Diagnostic Performance of 18F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study

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ABSTRACT

Purpose: Current FDA-approved imaging modalities are inadequate for localizing prostate cancer biochemical recurrence (BCR). 18F-DCFPyL is a highly selective, small-molecule prostate-specific membrane antigen–targeted PET radiotracer. CONDOR was a prospective study designed to determine the performance of 18F-DCFPyL-PET/CT in patients with BCR and uninformative standard imaging.

Experimental Design: Men with rising PSA ≥0.2 ng/mL after prostatectomy or ≥2 ng/mL above nadir after radiotherapy were eligible. The primary endpoint was correct localization rate (CLR), defined as positive predictive value with an additional requirement of anatomic lesion colocalization between 18F-DCFPyL-PET/CT and a composite standard of truth (SOT). The SOT consisted of, in descending priority: (i) histopathology, (ii) subsequent correlative imaging findings, or (iii) post-radiation PSA response. The trial was considered a success if the lower bound of the 95% confidence interval (CI) for CLR exceeded 20% for two of three 18F-DCFPyL-PET/CT readers. Secondary endpoints included change in intended management and safety.

Results: A total of 208 men with a median baseline PSA of 0.8 ng/mL (range: 0.2–98.4 ng/mL) underwent 18F-DCFPyL-PET/CT. The CLR was 84.8%–87.0% (lower bound of 95% CI: 77.8–80.4). A total of 63.9% of evaluable patients had a change in intended management after 18F-DCFPyL-PET/CT. The disease detection rate was 59% to 66% (at least one lesion detected per patient by 18F-DCFPyL-PET/CT by central readers).

Conclusions: Performance of 18F-DCFPyL-PET/CT achieved the study’s primary endpoint, demonstrating disease localization in the setting of negative standard imaging and providing clinically meaningful and actionable information. These data further support the utility of 18F-DCFPyL-PET/CT to localize disease in men with recurrent prostate cancer.

Introduction

A challenging clinical dilemma in the management of prostate cancer is the occurrence of a rising serum PSA after curative intent surgery or radiotherapy in the absence of informative conventional imaging (1, 2). This condition, known as biochemical recurrence (BCR), indicates the presence of persistent or recurrent disease, without defining its location, and occurs in 20%–50% of men within 10 years after definitive local therapy (3–6). This inability to define recurrent disease localization is an unmet need and reflects the shortcomings of both PSA and current standard-of-care imaging modalities. Conventional imaging (CT, MRI; bone scintigraphy) perform poorly in localizing sites of disease recurrence in patients with BCR, particularly when PSA values are low (<2.0 ng/mL; refs. 7–9). Novel PET radiotracers, including FDA-approved agents (11C-choline and 18F-fluciclovine), have shown promise, but their predictive performance degrades with PSA levels <2.0 ng/mL (10–12). These limitations have stimulated the development of other agents with improved diagnostic performance, including radiotracers targeting the cell surface protein, prostate-specific membrane antigen (PSMA; refs. 13–16).

18F-DCFPyL is a small molecule that binds to the extracellular domain of PSMA with high affinity (17) and has shown success in studies evaluating the detection of prostate cancer across a range of disease states, including studies where histopathology served as reference standard (14, 18–20). Building upon an earlier phase II/III multicenter trial (OSPReY; NCT02981368; ref. 20) that evaluated the performance of 18F-DCFPyL-PET/CT in initial staging of high-risk prostate cancer and in detection of suspected recurrent/metastatic lesions seen on
Translational Relevance

In men with biochemically recurrent (BCR) prostate cancer, there is an unmet medical need for accurate disease localization such that treatment planning will be appropriate to the distribution of disease. These clinical decisions are generally made at low PSA values, when standard imaging performs poorly at demonstrating disease. Prostate-specific membrane antigen (PSMA)-targeted PET has been a promising candidate to detect disease otherwise not demonstrated by standard techniques. CONDOR is a prospective, multicenter study designed to demonstrate the diagnostic performance of the PSMA-targeted PET radiotracer 18F-DCFPyL for regulatory approval. The trial demonstrated that the radiotracer correctly localized disease in approximately 85% of men with BCR, all of whom had uninformative conventional imaging. These findings changed planned management in 64% of men. These data support the use of 18F-DCFPyL-PET/CT for disease localization in men with BCR, as it is significantly superior to standard imaging.

Materials and Methods

Trial design

CONDOR was a phase III, prospective, multicenter, open-label, single-arm study designed to evaluate the diagnostic performance and safety of 18F-DCFPyL-PET/CT in patients with suspected recurrent or metastatic prostate cancer with negative or equivocal conventional imaging (including 18F-fluorocholine or 11C-choline PET, CT, MRI, and/or whole-body bone scintigraphy) per institutional standard of care. The study was conducted across 13 sites in the United States and one in Canada, and was approved by the Institutional Review Board/Research Ethics Board at each participating institution. The study was conducted in accordance with the Declaration of Helsinki and the International Council on Harmonization Guidelines for Good Clinical Practice.

Study population

Men ≥18 years of age with biochemically recurrent adenocarcinoma of the prostate treated with radical prostatectomy (RP) or radiotherapy were eligible for the study. BCR after RP was defined as a rising PSA to ≥0.2 ng/mL (21). For patients treated with radiotherapy, BCR was defined as a PSA value ≥2 ng/mL above the patient’s post-radiation nadir value (22). All enrolled patients required negative/equivocal findings for prostate cancer on standard-of-care imaging performed 60 days prior to 18F-DCFPyL injection. Before enrollment, written informed consent was obtained from all patients.

Exclusion criteria included administration of any high-energy (>300 KeV) gamma-emitting radiisotope within five physical half-lives prior to 18F-DCFPyL injection, and androgen deprivation therapy (ADT) within 3 months of imaging, or investigational therapy for prostate cancer within 60 days of imaging. Ongoing systemic therapy for prostate cancer was prohibited. Patients with medical conditions or circumstances that, in the opinion of the investigator, would compromise the safety or compliance of the patient to produce reliable data or completing the study were also excluded.

Screening

Demographic information, baseline characteristics (date of birth, race, ethnicity, height, and weight), and clinically relevant medical history were recorded. The patient’s prostate cancer medical history, including American Joint Committee on Cancer stage, Gleason score, pretreatment PSA, and all past/present therapies, were obtained. Standard-of-care imaging per local practice obtained within 60 days before 18F-DCFPyL administration was reviewed. This imaging could include CT or MRI, bone scintigraphy or PET with 18F-fluorocholine or 11C-choline. All baseline images were submitted to a central imaging core laboratory for assessment. A blood sample for total PSA obtained at screening or just before administration of 18F-DCFPyL from enrolled patients was analyzed by a central core laboratory.

18F-DCFPyL dosing and PET/CT

The protocol-specified dose of 18F-DCFPyL was 9 mCi (333 MBq) administered intravenously 1–2 hours before PET/CT (Supplementary Table S1). Patients voided before imaging, and PET and non-contrast CT images were acquired from mid-thigh through skull vertex. All 18F-DCFPyL-PET/CT scans were submitted to the central imaging core laboratory for assessment. Patients with positive 18F-DCFPyL-PET/CT scans based on local interpretation were scheduled for subsequent follow-up to verify suspected lesion(s) based on a composite standard of truth (SOT; Fig. 1).

Tiered composite SOT

Because of the expected absence of an amenable lesion for histologic verification in most patients, a composite SOT was employed following FDA discussions, based on assessment performed or initiated within 60 days following 18F-DCFPyL-PET/CT. These reference standards...
were defined (in order of priority) as (i) evaluable histopathology results from prostatectomy, salvage pelvic lymph node dissection or targeted biopsy; (ii) correlative follow-up imaging findings using $^{18}$F-flucloxacilone or $^{11}$C-choline PET, or focused MRI or CT; or (iii) if neither of the above was available or informative, confirmed PSA response up to 9 months post-radiation initiation (without concomitant ADT) of all PET-positive foci. PSA response was defined as PSA decline by $\geq 50\%$ from baseline that was confirmed on repeat measurement within 4 weeks, based on central laboratory results.

Central imaging review

A central imaging core laboratory was employed to independently manage image handling, reader training, reader sessions, and data collection. This review consisted of two discrete imaging evaluations:

(i) $^{18}$F-DCFPyL-PET/CT assessment was performed by three independent, blinded, board-certified nuclear medicine physicians trained in the interpretation of $^{18}$F-DCFPyL-PET. The readers had no access to any clinical information, including PSA values or other imaging available for a patient. Each reader independently evaluated a patient’s $^{18}$F-DCFPyL-PET/CT study without access to information from either of the other two readers, the Truth Panel, the local Investigator, or study sponsor. Each central reader also measured standardized uptake values (SUV) on up to 25 PET-positive lesions seen on each scan.

(ii) Each image obtained as part of the SOT was assessed by two independent, board-certified nuclear medicine and radiology readers (the Truth Panel), who assessed these images in conjunction with the $^{18}$F-DCFPyL-PET/CT images for the presence or absence of prostate cancer. These readers also adjudicated the accuracy of needle placement during image-guided biopsy, if performed. The Truth Panel members were not members of the central $^{18}$F-DCFpyL-PET/CT reader group and were blinded to all data generated by the central $^{18}$F-DCFpyL-PET/CT readers.

Efficacy outcomes

The primary endpoint of the study was the correct localization rate (CLR) of $^{18}$F-DCFpyL-PET/CT. CLR, a novel endpoint recommended by the FDA, is a measure of positive predictive value (PPV) at the patient level that employed anatomic lesion location matching (colocalization) of a lesion identified by $^{18}$F-DCFpyL-PET/CT central readers and the lesion identified by Truth Panel central readers and/or pathology. CLR was defined as the percentage of patients with a one-to-one correspondence between at least one lesion identified on $^{18}$F-DCFpyL-PET/CT by the central readers and the composite SOT.

The secondary endpoints were the percentage of patients with a change in intended prostate cancer treatment plans after $^{18}$F-DCFpyL-PET/CT based on the MMQ that was completed pre- and post-$^{18}$F-DCFpyL-PET/CT, as well as safety of $^{18}$F-DCFpyL.

Exploratory endpoints were evaluation of detection rates and PPVs of $^{18}$F-DCFpyL-PET/CT at the region level (i.e., prostate/prostate bed, pelvis, and extrapelvic regions) and detection rate of $^{18}$F-DCFpyL-PET/CT as a function of baseline PSA (<0.5, 0.5–<1.0, 1.0–<2.0, 2.0–<5.0, or $\geq 5.0$ ng/mL).

Statistical methods

A full description of the determination of sample size is provided in the study protocol (Supplementary Appendix). On the basis of a meta-analysis by Perera and colleagues (23) of $^{68}$Ga-PSMA PET/CT, approximately 76% of PSMA scans are positive in suspected prostate cancer recurrence. In this study, 60% of the imaged patients were expected to have a positive $^{18}$F-DCFpyL-PET/CT scan and of these 30% were expected to have a confirmatory SOT finding in patients with negative/equivocal baseline imaging. Therefore, $^{18}$F-DCFpyL-PET/CT was expected to detect/localize recurrent disease in approximately 18% of the study population versus $\leq 5\%$ identified by conventional imaging. This required a total of 81 positive $^{18}$F-DCFpyL scans, or 134 evaluable patients. Accounting for a 30% nonevaluable/loss rate, the sample size was 192 patients.

The safety and efficacy populations for analysis consisted of all patients who received $^{18}$F-DCFpyL.

Primary endpoint analysis

The CLR is computed as $100 \times TP/(TP+FP)$, where TP = true positive result and FP = false-positive result for each central imaging reader. A TP result is defined as a patient with both a positive lesion(s) on $^{18}$F-DCFpyL-PET/CT and a positive result on the composite SOT within the same anatomic location as defined within the statistical analysis plan. The classification of the anatomic locations is provided in Supplementary Table S2 (24). A FP result was defined as a patient with positive lesion(s) on $^{18}$F-DCFpyL-PET/CT identified by the central reader with negative findings for prostate cancer according to the composite SOT. The success criterion for the primary endpoint was the lower limit of the 95% confidence interval (CI) to exceed 20% for at least two of the three readers. This criterion was based on data from the performance characteristics of other molecular imaging agents at PSA values <2 ng/mL (25). The two-sided 95% CI for CLR for each reader was calculated using the normal approximation for a single binomial variable.

Secondary endpoint analysis

The percentage of patients with a change in intended prostate cancer treatment plan before and after $^{18}$F-DCFpyL-PET/CT was reported with the corresponding two-sided 95% CI using the normal approximation for the binomial variable.

Exploratory endpoint analysis

The disease detection rate was defined as the percent of positive $^{18}$F-DCFpyL-PET/CT scans identified by the central imaging readers. It was calculated as the number of patients with positive scans divided by the number of patients who have evaluable scan results reported $\times 100\%$. PPV within anatomic regions without lesion-level matching was calculated for patients with positive $^{18}$F-DCFpyL-PET/CT scans as TP/(TP+FP) $\times 100\%$. Detection rate and PPV by region (i.e., prostate/prostate bed, pelvis, extrapelvic) and as a function of baseline PSA were analyzed for each central imaging reviewer and for the local site interpretation separately using a two-sided 95% CI based on a normal approximation to the binomial distribution.

Interreader and intrareader agreement

Interreader agreement between the central readers at the subject level was assessed using Fleiss' generalized kappa. Agreement between each central reader and the local reader was calculated using Cohen pairwise kappa. For intrareader agreement, each central reader assessed 42 subjects (20%) twice as part of their reading schedule after a washout period of at least 28 days following the initial review, without knowledge that the cases were read twice. Cohen kappa was calculated to assess agreement for each reader. All kappa statistics are reported with their respective 95% CIs.
Table 1. Baseline characteristics and 18F-DCFPyL dosing/uptake time.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n = 208</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years): median (range)</td>
<td>68 (43–91)</td>
</tr>
<tr>
<td>Age ≥65 years, n (%)</td>
<td>141 (67.8)</td>
</tr>
<tr>
<td>Months from prostate cancer diagnosis: median (range)</td>
<td>71 (3–356)</td>
</tr>
<tr>
<td>Prior prostate cancer therapies</td>
<td></td>
</tr>
<tr>
<td>RP only, n (%)</td>
<td>103 (49.5)</td>
</tr>
<tr>
<td>RT only, n (%)</td>
<td>31 (14.9)</td>
</tr>
<tr>
<td>RP and RT, n (%)</td>
<td>74 (35.6)</td>
</tr>
<tr>
<td>At least one prior systemic therapy, n (%)</td>
<td>58 (27.9)</td>
</tr>
<tr>
<td>Total Gleason score, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>153 (73.6)</td>
</tr>
<tr>
<td>6 &lt; 3 + 6</td>
<td>12 (5.8)</td>
</tr>
<tr>
<td>3 + 4 = 7</td>
<td>78 (37.5)</td>
</tr>
<tr>
<td>4 &lt; 3 + 7</td>
<td>60 (28.8)</td>
</tr>
<tr>
<td>≥8</td>
<td>55 (26.4)</td>
</tr>
<tr>
<td>3 + 5 = 8</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>4 + 4 = 8</td>
<td>21 (10.1)</td>
</tr>
<tr>
<td>5 + 3 = 8</td>
<td>31 (14.9)</td>
</tr>
<tr>
<td>5 + 4 = 9</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>5 + 5 = 10</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PSA (ng/mL) (n = 202): median (range)</td>
<td>0.8 (0.17–98.45)</td>
</tr>
<tr>
<td>PSA sample collection study day prior to administration of 18F-DCFPyL (study day) (n = 202): median (range)</td>
<td>1 (–29–1)</td>
</tr>
<tr>
<td>PSA group (n = 202), n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;2.0 ng/mL</td>
<td>139 (68.8)</td>
</tr>
<tr>
<td>&lt;0.5 ng/mL</td>
<td>69 (34.2)</td>
</tr>
<tr>
<td>0.5 to &lt;1.0 ng/mL</td>
<td>37 (18.3)</td>
</tr>
<tr>
<td>1.0 to &lt;2.0 ng/mL</td>
<td>33 (16.3)</td>
</tr>
<tr>
<td>≥2.0 ng/mL</td>
<td>63 (31.2)</td>
</tr>
<tr>
<td>2.0 to &lt;5.0 ng/mL</td>
<td>33 (16.3)</td>
</tr>
<tr>
<td>≥5.0 ng/mL</td>
<td>30 (14.9)</td>
</tr>
<tr>
<td>18F-DCFPyL dosing and uptake time</td>
<td></td>
</tr>
<tr>
<td>Administered activity, mcCi: median (range)</td>
<td>9.42 (7.49–11.07)</td>
</tr>
<tr>
<td>Administered activity, MBq: median (range)</td>
<td>349 (277–410)</td>
</tr>
<tr>
<td>Time from injection to imaging (minutes): median (range)</td>
<td>79 (59–115)</td>
</tr>
</tbody>
</table>

Abbreviations: PSA, Prostate-specific antigen; RP, Radical prostatectomy; RT, Radiation therapy.

Safety outcomes

Safety assessments included monitoring for the incidence of treatment-emergent adverse events (AE) from the time of 18F-DCFPyL dosing up to 7 ± 3 days post-dose. AEs were graded according to the NCI Common Terminology Criteria for Adverse Events, Version 4.03.

Results

The Standards for Reporting of Diagnostic Accuracy (STARD) flow diagram is depicted in Fig. 1. A total of 208 patients were enrolled between November 2018 and August 2019. The median age was 68 years (range, 43–91); 67.8% were ≥65 years old. The median baseline PSA level was 0.8 ng/mL (range, 0.2–98.4); 68.8% of patients had PSA levels <2.0 ng/mL. The median time from the initial prostate cancer diagnosis was 71 months (range, 3–356). Prior treatment was RP in 49.5%, RP and radiotherapy in 35.6%, and radiation alone in 14.9%. Baseline characteristics, PET imaging, and baseline conventional imaging details are further summarized in Table 1; Supplementary Fig. S1; Supplementary Table S3.

18F-DCFPyL-PET/CT detected ≥1 lesion in 59.1% to 65.9% patients as assessed by three independent blinded central readers. The primary endpoint of CLR was met as the lower limit of 95% CI exceeded 20% for all three readers. The CLR ranged from 84.8% to 87.0% among the three readers (the lower bound of the 95% CI ranged from 77.8% to 80.4%; Table 2).

The performance of 18F-DCFPyL-PET/CT by CLR and PPV was maintained through all categories of the SOT: histopathology (N = 31): 78.6%–82.8% and 92.9%–93.3% for CLR and PPV, respectively; correlative imaging (N = 100): 86.1%–88.6% and 87.0%–89.5% for CLR and PPV, respectively; and PSA response (N = 1): 100% for both CLR and PPV. Further analyses of the correlative imaging results showed CLR maintained high across the different modalities used (i) 18F-flucilavone-PET/CT (N = 71): (86.8%–90.9%); (ii) MRI (N = 23): (80.0%–86.7%); and (iii) CT (n = 6): (80.0%–100%; Supplementary Tables S4–S6). The CLRs for each reader also were maintained across prior treatment regimens (Supplementary Table S7) and increased with the within-patient maximum standardized uptake value (SUVmax) of lesions identified on 18F-DCFPyL-PET/CT (Supplementary Table S8).

CLR by baseline PSA and detection rate

In patients with baseline PSA levels <0.5 ng/mL, the median CLR was 73.3% while patients with a PSA of ≥2.0 ng/mL had a median CLR of 96.4% (Fig. 2A; Supplementary Table S9). The detection rate rose with increasing PSA levels ranging from 36.2% (<0.5 ng/mL) to 96.7% (≥2.0 ng/mL; Fig. 2B; Supplementary Table S10).

PPV by anatomic region

PPV of 18F-DCFPyL-PET/CT was determined in detection of recurrent disease by anatomic regions (prostate/prostate bed, pelvis,

Table 2. Disease detection and CLR across three independent readers.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 208)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reader 1 95% CI (%)</td>
</tr>
<tr>
<td>Negative PyL scan</td>
<td>71 (34.1%)</td>
</tr>
<tr>
<td>Positive PyL scan</td>
<td>137 (65.9%)</td>
</tr>
<tr>
<td>Unevaluable*</td>
<td>33</td>
</tr>
<tr>
<td>CLR (TP/TP+FP)</td>
<td>89/104 (85.6%)</td>
</tr>
</tbody>
</table>

*Some patients were un evaluable for the primary endpoint, either because no SOT was submitted (between 17 and 25 patients, depending on the central reader), or because the 18F-DCFPyL-PET/CT scan was deemed a false negative based on lesion level colocalization (7–8 patients), which was not a component of the primary endpoint calculation (due in part to the lack of specificity of comparative conventional imaging modalities).
and extrapelvic regions) from the composite SOT in patients with at least one $^{18}$F-DCFPyL-positive lesion. The PPV was consistently high across all anatomic regions. The PPV in the prostatic region ranged between 75.0% and 83.3% among the three independent readers. Similarly, for pelvic lymph nodes, the PPV was between 67.2% and 72.7%, and for the extrapelvic regions, it ranged from 67.3% to 69.8%. (Fig. 3; Supplementary Tables S11 and S12). The distribution of positive $^{18}$F-DCFPyL-PET/CT findings by anatomic region is shown in Supplementary Table S13.

**Interreader and intrareader agreement**

Reader agreement results are summarized in Supplementary Table S14. Interreader agreement had a concordance of 75% and Fleiss’ kappa of 0.65 (95% CI: 0.58–0.73). Agreement between the central and local readers had concordances of 83.2% to 83.7% and kappas of 0.62 (95% CI: 0.50–0.73), 0.65 (95% CI: 0.54–0.75), and 0.64 (95% CI: 0.53–0.74) for the three readers. Intra-reader agreement had kappas of 0.94 (95% CI: 0.82–1.0), 1.0 and 0.81 (95% CI: 0.64–0.98) for the three readers.
Change in planned medical management

The treating physicians completed pre- and post-\[^{18}\text{F}-\text{DCFPyL}-\text{PET/CT}\] MMQs for 205 patients. Nearly two-thirds (63.9%; \(n = 131\)) of these patients had a change in intended disease management plan. Of these 131 patients, 103 (78.6%) were associated with positive \[^{18}\text{F}-\text{DCFPyL}-\text{PET/CT}\] findings, and 28 (21.4%) were associated with negative findings. Of the 144 patients that had a positive \[^{18}\text{F}-\text{DCFPyL}\] scan, 103 (72.5%) had a recommended change in the management plan. The most frequent changes to treatment management plans after the \(^{18}\text{F}-\text{DCFPyL}-\text{PET/CT}\) imaging results included salvage local therapy that was either supplemented or replaced by systemic therapy (\(n = 58; 28.3\%\)), observation to initiating therapy (\(n = 49; 23.9\%\)), systemic therapy to salvage local therapy (\(n = 43; 21.0\%\)), and planned treatment to observation (\(n = 9; 4.4\%\); Fig. 4; Supplementary Table S15).

Safety results

Fourteen (6.7%) patients experienced 21 AEs; headache (1.9%), fatigue (1.0%), and hypertension (1.0%) were most frequent. Only 1 patient (0.5%), with a significant history of allergic reactions, experienced serious, grade 3 AEs (hypersensitivity, headache, paresthesia), all of which resolved. There were no grade 4 AEs or deaths.

Discussion

This study was designed to evaluate the performance of \[^{18}\text{F}-\text{DCFPyL}-\text{PET/CT}\] in patients with prostate cancer with BCR and noninformative standard-of-care imaging. CONDOR used a central reader paradigm, and a novel primary efficacy endpoint with a composite SOT. The study demonstrated a high CLR that suggests \[^{18}\text{F}-\text{DCFPyL}-\text{PET/CT}\] is a superior and reliable tool for the detection and localization of sites of disease in men with BCR relative to conventional imaging.

The CONDOR population generally represents patients with BCR with low PSA values (median PSA 0.8 ng/mL), when crucial clinical decisions are made as to whether the patient warrants salvage therapy with curative intent, or systemic therapy without curative intent, or some combination of local and systemic treatments. An accurate
understanding of the location and burden of disease is key to well-informed treatment planning. In our study population, the PSA was <2.0 ng/mL in 68.8% of patients, <1.0 ng/mL in 52.5%, and <0.5 ng/mL in 34.2%. As such, the study provides prospective evidence of diagnostic accuracy to reliably detect prostate cancer recurrence or metastases in patients in whom currently available conventional imaging and approved molecular imaging modalities are suboptimal. Notably, a total of 59.6% to 65.9% of patients had at least one occult lesion detected among the three readers and the CLR was consistently high across all SOT determinations, anatomic regions, and in patients with PSA 0.2 to <2.0 ng/mL (>73%). This performance of 18F-DCFPyL-PET/CT is substantially better than the reported detection rates and PPVs of 18F-fluciclovine- and 11C-choline-PET in patients with similar PSA ranges, although each tracer may behave differently depending on risk factors beyond absolute PSA value, such as Gleason grade, growth rate, histologic subtype, and other measures (11, 12, 15).

Another PSMA-targeted PET radiopharmaceutical, 68Ga-PSMA-11, is widely used in clinical practice outside of the United States and recently received FDA approval (26). In a prospective study by Fendler and colleagues, this imaging agent had similar results, with PPV of 0.84 (95% CI: 0.75–0.90) by histopathologic comparator (primary endpoint, n = 87) and 0.92 (95% CI: 0.88–0.95) by a composite reference standard, in men with BCR; of note, unlike CONDOR, in the Fendler study, patients were eligible irrespective of prior conventional imaging findings (27). Eiber and colleagues were one of the first to report positive findings with 68Ga-PSMA-11 in patients with post-RP BCR with low PSA values (<0.5 ng/mL; ref. 28). However, retrospective studies with 68Ga-PSMA-11, while including prespecified endpoints and statistical designs, did not require negative standard imaging (29, 30).

This study furnishes direct evidence that clinicians intend to utilize the additional information provided by the 18F-DCFPyL scan to revise their treatment plans and goals of care relative to their original plans based on clinical presentation and noninformative standard imaging. The ability of 18F-DCFPyL-PET/CT to localize and detect the extent of recurrent disease offers physicians the opportunity to adjust and tailor their treatment planning and potentially improve treatment outcomes in men with recurrent prostate cancer. Although change in patient management after PET occurred frequently, this study was not designed to determine whether such changes were implemented or ultimately benefited patients. Furthermore, this study, which was designed to establish the relationship between a positive imaging finding and a positive composite SOT, does not establish that a given PSMA-avid lesion represents the only lesion that is producing PSA, or that a specifically identified lesion represents the clone of the disease likely to be lethal for the patient. However, a recent multicenter prospective study of PET/CT using 68Ga-PSMA-11 did show that negative or prostate-bed-only positive findings were highly predictive of

![Figure 4. Change in planned medical management.](image-url)
response to salvage radiotherapy after RP. These results show that PSMA-PET can help to select patients most likely to benefit from a particular therapy (31). However, future studies will be necessary to demonstrate whether 18F-DCEPPyL-PET/CT-directed changes in management lead to improved outcomes for patients with prostate cancer with BCR.

While prospective single-center trials with 18F-DCEPPyL-PET imaging in BCR have been reported recently, only Mena and colleagues reported PPV verified by a composite SOT (6, 14, 32, 33). CONDOR represents the first multicenter prospective trial of 18F-DCEPPyL-PET for the BCR population. By design, the study focused on CLR, which fundamentally is a patient-level PPV with the added criterion of anatomic cocolocalization. Consequently, a limitation of this study is that the “truth” in men with negative 18F-DCEPPyL-PET/CT per local radiology assessment is unknown, because verification of 18F-DCEPPyL-PET/CT results was not required in such patients. Trying to find occult disease not detected by PET would have required following these patients without treatment to see whether the disease became evident over time; this was not a practical or ethical option. Thus, we cannot determine whether these false-negative cases reflect PSMA-negative disease (which occurs in 5%–10% of prostate cancers; ref. 34), inexperience of local readers, or small-volume disease (similar to the poor detection of small nodal deposits in OSPREY cohort A: 20), or obscuration of lesions in or adjacent to organs with high uptake of 18F-DCEPPyL (e.g., liver) or structures containing excreted tracer (ureters, bladder, urethra). Accordingly, the negative predictive value of 18F-DCEPPyL-PET/CT in this patient population with noninformative imaging could not be assessed.

PSMA-targeted PET radiopharmaceuticals labeled with 18F can offer an alternative to 68Ga agents. There are few direct comparisons of the two tracers (35, 36), but these suggest that the performance of 18F-DCEPPyL is similar to that of the 68Ga agents. In summary, this study met its primary endpoint of high CLR and demonstrated that the additional information provided by 18F-DCEPPyL-PET/CT was associated with frequent changes in disease management plans. These data support 18F-DCEPPyL-PET/CT as a safe and robust imaging tool to reliably detect recurrent prostate cancer, even at low PSA levels, thus providing new actionable information by the localization of otherwise occult disease.

Authors’ Disclosures

M.J. Morris reports personal fees from Progenics prior to the conduct of the study, as well as personal fees from Orci and Curium and nonfinancial support from Endocyte and Fujifilm outside the submitted work. S.P. Rowe reports grants from Progenics Pharmaceuticals during the conduct of the study, as well as personal fees from Precision Molecular, Inc. and grants from FutureChem Co., Ltd. outside the submitted work. M.A. Gorin reports personal fees from BK Medical, KOELIS Inc, Corbin Clinical Resources (Perineologic), and OBS Medical outside the submitted work. CHU de Quebec received funds from Progenics Inc. to cover the direct costs of the study. K.L. Gage has been a consultant for Astellas, Janssen, Sanofi, Bayer, Amgen and Tersera. A.R. Pantel reports grants from Progenics during the conduct of the study, as well as personal fees from GE Healthcare and Advanced Accelerator Applications outside the submitted work. V. Wong has a patent for 18F-DCEPPyL patent pending and was an employee of Progenics Pharmaceuticals. L. Lin reports other from Progenics outside the submitted work. N. Stambler reports other from Progenics Pharmaceuticals, Inc. during the conduct of the study. P.R. Carroll reports personal fees from Progenics during the conduct of the study, as well as other from Nutcracker Therapeutics and personal fees from Inisightec and Francis Medical outside the submitted work. B.A. Siegel reports grants and personal fees from Progenics Pharmaceuticals during the conduct of the study, as well as grants and personal fees from American College of Radiology, Imaginab, Inc., and Blue Earth Diagnostics; personal fees from American Medical Foundation for Peer Review & Education, Avid Radiopharmaceuticals, Inc., Capella Imaging, LLC, Conven Capital Management (VI) General Partner Limited, Curium Pharma, Radiological Society of North America; and personal fees from Siemens Healthineers outside the submitted work. A.G. Wibner reports other from Memorial Sloan Kettering Cancer Center (MSKCC) during the conduct of the study. J.C. Durack reports nonfinancial support and other from Lantheus during the conduct of the study, as well as personal fees from Verix Medical outside the submitted work, and is Past Chair, Society of Interventional Radiology Foundation and Chair, American College of Radiology Interventional Radiology Research Committee. S.B. Solomon reports other from Lantheus during the conduct of the study, as well as grants from GE Healthcare outside the submitted work. P. Sprekel reports nonfinancial support and other from Progenics during the conduct of the study. T.B. Dorr reports personal fees from Advanced Accelerator Applications outside the submitted work. V. Narayan reports grants and personal fees from Pfizer, Merck, and Janssen; personal fees from Regeneron, Amgen, and Myovant Sciences; and grants from Tmunity Therapeutics outside the submitted work. Z.S. Morris reports personal fees and other from Archeus Technologies and other from Seneca Therapeutics outside the submitted work. A.S. Alva reports grants from Progenics; grants and personal fees from AstraZeneca, Merck, and BMS; personal fees from Pfizer/EMD Serono; and grants from Astellas/Seattle Genetics, Prometheus, Clovis, and Arcus Biosciences outside the submitted work. D. Spratt reports grants and personal fees from Janssen and personal fees from Blue Earth, Boston Scientific, and AstraZeneca outside the submitted work. J.P. Simko reports grants from Progenics during the conduct of the study, as well as grants from Intuitive Surgical outside the submitted work. J.W. Jennings reports grants from Progenics Pharmaceuticals during the conduct of the study. No disclosures were reported by the other authors.

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