Prostate Specific Antigen and Prostate Specific Antigen Doubling Time Predict Findings on ^{18}F-DCFPyL Positron Emission Tomography/Computerized Tomography in Patients with Biochemically Recurrent Prostate Cancer

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Abbreviations and Acronyms

BCR = biochemically recurrent prostate cancer

CT = computerized tomography

PET = positron emission tomography

PSA = prostate specific antigen

PSADT = prostate specific antigen doubling time

PSMA = prostate specific membrane antigen

Purpose: Prostate specific membrane antigen targeted ^{18}F-DCFPyL positron emission tomography/computerized tomography may offer superior image quality and sensitivity for the detection of biochemically recurrent prostate cancer. We examined the association of Gleason sum, serum prostate specific antigen and prostate specific antigen doubling time with any detectable and pelvic confined disease in patients with biochemically recurrent prostate cancer.

Materials and Methods: Data from 108 patients with biochemically recurrent prostate cancer after radical prostatectomy who underwent prostate specific membrane antigen targeted ^{18}F-DCFPyL positron emission tomography/computerized tomography were analyzed. Data were collected on positive positron emission tomography findings as well as pelvic confined disease. Associations between Gleason sum, prostate specific antigen and prostate specific antigen doubling time were retrospectively explored.

Results: Serum prostate specific antigen was associated with positive prostate specific membrane antigen targeted imaging as continuous (OR 3.08, 95% CI 1.60–7.95, p=0.005) and categorical values (ie prostate specific antigen greater than 2.0 to 5.0 vs 0.5 ng/ml or less, OR 16.92, 95% CI 3.13–315.81, p=0.008). No relationship between Gleason sum or prostate specific antigen doubling time with overall positive imaging was observed. Patients with a prostate specific antigen greater than 2.0 to 5.0 ng/ml were significantly less likely to be diagnosed with pelvic confined disease compared with the 0.5 ng/ml or less subgroup (OR 0.21, 95% CI 0.06–0.69, p=0.013). A prostate specific antigen doubling time of 9 months or more (OR 4.20, 95% CI 1.57–11.89, p=0.005) or prostate specific antigen doubling time of 12 months or more (OR 3.03, 95% CI 1.12–8.76, p=0.033) was

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significantly associated with pelvic confined disease. No relationship between Gleason sum and pelvic confined disease was observed.

Conclusions: Absolute prostate specific antigen was positively associated with the presence of findings on prostate specific membrane antigen targeted imaging and negatively associated with pelvic confined disease. Prostate specific antigen doubling time did not predict for overall disease detection, but long prostate specific antigen doubling times were associated with pelvic confined prostate cancer.

Key Words: pelvis, recurrence, prostatic neoplasms, neoplasm staging

NEARLY a third of men will experience biochemical recurrence following primary therapy for localized prostate cancer.[1,2] For men with BCR who underwent initial treatment with radical prostatectomy, salvage radiotherapy, with or without androgen deprivation therapy, has been shown to improve clinical outcomes.[3,4] Additionally, it is known that men with BCR who benefit most from salvage radiotherapy have low PSA values.[5,6] Specifically, men with BCR and a PSA less than 0.5 ng/ml had a more than 2.5-fold likelihood of disease-free survival after salvage radiotherapy compared to higher PSA levels.[5] More recent studies, based on new European Association of Urology guidelines, similarly found that patients with a PSA less than 0.5 ng/ml had the most protective benefit from salvage radiotherapy.[7,8] Thus, in men with BCR it is of critical importance to use clinical variables, and potentially imaging, to define the location and extent of disease before implementing salvage treatment.

PET/CT with small molecules directed against PSMA has gained considerable attention for its enhanced ability to detect sites of metastatic disease not seen on conventional imaging.[9–11] To date, PSMA targeted imaging has been explored in a number of clinical contexts, including staging, evaluation of response to therapy, determination of extent of systemic disease, and re-staging in patients with negative conventional imaging findings and an elevated PSA.[12–18] The majority of those data have been generated with ^{68}Ga-labeled agents, most notably ^{68}Ga-PSMA-11.[19–22] In this study we sought to investigate factors that predict the presence of abnormal uptake consistent with sites of recurrent prostate cancer detected by ^{18}F-DCFPyL PSMA targeted PET/CT in men with BCR.

METHODS

This study is a retrospective analysis of men with BCR prostate cancer who were imaged with ^{18}F-DCFPyL PET/CT as part of a larger, institutional review board approved prospective trial aimed at understanding the therapeutic impact of imaging findings on men with all stages of prostate cancer (ClinicalTrials.gov NCT02825875). PET/CT images were acquired on either a Siemens Biograph mCT 128-slice (Siemens Healthineers, Erlangen, Germany) or a GE Discovery RX 64-slice (GE Healthcare, Waukesha, Wisconsin) scanner operating in 3D emission mode with CT based attenuation correction. Scans were initiated 60 minutes after the intravenous infusion of 333 MBq (9 mCi) of ^{18}F-DCFPyL with a field of view from the mid thighs through the skull vertex. Intravenous iodinated contrast was not used. Images were reconstructed with a manufacturer supplied ordered subset expectation maximization method.

Patients in the current analysis met the inclusion criteria of history of adenocarcinoma of the prostate treated with radical prostatectomy, a serum PSA 0.1 to 5.0 ng/ml within 45 days prior to study enrollment, and negative complete staging evaluation with a bone scan as well as CT of the abdomen and pelvis or magnetic resonance imaging of the pelvis within 45 days prior to study enrollment. Patients with a history of other malignancy and/or an intention to enroll in a blinded therapeutic clinical trial were excluded from the study. All ^{18}F-DCFPyL PET/CT scans were interpreted by a single radiologist (SPR) with 5 years of experience in reading PSMA targeted PET studies. Radiotracer uptake outside of the normal biodistribution of ^{18}F-DCFPyL was categorized according to the PSMA-RADS version 1.0 interpretive framework and lesions that were PSMA-RADS-3A-5 were considered positive for prostate cancer.[18] A specific standardized uptake value was not used as a determinant of the presence or absence of disease; rather, qualitative focal uptake at a site typical for prostate cancer was used. The use of the PSMA targeted imaging result and subsequent clinical management of each patient was at the discretion of the treating providers.

Pelvic confined disease was defined by uptake of the ^{18}F-DCFPyL radiotracer in the prostate bed, pelvic soft tissue and/or pelvic lymph nodes (sacral, external/internal iliac, obturator). Any patient with bone disease, even if within the pelvic girdle, was considered to have extrapelvic disease. Extrapelvic disease was defined as any detectable sites outside of the prostate bed, pelvic soft tissue or pelvic lymph nodes.

PSADT was calculated using the natural log of 2 (=0.693) divided by the slope of the linear regression of the natural log of PSA vs time (in months). This was calculated using the 3 most recent PSA values prior to PSMA targeted PET. If the slope of the linear regression was 0 (elevated but constant PSA) or negative (decreasing PSA after initial increase), the PSADT was set to 100 months, as previously described.[4]

A Fisher's exact test was used to compare the number of positive/negative tests as well as pelvic confined/extrapelvic disease. Logistic regression analysis was used to estimate the association of Gleason sum, PSA and PSADT with positive ^{18}F-DCFPyL PET/CT results, or pelvic confined

disease in patients with positive PSMA targeted PET/CT. In addition, the performance of both PSA and PSADT for detecting any positive ^{18}F-DCFPyL PET/CT imaging or pelvic confined disease was assessed using the area under the receiver operating characteristic curve. All values 2-sided $p < 0.05$ were considered significant. All statistical analyses were performed using R version 3.5.3.

RESULTS

A total of 108 patients met the study inclusion criteria. Patient characteristics are described in table 1. The median patient age was 67 years (IQR 61—71) and 12.0% were of ethnic minority race. Patients had a median PSA of 0.7 ng/ml (IQR 0.3—1.8). ^{18}F-DCFPyL PET/CT detected radiographic evidence of prostate cancer in 82 (75.9%) men. In those patients with a positive PET/CT, pelvic confined disease was observed in 61.0% of cases.

We explored the relationship of Gleason sum, PSA and PSADT with ^{18}F-DCFPyL PET/CT result (ie dichotomized by positive or negative for the detection of prostate cancer). We observed improved detection of radiographic disease with increasing PSA values (fig. 1, *A*). For instance, 56.5% of PSMA targeted PET/CT scans were positive in the 0.5 ng/ml or less subgroup compared to 87.1% ($p=0.002$) and 95.7% ($p < 0.001$) in the greater than 0.5 to 2.0 ng/ml and greater than 2.0 to 5.0 ng/ml, respectively. Data that include more narrowly defined PSA subgroups are provided in the supplementary figure (https://www.jurology.com). Using logistic regression analysis, PSA as a continuous variable (OR 3.08, 95% CI 1.60—7.95, $p=0.005$) was significantly associated with a positive ^{18}F-DCFPyL PET/CT (table 2). As a categorical variable, PSA greater than 2.0 to 5.0 vs 0.5 ng/ml or less (OR 16.92, 95% CI 3.13—315.81, $p=0.008$) and greater than 0.5 to 2.0 vs 0.5 ng/ml or less (OR 5.23, 95% CI 1.84—17.42, $p=0.003$) was also associated with a positive scan result. Gleason sum and PSADT were not associated with detectable disease on ^{18}F-DCFPyL PET/CT (fig. 1, *B*; table 2).

We next investigated the association of Gleason sum, PSA and PSADT with pelvic confined disease in patients with a positive PSMA targeted PET/CT. The prevalence of pelvic confined disease decreased across higher PSA subgroups (0.5 ng/ml or less—19 of 26 [73.1%], greater than 0.5 to 2.0 ng/ml—19 of 34 [55.9%], greater than 2.0 to 5.0 ng/ml—8 of 22 [36.4%]) (fig. 1, *C*). As a continuous variable, PSA was nonsignificantly negatively associated with identifying pelvic confined disease on PSMA targeted PET/CT (OR 0.72, 95% CI 0.5—1.00, $p=0.056$, table 3). Using our defined PSA subgroups, a PSA greater than 2.0 to 5.0 ng/ml was significantly less likely to be associated with pelvic confined disease compared with the 0.5 ng/ml or less subgroup (OR 0.21, 95% CI 0.06—0.69, $p=0.013$). No difference between the greater than 0.5 to 2.0 ng/ml and 0.5 ng/ml or less subgroups was observed (OR 0.47, 95% CI 0.15—1.37, $p=0.174$). Next, we examined the association of PSADT with pelvic confined disease. We used the 2 cut points of 9 and 12 months for the analysis. Patients with a PSADT of 9 months or more had pelvic confined disease in 72.2% of cases vs 38.3% in the PSADT less than 9 months subgroup ($p=0.007$, fig. 1, *D*). Similar findings were observed in the PSADT 12 months or more (71.4%) vs less than 12 months (45.2%) cohorts ($p=0.009$). Using linear regression analysis, patients with a PSADT of 9 months or more (OR 4.20, 95% CI 1.57—11.89, $p=0.005$) or PSADT of 12 months or more (OR 3.03, 95% CI 1.12—8.76, $p=0.033$) were significantly associated with pelvic confined disease. We did not observe a significant association between Gleason sum (8 or more vs 7 or less) and pelvic confined disease (OR 1.21, 95% CI 0.45—3.36, $p=0.706$).

ROC curves were generated to demonstrate the ability of PSA and PSADT to predict positive ^{18}F-DCFPyL PET/CT imaging and pelvic confined disease (fig. 2). The AUC using PSA to predict positive ^{18}F-DCFPyL PET/CT imaging and pelvic confined disease was 0.75 and 0.66, respectively (fig. 2, *A* and *C*). The PSA that generated the maximum Youden index was 1.15 ng/ml for positive imaging and 1.77 ng/ml for pelvic confined disease. Using PSADT resulted in an AUC of 0.53 for positive imaging (fig. 2, *B*). For pelvic confined disease an AUC of 0.67 for PSADT was observed (fig. 2, *D*). A PSADT of 10.45 months generated the maximum Youden index for pelvic confined disease.

Table 1. *Patient characteristics and summarized PSMA PET findings*

Age:		
Median	67	
IQR	61—71	
No. race (%):		
White	95	(88.0)
Nonwhite	13	(12.0)
PSA (ng/ml):		
Median	0.7	
IQR	0.3—1.8	
No. ng/ml PSA categorical (%):		
0.5 or Less	46	(42.6)
Greater than 0.5—2.0	23	(21.3)
Greater than 2.0	39	(36.1)
No. mos PSADT (%):*		
Less than 9/9 or more	43	(46.7)/49 (53.3)
Less than 12/12 or more	52	(56.5)/40 (43.5)
No. Gleason sum (%):		
7 or Less	76	(70.4)
8 or Greater	29	(26.8)
Unknown	3	(2.8)
No. PSMA imaging result (%):		
Pos	82	(75.9)
Neg	26	(24.1)
No. pelvic confined disease (%):†		
Yes	50	(61)
No	32	(39)

* In 92.
† In 82, positive only.

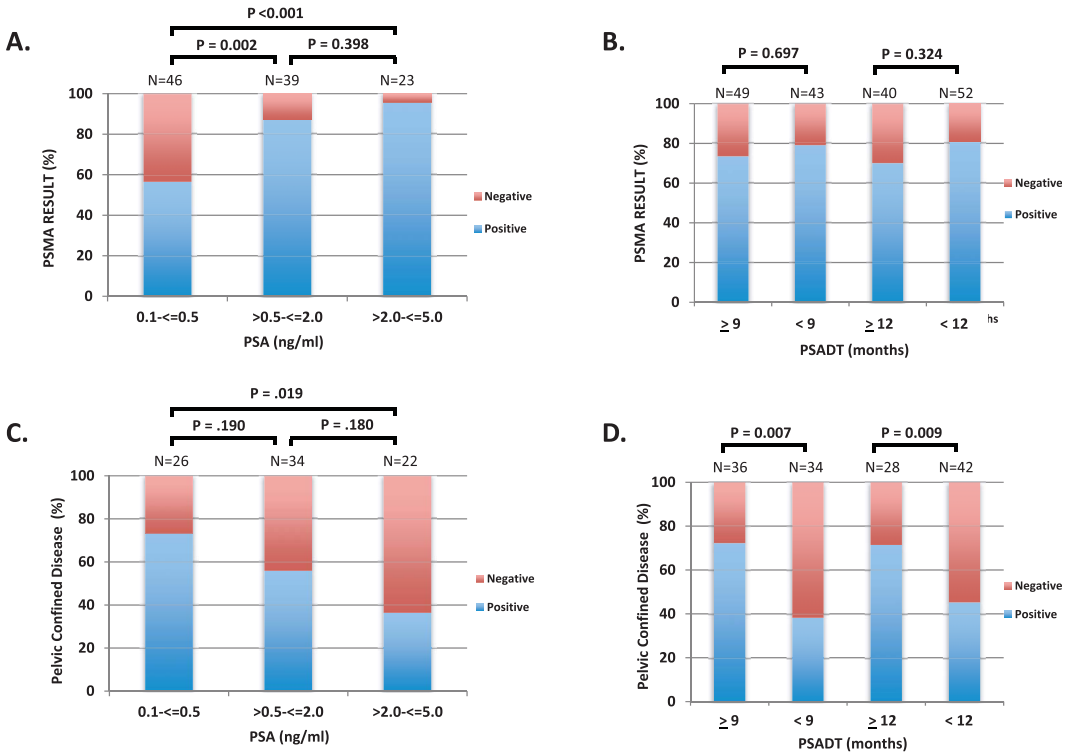

Figure 1. Prostate cancer disease detection and prevalence of pelvic confined disease by ^{18}F-DCFPyL PSMA targeted imaging in patients with biochemically recurrent prostate cancer. Percentage of ^{18}F-DCFPyL PSMA targeted PET scans that detected prostate cancer stratified by absolute PSA (*A*) and PSADT (*B*). Prevalence of pelvic confined disease decreased with higher PSA (*C*) and shorter PSADTs (*D*).

DISCUSSION

In this cohort of patients with BCR and PSA less than 5.0 ng/ml the percentage of patients with a positive scan increased with higher PSA values. Using discrete subgroups, nearly 90% of patients with a PSA greater than 0.5 ng/ml had detectable disease compared with approximately 50% of the 0.5 ng/ml or less cohort, consistent with prior studies using ^{68}Ga-PSMA.[22] This may suggest that the clinical utility of these scans is greatest when the PSA is greater than 0.5 ng/ml, although the detection rate at PSA levels between 0.1 and 0.5 ng/ml is still higher than other imaging modalities. We suspect that many patients may still have their treatment effectively guided by PSMA targeted PET despite low PSA. To this end, European Association of Urology guidelines for prostate cancer suggest the use of PSMA targeted PET in men with BCR after prostatectomy and PSA greater than 0.2 ng/ml.[23] Larger randomized studies are still needed to demonstrate improved outcomes with the use of PSMA targeted imaging for patients with BCR with low serum PSA.

A standard of care approach to BCR post prostatectomy is to consider salvage radiotherapy with the premise being that early disease relapse will be confined to the pelvis.[3,4] Using ^{68}Ga-PSMA PET imaging, negative scans and prostate bed confined disease independently predicted for benefit from salvage radiotherapy suggesting PSMA targeted imaging modalities may better define ideal candidates for local versus systemic therapy.[24,25] Similarly, PSA at the time of imaging was associated with disease outside of standard salvage radiation fields using PSMA targeted PET. In patients with a positive ^{18}F-DCFPyL PET/CT, we observed a significant association with pelvic confined disease in those patients with a PSA 0.5 ng/ml or less. This finding may provide a radiographic rationale for improved

Table 2. *Association of Gleason sum, PSA and PSADT with positive PSMA PET using logistic regression analysis*

	Value	Reference	OR	95% CI	p Value
PSA ng/ml (continous)	—	—	3.08	1.60—7.95	0.005
PSA ng/ml (categorical):	Greater than 2	0.5 or Less	16.92	3.13—315.81	0.008
	Greater than 0.5—2	0.5 or Less	5.23	1.84—17.42	0.003
Mos PSADT (categorical):	9 or Greater	Less than 9	0.73	0.27-1.92	0.531
	12 or Greater	Less than 12	0.56	0.21—1.46	0.233
Gleason sum (categorical)	8 or Greater	7 or Less	1.05	0.40—2.99	0.927

Table 3. *Association of Gleason sum, PSA and PSADT with PSMA PET confirmed pelvic confined disease using logistic regression analysis*

	Value	Reference	OR	95% CI	p Value
PSA ng/ml (continous)	—	—	0.72	0.5—1.00	0.056
PSA ng/ml (categorical):	Greater than 2	Less than 0.5	0.21	0.06—0.69	0.013
	Greater than 0.5—2	Less than 0.5	0.47	0.15—1.37	0.174
Mos PSADT (categorical):	Greater than 9	Less than 9	4.20	1.57—11.89	0.005
	Greater than 12	Less than 12	3.03	1.12—8.76	0.033
Gleason sum (categorical)	Greater than 8	Less than 7	1.21	0.44—3.36	0.706

outcomes observed following salvage radiotherapy in patients with BCR with a PSA 0.5 ng/ml or less.[5,8] Those patients with an intermediate PSA (0.5 to 2.0 ng/ml) may benefit the most from having PSMA targeted imaging when considering salvage radiotherapy. More than half of patients with a PSA between 0.5 and 2.0 ng/ml had disease limited to the pelvis, suggesting PSMA targeted PET may help discriminate between truly pelvic confined versus distant M1 disease in this subset.

Prior studies have shown that PSADT was a strong predictor for developing metastatic disease using conventional imaging.[26,27] However, our data with ^{18}F-DCFPyL PSMA targeted PET found no association between PSADT and a positive PET. In addition, long PSADTs (eg greater than 9 or greater than 12 months) were associated with pelvic confined disease. These PSADT cut points have previously been associated with longer metastasis-free survival in patients with BCR.[26,27] Since shorter PSADTs were associated with extra pelvic disease in this study, but not scan positivity, we speculate that a shorter PSADT may reflect a more aggressive biology rather than predicting the underlying volume of disease. We also did not find an association between pelvic confined disease or positive imaging with Gleason sum, similar to the data with ^{68}Ga-PSMA imaging.[22] In the absence of PSMA targeted imaging, PSA and PSADT should be taken into account when counseling patients with BCR after prostatectomy prior to salvage radiotherapy.

There are several limitations to our study. Gleason sum, PSA and PSADT were examined only

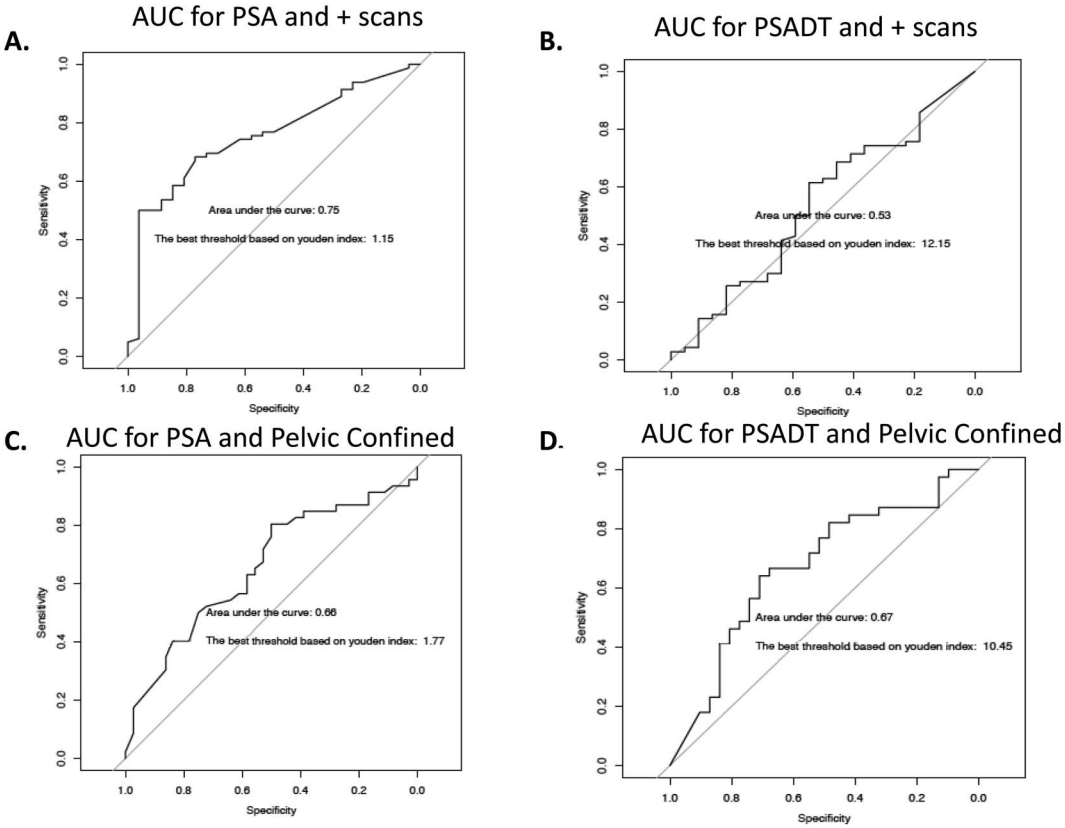

Figure 2. AUC for detection of prostate cancer and pelvic confined disease stratified by PSA and PSADT in biochemically recurrent prostate cancer using ^{18}F-DCFPyL PSMA targeted imaging. AUC for radiographic detection of prostate cancer (*A, B*) and pelvic confined disease (*C, D*) using ^{18}F-DCFPyL PSMA targeted imaging is shown based on absolute PSA and PSADT.

in univariate analyses when investigating associations with positive imaging and pelvic confined disease. A larger number of patients would be needed to perform a more in-depth, multivariate analysis. Nearly 50% of patient with a PSA 0.5 ng/ml or less had a negative ^{18}F-DCFPyL PET/CT. Only those patients with a positive scan were considered for the pelvic confined analysis. We cannot infer that those patients with negative PSMA imaging would have a similar prevalence of pelvic confined disease. Our analysis of Gleason sum may have been underpowered given the predominance of Gleason 7 or lower disease represented in the study population. Lastly, we did not collect prospective outcome data following PSMA targeted imaging. We do not know whether those patients with pelvic confined prostate cancer had more favorable outcomes versus those patients with distant M1 disease.

In conclusion, our results indicate that PSMA targeted PET may allow for the improved selection of salvage therapies following BCR. Distinguishing between a local recurrence in the pelvis and distant metastases is critical, as treatment may entail local salvage therapy to eradicate disease or systemic treatment to prevent disease progression. Currently, clinical decision making should be tailored based on clinical results (such as serum PSA and PSADT), conventional imaging and genomic characteristics. When appropriate and available, PSMA targeted PET may be used to provide additional clinical data.

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EDITORIAL COMMENT

There are now convincing data that report the value of PSMA PET/CT in identifying the location of disease in men with biochemical recurrence following radical prostatectomy. However, most of these studies use the generator derived ^{68}Ga-PSMA 11 ligand to target the PSMA molecule (reference 22 in article).[1] While there are certain advantages to this technology such as lack of requirement for a cyclotron on site, relatively cheap costs and much data on which to determine utility, there are also some compelling reasons why fluorine based PSMA ligands such as DCFPyL might be of interest.

Markowski et al report their experience of using DCFPyL PSMA PET/CT in 108 men with BCR following RP. At a median PSA of 0.7 ng/ml (IQR 0.3—1.8 ng/ml), 76% of the men have identifiable disease. This extraordinary sensitivity at low levels of PSA is in line with data seen with patients with BCR undergoing ^{68}Ga-PSMA-11 PSMA PET/CT (reference 22 in article). Furthermore, the authors report that neither PSA doubling time nor Gleason score were predictive of a positive PSMA PET/CT.

Notwithstanding some significant limitations, the authors are to be congratulated for their ongoing work in this area. Although all small molecule ligands targeting the PSMA molecule appear to have similar (impressive) performance characteristics,[2] there are a number of reasons why DCFPyL may be preferred, and this study goes a long way toward supporting its value, at least in BCR. Of course, PSMA PET/CT using ^{68}Ga-PSMA 11 is now well established for primary staging of prostate cancer, and we would welcome similar data for DCFPyL,[3] or studies that demonstrate equivalence between small molecule ligands targeting the PSMA molecule.

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