18F-DCFBC PET/CT for PSMA-Based Detection and Characterization of Primary Prostate Cancer

Steven P. Rowe*1, Kenneth L. Gage*1, Sheila F. Faraj2, Katarzyna J. Macura1,3,4, Toby C. Cornish2, Nilda Gonzalez-Roibon2, Gunes Guner2, Enrico Munari2, Alan W. Partin3, Christian P. Pavlovich3, Misop Han3, H. Ballentine Carter3, Trinity J. Bivalacqua2, Amanda Blackford1, Daniel Holt1, Robert F. Dannals1, George J. Netto2–4, Martin A. Lodge1, Ronnie C. Mease1, Martin G. Pomper1, and Steve Y. Cho1–4

1The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins Medical Institutions, Baltimore, Maryland; 2Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, Maryland; 3The James Buchanan Brady Urological Institute and Department of Urology, Johns Hopkins Medical Institutions, Baltimore, Maryland; and 4Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, Maryland

We previously demonstrated the ability to detect metastatic prostate cancer using N-[4-18F]-fluorobenzyl-L-cysteine (18F-DCFBC), a low-molecular-weight radiotracer that targets the prostate-specific membrane antigen (PSMA). PSMA has been shown to be associated with higher Gleason grade and more aggressive disease. An imaging biomarker able to detect clinically significant high-grade primary prostate cancer reliably would address an unmet clinical need by allowing for risk-adapted patient management. Methods: We enrolled 13 patients with primary prostate cancer who were imaged with 18F-DCFBC PET before scheduled prostatectomy, with 12 of these patients also undergoing pelvic prostate MR imaging. Prostate 18F-DCFBC PET was correlated with MR imaging and histologic and immunohistochemical analysis on a prostate-segment (12 regions) and dominant-lesion basis. There were no incidental extraprostatic findings on PET suggestive of metastatic disease. Results: MR imaging was more sensitive than 18F-DCFBC PET for detection of primary prostate cancer on a per-segment (sensitivities of up to 0.17 and 0.39 for PET and MR imaging, respectively) and per-dominant-lesion analysis (sensitivities of 0.46 and 0.92 for PET and MR imaging, respectively). However, 18F-DCFBC PET was more specific than MR imaging by per-segment analysis (specificities of 0.96 and 0.89 for PET and MR imaging for corresponding sensitivity, respectively and specific for detection of primary prostate cancer (Gleason 9 and 9) greater than 1.0 mL in size (4/4 of these patients positive by PET). 18F-DCFBC uptake in tumors was positively correlated with Gleason score (r = 0.64; PSMA expression, r = 0.47; and prostate-specific antigen, r = 0.52). There was significantly lower 18F-DCFBC uptake in benign prostatic hypertrophy than primary tumors (median maximum standardized uptake value, 2.2 vs. 3.5; P = 0.004).

Conclusion: Although the sensitivity of 18F-DCFBC for primary prostate cancer was less than MR imaging, 18F-DCFBC PET was able to detect the more clinically significant high-grade and larger-volume tumors (Gleason score 8 and 9) with higher specificity than MR imaging. In particular, there was relatively low 18F-DCFBC PET uptake in benign prostatic hypertrophy lesions, compared with cancer in the prostate, which may allow for more specific detection of primary prostate cancer by 18F-DCFBC PET. This study demonstrates the utility of PSMA-based PET, which may be used in conjunction with MR imaging to identify clinically significant prostate cancer.

Key Words: primary prostate cancer; prostate specific membrane antigen (PSMA); PET/CT; MRI; prostatectomy

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Those radiotracers are able to demonstrate increased PET uptake at sites of primary prostate cancer, compared with normal prostate tissue, but generally have limited specificity for differentiating malignant from nonmalignant processes, such as BPH and prostatitis, and have low sensitivity for small tumors. Additional new PET radiotracers are being developed, including small molecules that target the prostate-specific membrane antigen (PSMA), gastrin-releasing peptide receptor, and glutamine, all of which show promise for imaging prostate cancer but have not been systematically evaluated for detection of primary disease (15–18).

PSMA is a rational and promising target for imaging prostate cancer given its high expression in this disease. Expression in primary and metastatic lesions is associated with tumor grade and clinical outcome (19–21). We have previously demonstrated the ability of \( N-[N-(3)-13\text{dicarboxypropyl}][\text{carbamoyl}-4\text{-18F-fluorobenzyl-}l\text{-cysteine (18F-DCFBC; Fig. 1) to bind to prostate tumors with high PSMA expression in preclinical studies (22) and in a first-in-human study, to localize prostate metastases to both bone and soft tissue accurately (23). In this prospective study, we further evaluated 18F-DCFBC PET for detection and characterization of primary prostate cancer in men undergoing definitive surgery with correlation to pelvic MR imaging and pathology postprostatectomy.

**MATERIALS AND METHODS**

**Patient Population and Selection**

All studies were performed in accordance with the Johns Hopkins University Institutional Review Board under a Food and Drug Administration exploratory investigational new drug application (eIND 108943). Written, informed consent was obtained from all patients. Pertinent inclusion criteria for this study included newly diagnosed patients with biopsy-proven prostate cancer with a Gleason score of 6 or greater, considered as candidates for and medically fit to undergo prostatectomy, and at least 10 d after the most recent prostate biopsy at the time of PET imaging. Pertinent exclusion criteria included prior prostatectomy, and at least 10 d after the most recent prostate biopsy at the time of PET imaging. Pertinent exclusion criteria included prior prostatectomy, and at least 10 d after the most recent prostate biopsy at the time of PET imaging. Pertinent exclusion criteria included prior prostatectomy, and at least 10 d after the most recent prostate biopsy at the time of PET imaging. Pertinent exclusion criteria included prior prostatectomy, and at least 10 d after the most recent prostate biopsy at the time of PET imaging.

**PET/CT Protocol**

Patients were instructed to be nil per os (except for water and some medications) for at least 6 h before the administration of 18F-DCFBC. Patients were specifically asked not to take multivitamins and folic acid supplements on the day of the examination because folic acid is a substrate for PSMA and high folate levels can potentially reduce 18F-DCFBC binding (15,27). Serum folate was obtained before 18F-DCFBC administration. A coudé catheter was placed in the urinary bladder as tolerated, which allowed for a consistent reference point between both PET and MR imaging in these patients, permitting improved PET and MR imaging coregistration.

PET/CT was performed on a Discovery DRX PET/CT scanner (GE Healthcare) operating in 2-dimensional (2D) and 3-dimensional (3D) emission acquisition mode with CT for attenuation correction. Scans were obtained with patients supine. A bolus of 370 ± 37 MBq (10 ± 1 mCi) of 18F-DCFBC was injected by slow intravenous push. Two hours after injection, a CT of the pelvis was obtained (120 kVp, 80 mA maximum [auto-adjusting]), followed by a 30-min dynamic list-mode 2D PET emission acquisition, then an additional 5-min pelvic 3D PET, both with the prostate in the center of the field of view. Two-dimensional PET acquisition mode was used for this pelvic PET imaging to minimize potential scatter caused by a PET quantitation artifact from the high urinary radioactivity in the bladder. Six 5-min frames were reconstructed with a high-resolution filter and summed to produce the 2D pelvic PET images. Pelvic PET images were acquired with the patient on a flat table with arms raised to allow for optimal coregistration with the corresponding MR images. After completion of the dynamic pelvic PET/CT scans at approximately 2.5 h after injection, a whole-body (WB) PET/CT was acquired from the vertex of the skull through the mid thigh in 3D mode for 4 min and 15 s at each bed position. All PET images were reconstructed using a standard clinical ordered-subset expectation maximization algorithm.

**MR Imaging Acquisition**

All pelvic MR imaging studies were obtained on the same day as the PET acquisitions except for 1 patient imaged 9 d later. MR imaging studies were performed on a 3-T WB TRIO scanner with a TIM body matrix coil (Siemens Medical Solutions). The sequences acquired included thin-section high-resolution axial, coronal, and sagittal T2-weighted fast spin-echo, diffusion-weighted imaging with corresponding apparent diffusion coefficient (ADC) maps from a 2D multislice single-shot diffusion-weighted echo planar sequence and a single-slab 3D isotropic T2-weighted turbo spin-echo sequence (SPACE or sampling perfection with application-optimized contrast...
using different flip-angle evolution). The 3D T2-weighted SPACE sequence was acquired to allow high-fidelity coregistration with the PET and CT images given that its isometric voxels could be reconstructed in any needed plane. Axial T1 noncontrast images were obtained using a gradient echo technique with low flip angles (FLASH or fast low-angle shot). No gadolinium contrast-enhanced imaging was acquired as the T1 sequence was primarily used to identify areas of hemorrhage.

Image Analysis

Three experienced nuclear medicine interpreters, who were masked to the MR imaging and histopathologic results, reached a consensus determination on 18F-DCFBC uptake within the prostate on both a lesion and a sector basis. Visual analysis was used to define focal 18F-DCFBC uptake as being above background activity in the prostate and blood pool in the periprostatic vascular plexus. For the subsequent analysis, foci of uptake were defined on a 3-point scale as 1, negative; 2, equivocal; or 3, positive. PET maximum standardized uptake values (SUVR) corrected for lean body mass were calculated for the foci of PET uptake in the prostate on the 2D pelvis, 3D pelvis, and WB PET acquisitions using XD Software (Mirada Medical USA). For sites of prostate tumors seen on pathology that were occult on PET, a tumor SUVR max was obtained using a representative spheric 1-cm diameter volume of interest placed in the approximate tumor location on each PET acquisition, using the prostatectomy specimen as a guide. To evaluate uptake in BPH, the axial T2-weighted MR images were virtually fused to each of the 2D pelvis, 3D pelvis, and WB PET acquisitions using rigid registration with the femoral heads as fiducial markers on the Mirada Medical workstation. Ellipsoid volumes of interest corresponding to the T2 signal abnormalities deemed to be representative of BPH on the MR images were then drawn, and the SUVR max for each focus of BPH was determined. Care was taken in drawing the volume of interest of all cases of both tumor and BPH to include only the strongly staining portions of the tumor (H score str) or only the strongly staining portions of the tumor (H score mod-str) multiplied by the extent of expression (0%–100%).

Histopathologic Analysis

All 13 patients who participated in the imaging portion of the study proceeded to have radical prostatectomy with lymph node dissection as is the standard of surgical care at our institution. Briefly, prostate specimens were injected with formalin. Nine were subsequently microwave-fixed, and 4 were fixed in formalin overnight. After fixation, the external surface was differentially inked to indicate the surgical margins per our laboratory standard protocol. The prostatectomy specimens were axially serially sectioned at 4-mm intervals after the proximal and the distal margins and seminal vesicles were removed and entirely submitted for histologic examination. All prostate slices were photographed with a ruler, labeled, and then quartered to produce right anterior, left anterior, right posterior, and left posterior segments; in combination with the base, mid, and apex designations, this method of sectioning the gland provided the basis for the 12-segment model used extensively for lesion localization.

The prostate tissue fragments were embedded in paraffin and stained with hematoxylin and eosin using standard methods. An expert urologic pathologist reviewed the slides and noted the presence of any prostate cancer, Gleason grades, and the size of the tumors. A representative section from the dominant (index) nodule in each prostatectomy specimen was selected for immunohistochemical analysis. The dominant nodule was defined as the nodule with the highest Gleason score tumor, which in most cases was also the largest in size. If a higher Gleason grade was noted in a smaller nodule, that smaller nodule was considered the dominant.

The representative sections from the dominant (index) tumor nodule were then analyzed by immunohistochemical methods for the expression of PSMA, prostate-specific antigen (PSA), ERG, and Ki-67. Appropriate internal and external controls were also processed and assessed in parallel. An H score was assigned as the sum of the products of the intensity (0 for negative, 1 for weakly positive, 2 for moderately positive, and 3 for strongly positive) multiplied by the extent of expression (0%–100%), obtaining a value ranging from 0 to 300 (28). The presence of Ki-67 was reported as a percentage of the tumor cells that demonstrated positive staining. Modified H scores were calculated for PSMA, taking into account only the strongly and moderately staining portions of the tumor (H score mod-str = [(percentage of tumor strongly staining × 3) + (percentage of tumor moderately staining × 2)]) or only the strongly staining portions of the tumor (H score str = [percentage of tumor strongly staining × 3]). The PSMA H scores (including H score mod-str

![Table 1](jnm.snmjournals.org)
TABLE 2
PET and MR Imaging Detection of Prostate Cancer on 12-Segment Prostatectomy Pathology

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All positive</td>
<td>0.39 (0.25–0.54), n = 69</td>
<td>0.89 (0.81–0.94), n = 75</td>
<td>0.73 (0.53–0.87), n = 34</td>
<td>0.58 (0.37–0.77), n = 110</td>
<td>0.65 (0.51–0.76), n = 144</td>
</tr>
<tr>
<td>Stringent</td>
<td>0.35 (0.20–0.55), n = 69</td>
<td>0.91 (0.82–0.95), n = 75</td>
<td>0.73 (0.50–0.88), n = 29</td>
<td>0.58 (0.36–0.77), n = 115</td>
<td>0.62 (0.48–0.75), n = 144</td>
</tr>
<tr>
<td>18F-DCFBC PET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All positive</td>
<td>0.17 (0.09–0.29), n = 77</td>
<td>0.96 (0.87–0.99), n = 79</td>
<td>0.81 (0.51–0.95), n = 16</td>
<td>0.53 (0.35–0.70), n = 140</td>
<td>0.57 (0.42–0.71), n = 156</td>
</tr>
<tr>
<td>Stringent</td>
<td>0.10 (0.04–0.25), n = 77</td>
<td>1.00 (1.00–1.00), n = 79</td>
<td>1.00 (1.00–1.00), n = 8</td>
<td>0.53 (0.35–0.70), n = 148</td>
<td>0.56 (0.39–0.71), n = 156</td>
</tr>
</tbody>
</table>

Data in parentheses are 95% confidence intervals.

and H score×volume) were also multiplied by the dominant nodule volumes to provide additional metrics designated by (H-score × volume).

Correlation Between Histopathology and Imaging
Hematoxylin and eosin slides were scanned at 20× using iScan Coreo (Ventana). Photoshop CS6 (Adobe Systems) was used to manually reassemble the prostate quarters into full slices and to register the histology sections to the gross photographs. For each reassembled slice, outlines of tumor, urethra, and prostate gland were then created as layers in Photoshop.

Correlation between histology and the imaging modalities was performed on a per-segment and per-lesion basis. First, the 12-segment prostate model was used, designating each segment containing prostate cancer determined at pathology. Each suggestive finding previously performed on a per-segment and per-lesion basis. First, the 12-segment slice, outlines of tumor, urethra, and prostate gland were then created from the histology sections to the gross photographs. For each reassembled slice, outlines of tumor, urethra, and prostate gland were then created as layers in Photoshop.

Correlation between histology and the imaging modalities was performed on a per-segment and per-lesion basis. First, the 12-segment prostate model was used, designating each segment containing prostate cancer determined at pathology. Each suggestive finding previously noted on 18F-DCFBC PET and prostate MR imaging interpretation was assigned to 1 or more contiguous segments depending on its location and extent. Additionally, BPH and hemorrhage identified on MR imaging were assigned to segments in which they were present. In that particular set of patients, mild diffuse T2 signal hypointensity within the prostate that might have indicated prostatitis was not observed. Furthermore, a lesion-based correlation was performed between the dominant tumor on pathology, the corresponding uptake on 18F-DCFBC PET, and detection by MR imaging signal abnormality.

Statistical Analysis
Using the 12-segment model described above, we calculated the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of 18F-DCFBC PET/CT and multiparametric MR imaging with hematoxylin and eosin as the reference standard. Those values were determined with both nonstringent and stringent reading of the imaging modalities, with nonstringent reading defined with equivocal findings (2 on PET, 3 on MR imaging) considered to be positive and stringent reading defined with equivocal findings as negative. For that analysis, 1 and 2 on the 5-point scale were considered negative on MR imaging. Estimates of sensitivity, specificity, positive predictive value, negative predictive value, overall accuracy, and their corresponding 95% confidence limits were derived from intercept-only generalized estimating equation regression models. The same 12-segment model was used to correlate findings of hemorrhage and BPH between PET and MR imaging using a logistic regression model estimated via a generalized estimating equation to arrive at between-group differences. The sensitivity of PET and MR imaging for the detection of the dominant nodule in each patient was also determined on both a non-stringent and a stringent basis.

Several additional correlations were drawn between PET and MR imaging parameters and the pathologic findings. Those included PSMA H score and (H score × volume) metrics versus 2D pelvis, 3D pelvis, and WB PET SUV\textsubscript{max}, PSMA H score and (H score × volume) metrics versus MR imaging ADC values, and PET SUV\textsubscript{max} versus MR imaging ADC values. Nonparametric Pearson correlation coefficients were calculated to describe associations.

Further analysis was performed with uptake in BPH in comparison to the visually positive tumors, both nonstringently and stringently assessed. Generalized estimating equation regression analysis was used to determine between-group differences in the PET uptake among BPH and the visually positive tumors.

RESULTS
Table 1 includes selected demographic information for the 13 patients recruited. The average age was 62 y (with an SD of 6 y and a range from 54 to 71 y). The most recent available PSA values at the time of the 18F-DCFBC PET/CT scan were also noted, with an average of 8.4 ng/mL (with an SD of 2.9 ng/mL and range from 3.3 to 17.0 ng/mL).

A 12-segment prostate analysis for cancer detection with both PET and MR imaging, compared with histology at prostatectomy for tumor, is summarized in Table 2, including nonstringent (rows 1 and 3) and stringent (rows 2 and 4) image analyses. Of note,
neither $^{18}$F-DCFBC PET nor MR imaging demonstrated high sensitivity for cancer detection (sensitivities of 0.17 and 0.39 for PET and MR imaging for nonstringent analysis and 0.10 and 0.35 for stringent analysis, respectively), likely reflecting the ability of the interpreting pathologists to identify small to microscopic amounts of tumor in many segments that would be occult on any imaging modality. Although overall accuracy for both modalities using the 12-segment analysis was modest, both $^{18}$F-DCFBC PET and MR imaging demonstrated high specificity and positive predictive value for segment-based prostate cancer detection (specificity of 0.96 and 0.89 for PET and MR imaging, respectively, for non-stringent analysis). There was a trend toward $^{18}$F-DCFBC PET being marginally more specific than MR imaging in this portion of the analysis (0.96 vs. 0.89 for nonstringent analysis and 1.00 vs. 0.91 for stringent analysis, respectively).

In a lesion-based analysis of dominant (index) primary prostate tumor, both modalities had improved sensitivity, compared with the 12-segment analysis, as seen in Table 3, although MR imaging had an increased sensitivity, compared with $^{18}$F-DCFBC PET. Specificity was not calculated because of the small sample size of the dominant lesions. The gap in lesion sensitivity between the 2 modalities decreased when the analysis was limited to only Gleason 8 and 9 cancers (MR imaging, 1.00 nonstringent and 0.80 stringent; PET, 0.80 nonstringent and 0.60 stringent). As expected, the sensitivities of both modalities trended lower when equivocal findings were considered negative. Interestingly, the detection of dominant lesions with $^{18}$F-DCFBC PET was not solely dependent on tumor size, as would be of concern for any modality in which partial-volume effects can obscure small lesions. Table 4 shows that primary prostate tumor size and Gleason score must both influence lesion detectability by $^{18}$F-DCFBC PET as seen by an undetectable Gleason 7 tumor greater than 5 mL in volume and positive uptake in a smaller 1.1-mL Gleason 9 lesion. Tumors less than 1.1 mL and Gleason 4+3=7 were limited in detection by PET, likely in part due to small size and in part to low PSMA expression. On a per-patient basis, as per Table 4, 6 of 13 patients were $^{18}$F-DCFBC PET–positive (4 positive on stringent and 6 positive on nonstringent PET reads). All 4 of 4 patients with high-grade (Gleason 8 and 9) and large-volume dominant lesions (>1.0 mL) were detectable by PET. However, 2 patients with low-volume (<1.0 mL) Gleason 4+4=8 and 4+3=7 disease and others with lower grade Gleason grade tumors were not detectable by $^{18}$F-DCFBC PET. Figure 2 shows an example of PET and MR imaging of primary prostate cancer in a patient with a Gleason 9 tumor with corresponding pathology and demonstration of high tumor PSMA expression.

Our original rationale to acquire 2D and 3D pelvic PET images, as well as later WB 3D PET acquisition, was to control for the

### Table 4

<table>
<thead>
<tr>
<th>Dominant nodule size (mL)</th>
<th>Patient no.</th>
<th>Prostatectomy</th>
<th>Visually detected with $^{18}$F-DCFBC PET</th>
<th>$^{18}$F-DCFBC PET SUV&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.92</td>
<td>13</td>
<td>4 + 4 = 8</td>
<td>Equivocal</td>
<td>3.3</td>
</tr>
<tr>
<td>7.07</td>
<td>5</td>
<td>4 + 5 = 9</td>
<td>Yes</td>
<td>3.5</td>
</tr>
<tr>
<td>5.48</td>
<td>12</td>
<td>3 + 4 = 7</td>
<td>No</td>
<td>1.7</td>
</tr>
<tr>
<td>4.86</td>
<td>7</td>
<td>3 + 4 = 7</td>
<td>Yes</td>
<td>4.6</td>
</tr>
<tr>
<td>2.41</td>
<td>2</td>
<td>4 + 5 = 9</td>
<td>Yes</td>
<td>4.1</td>
</tr>
<tr>
<td>1.23</td>
<td>9</td>
<td>3 + 4 = 7</td>
<td>No</td>
<td>1.4</td>
</tr>
<tr>
<td>1.12</td>
<td>6</td>
<td>4 + 5 = 9</td>
<td>Yes</td>
<td>7.5</td>
</tr>
<tr>
<td>0.73</td>
<td>11</td>
<td>5 + 3 = 8</td>
<td>No</td>
<td>2.3</td>
</tr>
<tr>
<td>0.56</td>
<td>10</td>
<td>3 + 4 = 7</td>
<td>No</td>
<td>1.9</td>
</tr>
<tr>
<td>0.49</td>
<td>1</td>
<td>3 + 3 = 6</td>
<td>No</td>
<td>2.4</td>
</tr>
<tr>
<td>0.44</td>
<td>3</td>
<td>4 + 3 = 7</td>
<td>No</td>
<td>1.1</td>
</tr>
<tr>
<td>0.37</td>
<td>4</td>
<td>3 + 4 = 7</td>
<td>No</td>
<td>1.5</td>
</tr>
<tr>
<td>0.26</td>
<td>8</td>
<td>4 + 3 = 7</td>
<td>Equivocal</td>
<td>2.9</td>
</tr>
</tbody>
</table>

**FIGURE 2.** Correlation between focal uptake in right lateral prostate apex (arrowhead) on $^{18}$F-DCFBC PET (A), abnormal low T2 signal (arrowhead) on MR imaging (B), and tumor on gross surgical pathology, as outlined in green (C). Pathologic specimen from same tumor shows strong immunohistochemical staining for PSMA (brown color) (D).
our study (Supplemental Fig. 2). When correlating SUV max to nearly no relationship between Gleason score and ADC values in standardized uptake values for all 3 acquisitions (Fig. 3). We observed the Gleason scores of the tumors and the obtained maximum standardized uptake value (SUV max) with a trend toward but no statistical significance (Supplemental Fig. 3, 0.51; P value of 0.1, 0.07, and 0.3, respectively). In regards to non-PSMA immunohistochemical findings, we observed a positive correlation between PSA H score and SUV max, a negative correlation between ERG H score and SUV max (ρ = 0.31), and a negative correlation between Ki-67 staining and SUV max (ρ = 0.28) (Supplemental Fig. 3); none of these associations reached statistical significance. More details on these correlations, as well as correlation of MR imaging ADC to immunohistochemical parameters, are presented in the supplemental data section.

DISCUSSION

Major considerations in the management of prostate cancer are accurate initial diagnosis and distinguishing aggressive from indolent disease for selection of appropriate therapy. Patient care initially requires accurate tumor evaluation to select the optimal therapy from a growing array of alternatives that include active surveillance, androgen ablation, radical prostatectomy (radical retropubic or laparoscopic/robotic), radiation therapy (brachytherapy, external-beam radiation therapy, or combinations of these choices), and possibly focal ablative therapies (cryoablation, high-versus low-intensity focused ultrasound, laser ablation, and focused ultrasound) (3,29,30). Patients are risk-stratified based on serum PSA level, tumor grade, and clinical stage, with predictive models having been developed to determine pathologic stage and time to recurrence based on retrospective patient data (31). However, those outcome models, while effective, do not adequately identify all patients at risk of developing biochemical recurrence and provide no anatomic localization of tumor spread (32).

The combined anatomic and functional imaging provided by PET suggests that a PET radiotracer for the proper target may dramatically improve imaging of prostate cancer. Studies with 18F-FDG, the most

### TABLE 5

Average 18F-DCFBC Uptake in Positive and Negative Prostate Cancers As Well As Background Blood Pool and Musculature

<table>
<thead>
<tr>
<th>Anatomic site</th>
<th>2D pelvis</th>
<th>3D pelvis</th>
<th>WB</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Average SUV max</td>
<td>SD</td>
<td>Average SUV max</td>
</tr>
<tr>
<td>Prostate cancer with positive uptake (n = 6)</td>
<td>4.7</td>
<td>1.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Prostate cancer with negative uptake (n = 7)</td>
<td>1.8</td>
<td>0.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Blood pool (right common femoral vasculature)</td>
<td>3.8</td>
<td>0.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Muscle (right gluteus musculature)</td>
<td>2.0</td>
<td>0.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

In reviewing the data from the 3 different PET acquisitions (2D pelvis, 3D pelvis, and WB), it was observed that there was a statistically significant positive correlation (P < 0.05) between the Gleason scores of the tumors and the obtained maximum standard uptake values for all 3 acquisitions (Fig. 3). We observed nearly no relationship between Gleason score and ADC values in our study (Supplemental Fig. 2). When correlating SUV max to PSMA expression (PSMA H score, PSMA H score_mod-str, and PSMA H score_His), positive relationships were noted for all 3 PSMA immunohistochemical scores with a trend toward but no statistical significance (Supplemental Fig. 3, P values between 0.31 and 0.51;
commonly used clinical PET radiotracer, have demonstrated low uptake in prostate cancer except for advanced metastatic disease (33,34). However, several new radiotracers for prostate cancer are in various stages of development as noted in the introduction. In particular, choline, acetate, and 18F-FACBC PET imaging have been hampered by decreased specificity in differentiating malignant from benign hyperplastic prostatic lesions (11,12,14), although the PET radiotracer synthetic bombesin receptor antagonist for gastrin-releasing peptide was able to differentiate between malignant and benign hyperplastic prostate lesions (18).

PSMA is a promising, well-characterized biomarker specific for prostate cancer, which has also been associated with prostate tumor aggressiveness. Histologic studies have associated high PSMA expression with metastatic spread (35–37) and androgen independence (38), and expression levels have been found to be predictive of prostate cancer progression (19,21).

Our prospective study evaluated the utility of 18F-DCFBC, a small-molecule PSMA inhibitor, for the detection of primary prostate cancer. We were able to detect clinically significant high-grade (Gleason 8 and 9) and larger-sized (> 1.1 mL) primary prostate tumors reliably, with no evidence of uptake in BPH. 18F-DCFBC PET was, however, limited for detection of smaller-sized (< 1.1 mL) and lower-grade (Gleason 7 or 6) tumors. Although low-grade tumors were found to have variable and generally low-level uptake, there was nevertheless a positive correlation between 18F-DCFBC uptake, as measured by SUVmax and Gleason score of the prostate cancers included in this trial. We have observed a trend toward a positive correlation between 18F-DCFBC PET tumor uptake, compared with PSA tumor expression by immunohistochemistry, although a study with a larger sample size is needed to confirm these preliminary results. MR imaging demonstrated greater sensitivity for the detection of prostate cancer but can oftentimes reveal multiple lesions whereas 18F-DCFBC PET can potentially allow for more specific localization of the highest-grade and most clinically significant lesion.

This study had several limitations. First, the overall detection rate of prostate cancer by 18F-DCFBC PET/CT in our patient cohort was lower than multiparametric MR imaging, although the detection rate improved with higher-grade tumors (Gleason 8 and 9). We were limited by the accrual pattern of patients who entered our study having predominantly low-grade tumors (Gleason 6 and 7), which are known to have relatively low PSMA expression levels (19,21). Attempting to include more patients with tumors of higher Gleason grade in the initial recruitment process would likely have improved our rate of detection. Another important consideration is that many tumors in the prostate are small (significantly < 1 cm in diameter), rendering them susceptible to partial-volume effects. However, when correcting for lesion size we showed that the detection of dominant lesions with 18F-DCFBC PET was not solely dependent on tumor size but also involved tumor PSMA expression. It is likely that small tumors may have been volume-averaged with surrounding normal prostate tissue, preventing their detection on PET imaging in patients with low-grade tumors and corresponding low levels of PSMA expression.

Another consideration arises from the intrinsic properties of 18F-DCFBC. 18F-DCFBC is a first-generation 18F-labeled agent that demonstrated high and specific uptake in PSMA-expressing experimental models and in patients with metastatic disease (22,23). 18F-DCFBC tends to persist in the blood pool, likely secondary to plasma protein binding, which limits optimal clearance from soft tissue and diminishing tumor-to-background ratio and detection of lower avidity or smaller lesions. 68Ga-PSMA (39) and a new second-generation 18F-PSMA–targeted agent (18F-DCFPyL) (40) demonstrate high tumor uptake with lower-background, which promises improved signal for better detection of lower-grade or smaller-sized primary prostate tumors, compared with 18F-DCFBC. The low 18F-DCFBC PET uptake in BPH shown in this study demonstrates that these emerging PSMA-based PET imaging agents can also potentially greatly improve the specificity for differentiating benign hyperplastic from malignant prostate lesions, which has also been an important reported feature of a new gastrin-releasing peptide receptor radiopharmaceutical (18) but a limitation of acetate, choline, and 18F-FACBC PET imaging for this application (11,12,14).

CONCLUSION

18F-DCFBC PET can detect clinically significant, high-grade prostate cancer and shows promise for differentiating malignant prostate cancer from nonmalignant prostate lesions such as BPH. With further validation, PSMA-targeted PET imaging, in conjunction with MR imaging, may allow for directed biopsy of the most clinically significant lesions and function as a noninvasive imaging biomarker for differentiating indolent versus aggressive disease, thus improving risk-adaptive management.

DISCLOSURE

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