bone lesions had SUV_{max} values of 17.3 and 19.9. Examples of uptake in the prostate bed and a pelvic lymph node are found in Figure 1 and Figure 2, respectively.

Discussion

This study provides a prospective evaluation of the ^{18}F-labeled PSMA-targeted radiotracer ^{18}F-DCFPyL in men with biochemical failure following radical prostatectomy. Despite negative conventional imaging, no prior treatment with systemic therapy, and relatively low PSA levels, ^{18}F-DCFPyL PET/CT yielded a high detection rate for putative sites of disease. While these findings should be confirmed in larger, multi-center trials, the findings in this study nonetheless suggest a future role for PSMA-targeted PET imaging in supplanting evaluation with conventional imaging in patients with biochemical failure. Further, as the number of men worldwide with access to PSMA-targeted PET imaging continues to increase, the intrinsic advantages of ^{18}F as a radionuclide will become more apparent, and studies that build upon previous findings with ^{68}Ga-labeled PSMA-targeted PET agents will be of increasing importance.

Given the overall low serum PSA levels of the majority of patients, the preponderance of lesions in the pelvis is not surprising. Only 4/31 (12.9%) patients were found to have occult M1a or M1b disease. When taking into account differences in inclusion criteria, the overall detection rate of ^{18}F-DCFPyL in this trial is in line with other recent studies with ^{18}F-labeled agents, including a larger cohort of patients imaged with ^{18}F-DCFPyL (*12*) and the compound ^{18}F-PSMA-1007 (*7*).

Although the current study addresses some weaknesses of the available literature on PSMA-targeted PET imaging, it nonetheless has limitations. First, given that the findings of suspected disease in these patients did not have definitive conventional imaging correlates, confirmatory biopsy was not practical to perform and histopathologic confirmation is not available. This is somewhat ameliorated by the high specificity of PSMA-targeted PET in other clinical contexts (*13*), although the known pitfalls of PSMA-targeted PET interpretation leave open the possibility of false positive uptake (*14*). Second, given that this was an externally-funded, prospective trial, we were limited in the number of patients that could be accrued. A multi-center trial with this radiotracer is expected in the near-future (i.e. the CONDOR trial, ClinicalTrials.gov NCT03739684). Lastly, the imaging central review was carried out such that the readers were asked to make a definitive decision on the presence or absence of findings of PCa. A more nuanced approach allowing for gradations of confidence in findings (*15*) may more closely mirror a real-world clinical setting.

Conclusions

In this prospective study utilizing the PSMA-targeted PET agent ^{18}F-DCFPyL, significant added value for the detection of lesions compatible with sites of PCa was found over conventional imaging. This was true even at low serum PSA levels and adds to the evidence that PSMA-targeted PET is a promising modality for imaging patients with biochemical failure.

Key Points

Question: How frequently can PSMA-targeted PET with ^{18}F-DCFPyL detect sites of suspected recurrent PCa in men with negative conventional imaging?

Pertinent Findings: In this prospective study, 67.7% patients had at least one site of ^{18}F-DCFPyL uptake consistent with PCa. Even with low PSA values (< 1.0 ng/mL), 59.1% patients had findings compatible with sites of PCa.

Implications for Clinical Care: PSMA-targeted PET with ^{18}F-DCFPyL is sensitive for detecting suspected sites of recurrent PCa and may obviate the need for conventional imaging.

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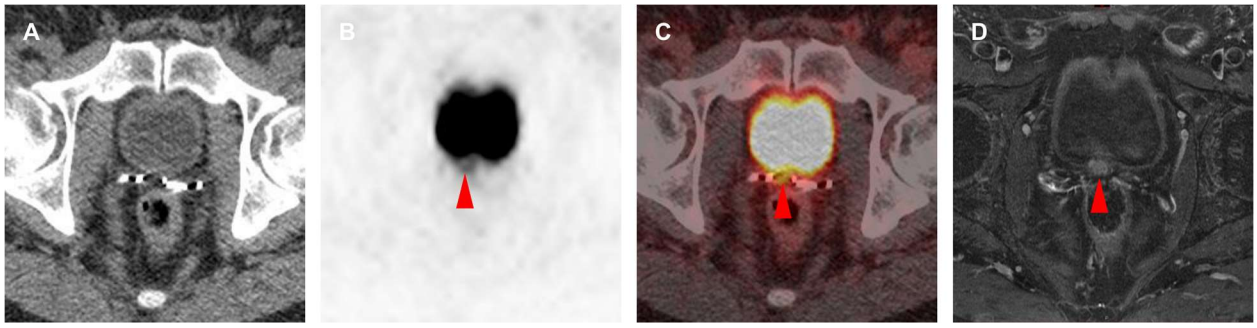

Figure 1. Local recurrence detected on ^{18}F-DCFPyL PET/CT in a patient with a PSA level of 0.3 ng/mL. (A) Axial, attenuation-correction CT, (B) axial ^{18}F-DCFPyL PET, and (C) axial ^{18}F-DCFPyL PET/CT images demonstrating subtle uptake in the prostate bed (SUV_{max} 3.8, red arrowheads). (D) Given the subtlety of the finding, confirmation was sought with pelvic magnetic resonance imaging, which demonstrated corresponding nodular enhancement (red arrowhead) on an axial, T1, post-contrast, fat-saturation sequence.

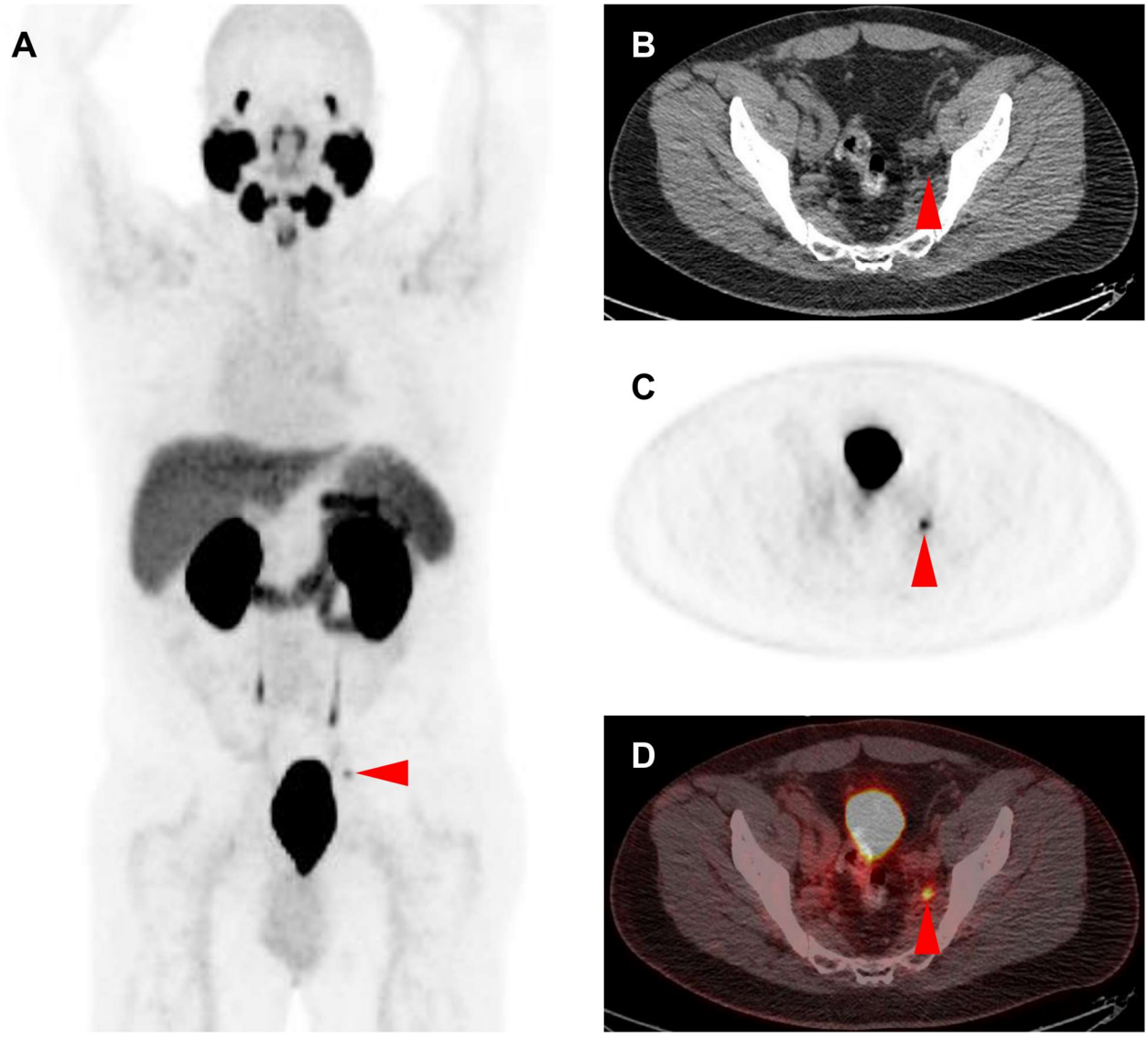

Figure 2. Pelvic lymph node recurrence detected on ^{18}F-DCFPyL PET/CT in a patient with a PSA level of 0.5 ng/mL. (A) Maximum intensity projection (B) axial, attenuation-correction CT, (C) axial ^{18}F-DCFPyL PET, and (D) axial ^{18}F-DCFPyL PET/CT images demonstrating positive uptake in a small left pelvic lymph node (SUV_{max} 4.3, red arrowheads).

Tables

Table 1. Selected demographics and clinical data for the study cohort

Parameter	Median (Range) / n (%)
Age (years)	63 (45 – 74)
White Race	27 (87.1)
Months Since Radical Prostatectomy	30 (4 – 152)
Gleason Grade Group	
1	2 (6.4)
2	6 (19.4)
3	13 (41.9)
4	1 (3.2)
5	9 (29.0)
Pathologic Stage	
pT2	11/31 (35.5)
pT3a	14/31 (45.2)
pT3b	6/31 (19.4)
N1	8/31 (25.8)
Positive Surgical Margin	13/31 (41.9)
PSA (ng/mL)	0.4 (0.2 – 28.3)

PSA = prostate specific antigen

Table 2. Sites of recurrent/metastatic PCa detected on PSMA-targeted ^{18}F-DCFPyL PET/CT

Anatomic Location	All Patients (n = 31) n (%)	PSA 0.2 – 1.0 ng/mL (n = 22) n (%)	PSA > 1.0 ng/mL (n = 9) n (%)
Prostate Bed	8 (25.8)	6 (27.2)	2 (22.2)
Pelvic Lymph Node(s)	14 (45.1)	6 (27.2)	8 (88.9)
Non-Pelvic Lymph Node(s)	2 (6.5)	0 (0.0)	2 (22.2)
Bone	2 (6.5)	1 (4.5)	1 (11.1)
Viscera	0 (0.0)	0 (0.0)	0 (0.0)
Any Site	21 (67.7)	13 (59.1)	8 (88.9)
>1 Site	5 (16.1)	0 (0.0)	5 (55.6)

PSA = prostate specific antigen