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Original Article

Pathological predictors of ^{18}F-DCFPyL prostate-specific membrane antigen-positive recurrence after radical prostatectomy

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Objectives

To assess the correlation of pathological radical prostatectomy (RP) specimen features and prostate-specific antigen (PSA) characteristics to imaging findings on subsequent ^{18}F-DCFPyL positron emission tomography/computed tomography (PET/CT) in patients with biochemical failure (BF).

Patients and Methods

Retrospective analysis of combined ^{18}F-DCFPyL PET/CT database of patients from centres in Australia and New Zealand was performed. A total of 205 patients presenting with BF after RP were included in this study. Imaging findings on ^{18}F-DCFPyL PET/CT were recorded and correlated with the PSA characteristics at BF and pathological features of the original tumour.

Results

Of the 205 patients, 120 (58.5%) had evidence of abnormal prostate-specific membrane antigen (PSMA) expression compatible with recurrent prostate cancer. Increasing PSA velocity ($P = 0.01$), International Society of Urological Pathology (ISUP) Grade Group ($P = 0.02$), lymphovascular invasion ($P = 0.05$) and nodal positivity ($P = 0.02$) at the time of RP were more likely to demonstrate PSMA positivity. Multivariable logistic regression revealed a higher PSA level prior to PSMA PET/CT ($P < 0.01$), adjuvant radiotherapy ($P = 0.09$), Gleason score ≥8 ($P < 0.01$) and nodal positivity ($P = 0.05$) were all predictive of PSMA positivity.

Conclusion

^{18}F-DCFPyL PET/CT positivity, both generally and site specific, correlates with PSA and RP pathological factors. Our results echo cohorts focussing on post-RP patients, those imaged with ^{68}Ga-PSMA and those concerning biochemical persistence. Nomograms that include risk factors for 'PSMA-positive recurrence' in the BF population may increase the catchment of patients with disease confined to the prostate bed or pelvis who have a greater probability of prolonged disease-free survival.

Keywords

^{18}F-DCFPyL, PET/CT, PSMA, prostate cancer, biochemical recurrence, histopathology

Introduction

Prostate cancer is the most commonly diagnosed cancer in men, accounting for 15% of all cancers diagnosed [1]. The standard of care for patients eligible for curative-intent treatment is radical prostatectomy (RP) or radical radiotherapy (RRT); however, up to 40% will either demonstrate biochemical persistence after definitive therapy or will later develop PSA recurrence, both of which are classified as biochemical failure (BF) [2,3].

Historically, radiological characterisation of recurrent disease after RP has been limited. Due to highly sensitive PSA assays, BF invariably precedes radiological recurrence/progression and conventional imaging, comprising bone scan and CT, has low diagnostic yield especially in

asymptomatic patients and at low PSA values [4–6]. It is also challenging to identify small foci of recurrent or residual disease in the context of postoperative changes on MRI [7]. Identification of sites of recurrence is of utmost clinical significance as this has a major impact on clinical decision-making, enabling patients to receive appropriate management and to avoid unnecessary toxic or otherwise morbid treatment [8].

The introduction of prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT has revolutionised diagnosis and localisation of tumour recurrence in this group with validated high sensitivity and specificity compared to conventional imaging, even at low PSA values, resulting in management change in up to 63.9% of cases [9–12]. PSMA is a transmembrane glycoprotein with high expression in most prostate cancer cells. There are a variety of PSMA PET probes available and the majority of studies to date examining BF in prostate cancer have focussed on gallium (Ga) probes. The 2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine 3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (^{18}F-DCFPyL) is a commercially available PSMA PET probe used at our institutions, which is at least equivalent to ^{68}Ga-PSMA-HBED-CC in the assessment of BF with some advantages, such as higher lesion to background ratio, longer half-life, suitability for reproducible mass production and transportation, and lower urinary excretion [13]. Recent studies also suggest that ^{18}F-DCFPyL performs well at lower PSA values [10,11,14–16].

Identifying factors predicting positive-PSMA imaging with respect to site in BF could aid appropriate patient selection for PSMA imaging in resource limited health systems. Factors that predict BF after RP in general include pre-treatment PSA level, short PSA-doubling time (PSAdt), time interval from RP to BF (IBF), and pathological features of the original tumour specimen including Gleason score, pathological T stage, extracapsular extension (ECE), seminal vesicle involvement (SVI), surgical margin positivity, and lymph node involvement [17–19]. These factors have been used to create risk groups and nomograms predicting postoperative prostate cancer-specific mortality (PCSM); however, such models are unable to predict the site and extent of disease. The correlation between PSA and Gleason score with positive ^{68}Ga-PSMA imaging and sites of recurrence has been previously examined; however, this has not been determined for ^{18}F-DCFPyL [20].

The aim of this study was to evaluate PSA characteristics and RP specimen pathological factors predicting ^{18}F-DCFPyL PET/CT positivity in subsequent BF and also to investigate more specific factors to predict a site of recurrence. This study is, to our knowledge, the first to examine this using ^{18}F-DCFPyL.

Patients and Methods

Study Population

Retrospective multicentre international study using combined data from Pacific Radiology Canterbury, New Zealand (PRC) and St. Vincent's Hospital, Melbourne, Australia (STV). Our database includes all patients who have had ^{18}F-DCFPyL PET/CT between January 2017 and July 2020. Ethics was waived under New Zealand Health and Disability Ethics Committee exemption criteria for minimal risk de-identified retrospective observational studies [21,22]. Formal ethics was obtained at STV for a PSMA-PET Prostate Cancer Registry (STV Local Ref. No.: 195/19). Under such provision, patients are not contacted individually for consent; however, consent for retrospective de-identified images to be used for research is included in the general imaging consent forms.

Included were patients after RP, with or without adjuvant RT, for prostate adenocarcinoma meeting clinical criteria for BF. Biochemical recurrence (BCR) in our cohort is defined as those who achieve an undetectable PSA after RP with a subsequent detectable PSA level that increases on two or more subsequent samples. Biochemical persistence is defined by the European Association of Urology (EAU) guidelines as any PSA value (≥0.1 ng/mL) within 4–8 weeks of RP [23]. All included patients had a PSA test performed within 62 days prior to ^{18}F-DCFPyL PET/CT. Patients who had already undergone salvage RT or second-line androgen-deprivation therapy (ADT) were excluded, as were patients with castrate-resistant metastatic disease and those with other primary malignancies (not including non-melanoma skin cancers).

Imaging Protocols and Reconstruction

^{18}F-DCPyL for both centres was sourced from Cyclotek (Melbourne, Australia and Wellington, New Zealand) produced by the same method described previously [11].

At the PRC, patients were required to drink 1–2 L of water prior to their appointment and void immediately before scanning. No diuretics were administered. Patients were imaged on a GE Discovery 690 (General Electric Medical Systems, Milwaukee WI, USA). Low-dose attenuation correction CT images were acquired and reconstructed to 3.75-mm slice thickness with an increment of 3.27 mm using iterative reconstruction (50% adaptive statistical iterative reconstruction [ASiR]). All patients at both centres were administered 250 (± 50) MBq of ^{18}F-DCFPyL intravenously in accordance with reference standards outlined by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) [24]. Imaging was performed at 120 (±10) min after injection. [ARPANSA] PET images were acquired at 3.5 min/bed through the pelvis and 3.0 min/bed to the lung apices. Images were reconstructed from time-of-flight

emission data using VUE Point FX and Q-Clear™ 'GE Healthcare' iterative technique with a β value of 400. Sharp IR function was applied with no *Z*-axis filter. PET images were reconstructed on a 256 matrix.

At the STV, patients were imaged on a GE Discovery 710 PET/CT (General Electric Medical Systems). Otherwise the scanning protocol matched that described above.

Image Analysis

At the PRC, all images were reviewed by two of seven consultant radiologists with subspecialist PET/CT practice.

At the STV, all images were reviewed by a nuclear medicine physician or radiologist with nuclear medicine accreditation.

Focal uptake higher than background with anatomical correlation consistent with sites of recurrent prostate cancer and inconsistent with physiological uptake were considered suspicious for malignancy as described in previous studies [15,25,26]. Findings were recorded as prostate bed local recurrence, locoregional nodal involvement (subdivided into uni- or bilateral pelvic nodes) and metastases (non-regional nodes, bone, or other) according to the Prostate Cancer Molecular Imaging Standardised Evaluation (PROMISE) criteria [27].

Pathological Analysis

The IBF was recorded. The PSAdt and PSA velocity (PSAvel) were analysed in a cohort of patients using the method described by the Memorial Sloan-Kettering Cancer Center (MSKCC) research group [21]. The PSA level at the time of RP was collected. Gleason score, ISUP Grade Group, index lesion size, tumour laterality, ECE, perineural invasion (PNI) and lymphovascular invasion (LVI), margin positivity, SVI, and lymph node involvement were recorded.

Statistical Analysis

Patient characteristics are presented as median (interquartile range [IQR]) or mean (SD) and frequency (percentage). Logistic regression was used to evaluate the association between each variable and ^{18}F-DCFPyL PET/CT positivity. Variables with a $P < 0.20$ on univariable analysis were entered into a multivariable model (developed using a backward stepwise procedure). Model fit was evaluated using the Hosmer–Lemeshow goodness-of-fit statistic, area under the receiver operating characteristics (ROC) curve (AUC) and by inspection of the calibration plot. Similar sensitivity analyses were subsequently performed for subsets of patients with positive ^{18}F-DCFPyl PET/CT, based on location of recurrent disease in the following groups: disease limited to prostate bed, extraprostatic but intrapelvic, and disease limited to the pelvis. A level of significance (α) of 5% was used. Statistical analyses were conducted using Stata version 16.1 (StataCorp LLC, College Station, TX, USA).

Results

Study Population

A total of 205 patients had ^{18}F-DCFPyL PET/CT to investigate BF after RP (PRC, 126; STV, 79). Patient characteristics are summarised in Table 1. In our cohort, 154 patients had sufficient PSA data for calculation of PSA kinetics. The median PSA level was 0.50 ng/mL at the time of ^{18}F-DCFPyL PET/CT. The mean (SD) PSAvel was 0.72 (2.38) ng/mL/year, with a mean PSAdt of 11.2 months.

Patients without sufficient PSA data had lower PSA levels (0.38 vs 0.70 ng/mL, $P < 0.001$), were less likely to receive adjuvant RT and/or ADT (1% vs 10%, $P < 0.001$), and had their RP more recently (median 1.5 vs 2.6 years, $P < 0.001$).

Pathological Features

The pathological features from specimens following RP are shown in Table 2. The majority of cases were ISUP Grade Group 3 (36.1%) and 2 (31.2%). Bilateral locality of tumour was most common (53.4%). The mean (SD) tumour volume of specimens following RP was 5.5 (4.5) mL and the mean (SD) tumour percentage involvement was 21.1 (18.6)% of prostate volume.

On review of the RP specimens, ECE was present in 123/205 cases (60.0%) and surgical margins were involved in 87/201 (43.3%). PNI was common and found in 144/192 cases (75.0%), while LVI was present in only 35/186 (18.8%). SVI was present in 57/199 (28.6%) cases. Where local lymph nodes were sampled at the time of surgery, 20/111 (18.0%) cases demonstrated nodal positivity.

Table 1 Baseline characteristics.

Characteristic	Value
Total number of patients (%)	205 (100)
Biochemical recurrence, *n* (%)	188 (91.7)
Biochemical failure, *n* (%)	17 (8.3)
Age, years, median (SD)	67.0 (7.37)
PSA level, ng/mL, *n* (%)	
<0.2	11 (5.4)
0.2–0.49	90 (43.9)
0.5–0.99	37 (18.0)
1.0–1.99	27 (13.2)
>2	40 (19.5)
PSA level, median (IQR)	0.50 (0.30–1.60)
PSAvel, ng/mL/year, mean (SD)	0.72 (2.38)
PSAdt, months, mean (range)	11.2 (0.2–108)
Further treatment	
Adjunctive RT, *n* (%)	6 (2.9)
Antihormonal treatment, *n* (%)	10 (4.9)

Table 2 RP pathological characteristics.

Characteristic	Value
Time since RP, years, median (IQR)	2.03 (0.68–3.80)
Gleason score, *n* (%)	
≤6	7 (3.4)
7	138 (67.3)
8	26 (12.7)
9	34 (16.6)
Primary Gleason score, *n* (%)	
≤3	84 (41.0)
≥4	121 (59.0)
Secondary Gleason score, *n* (%)	
≤3	89 (43.4)
≥4	116 (56.9)
ISUP Grade Group, *n* (%)	
1	7 (3.4)
2	64 (31.2)
3	74 (36.1)
4	26 (12.7)
5	34 (16.6)
ECE, *n*/*N* (%)	123/205 (60.0)
PNI, *n*/*N* (%)	144/192 (75.0)
LVI, *n*/*N* (%)	35/186 (18.8)
SVI, *n*/*N* (%)	57/199 (28.6)
Positive margin, *n*/*N* (%)	87/201 (43.3)
Node positivity, *n*/*N* (%)	20/111 (18.0)

Influence of PSA and ^{18}F-DCFPyL PET/CT Positivity

Of the 205 patients, 120 (58.5%) had one or more areas suggestive of recurrent prostate cancer. The detection efficacies for ^{18}F-DCFPyL PET/CT were 92.5% (37/40) for PSA levels of ≥2 ng/mL, 88.9% (24/27) for PSA levels of 1–1.99 ng/mL, 62.2% (23/37) for PSA levels of 0.5–0.99 ng/mL, 36.7% (33/90) for PSA levels of 0.2–0.49 ng/mL, and 18.2% (2/11) for PSA levels of ≤0.2 ng/mL (Fig. 1). The mean PSA level was significantly higher in patients with positive ^{18}F-DCFPyL PET/CT findings than in those with negative findings (median [IQR] 1 [0.4, 3] vs 0.3 [0.2, 0.5], $P = 0.001$).

In our cohort, those patients with a PSAvel of ≥0.2 ng/mL/year were more likely to demonstrate ^{18}F-DCFPyL PET/CT positivity than in those with negative findings ($P = 0.01$), while there was no statistical difference in PSAdt between the two groups, at a mean (SD) of 11.2 (14.0) vs 11.4 (7.1) months ($P = 0.944$).

Sites of recurrent disease are shown in Fig. 2 and Table 3, stratified by region and PSA levels. The frequency of local recurrence increased with rising PSA levels. While no patients were detected with local recurrence at PSA levels of <0.2 ng/mL, increased PSMA expression was identified in the prostate bed in 30% (12/40) at PSA levels of >2 ng/mL. Locoregional pelvic lymph node metastases were present in one of 11 patients with PSA levels of <0.2 ng/mL and 24/40 (60%) of patients with PSA levels of >2 ng/mL. There was a steady increase in any location of metastases from one of 11 at PSA levels of <0.2 ng/mL to 17/40 (42.5%) with PSA levels of >2 ng/mL. Findings indicating bony metastases increased with increasing PSA levels; however, visceral lesions were uncommon in all patient groups.

Interval to BF vs ^{18}F-DCFPyL PET/CT Positivity

The mean (SD) time to recurrence across our cohort was 3.1 (2.4) years. When stratified according to their PSA group, no statistical significance was demonstrated when comparing IBF and ^{118}F-DCFPyL PET/CT positivity.

Pathological Factors Determining ^{18}F-DCFPyL PET/CT Positivity

Univariable logistic regression of anatomical specimens from RP revealed that increasing ISUP Grade Group (odds ratio [OR] 2.98, 95% CI 1.51–5.90, $P = 0.020$) was statistically significant in determining ^{18}F-DCFPyL PET/CT positivity. In particular, patients with a higher ISUP Grade Group ≥4 ($P = 0.002$) were more likely to have a positive ^{18}F-DCFPyL PET/CT. Patients with LVI ($P = 0.047$) and positive nodes ($P = 0.016$) at the time of RP were also more likely to demonstrate PSMA positivity.

Although there was a trend towards correlation, no statistical difference was identified in patients with ^{18}F-DCFPyL PET/CT positivity and tumour volume, at a mean (SD) of 6.8 (4.8) vs 3.2 (2.9) mL ($P = 0.09$). ECE ($P = 0.196$), PNI ($P = 0.724$), positive margins ($P = 0.789$) and SVI ($P = 0.118$) were not statistically significant factors in determining overall ^{18}F-DCFPyL PET/CT positivity.

A multivariable logistic regression revealed that a higher PSA level prior to PSMA (OR 1.95, 95% CI 1.28–2.98, $P = 0.002$), adjuvant RT (OR 3.31, 95% CI 0.83–13.18, $P = 0.09$), Gleason Score ≥8 (OR 1.99, 95% CI 1.38–6.49, $P = 0.005$) and surgical node positivity (OR 8.52, 95% CI 0.99–73.27, $P = 0.05$) were all predictive of PSMA positivity. This model was of good fit (Hosmer–Lemeshow goodness-of-fit test, $P = 0.531$) with good predictive ability (AUC 0.807) (Fig. 3a). Model calibration was good; however, there was an overprediction of PSMA positivity for patients with a PSA level of <0.2 ng/mL (Fig. 3b).

Sub-Group Analysis of Pathological Factors Predicting Site of Recurrence

Intrapelvic Recurrence

In all, 69 of 122 (56.6%) patients within our cohort had detectable recurrent prostate cancer limited to the pelvis. Having LVI (OR 0.27, 95% CI 0.09–0.77, $P = 0.014$) and positive nodes at the time of surgery (OR 0.09, 95% CI 0.02–0.44, $P = 0.003$) were associated with lower odds of having recurrence limited to the pelvis. This model was of good fit (Hosmer–Lemeshow test, $P = 0.829$), with good calibration

Fig. 1 Detection efficacy of ^{18}F-DCFPyL PET/CT vs PSA levels.

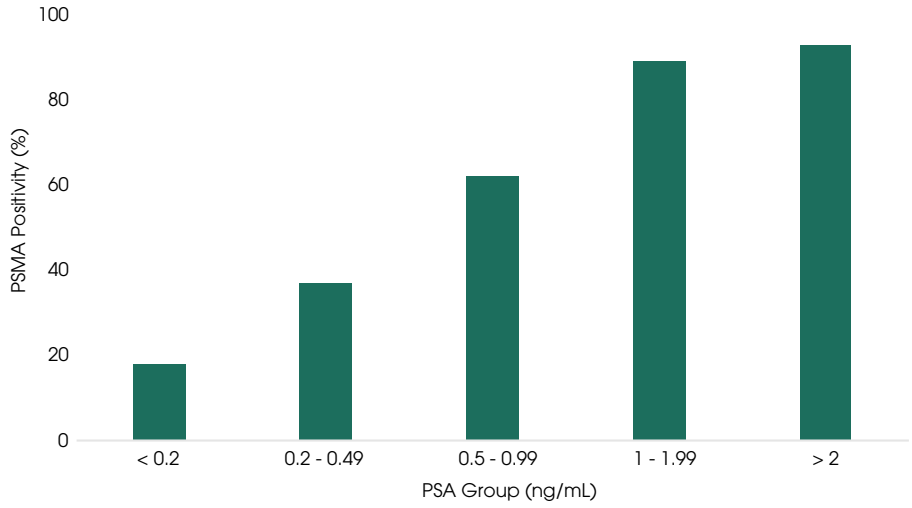
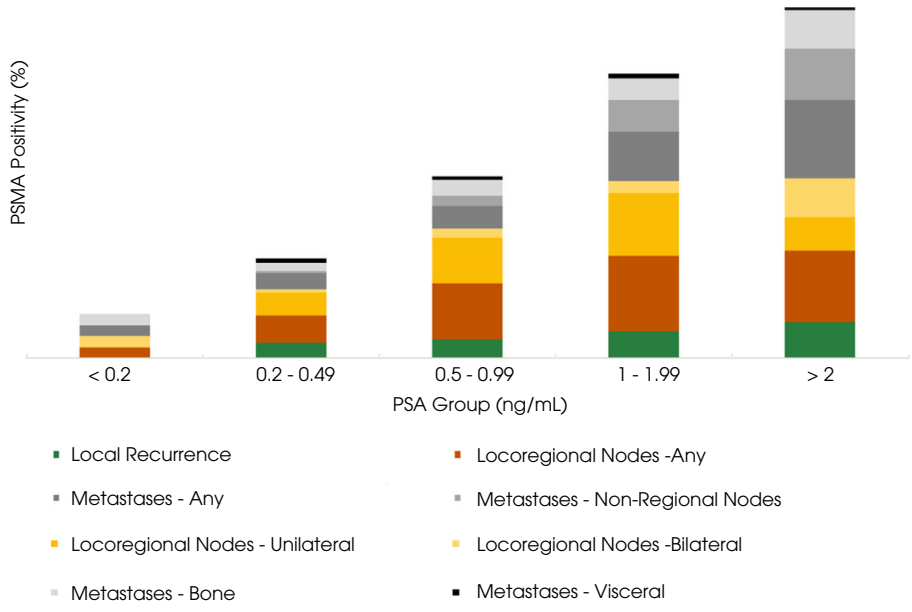


Fig. 2 Site of disease recurrence stratified by PSA group.



and fair discrimination (AUC 0.703) (Fig. S1). Of the 20 patients that had node positivity at the time of RP, seven had recurrent node metastases on ^{18}F-DCFPyL PET/CT. Of these, all seven patients had extra-pelvic nodal involvement.

Prostatic Bed Recurrence

Sensitivity analysis of this cohort revealed 23 of 122 (18.9%) patients had recurrent prostate cancer isolated to the prostate bed alone. Multivariable analysis revealed that having a more recent PSA value, regardless of its level (OR 2.2, 95% CI 1.2–3.9, $P = 0.012$), having a more recent RP (OR 1.3, 95% CI 1.0–1.5, $P = 0.025$) and absence of SVI (OR 0.14, 95% CI 0.03–0.77, $P = 0.023$) were predictors of recurrent prostate cancer isolated to the prostate bed alone. Model was of good fit (Hosmer–Lemeshow test, $P = 0.497$) with good discrimination (AUC 0.807) and calibration (Fig. S1).

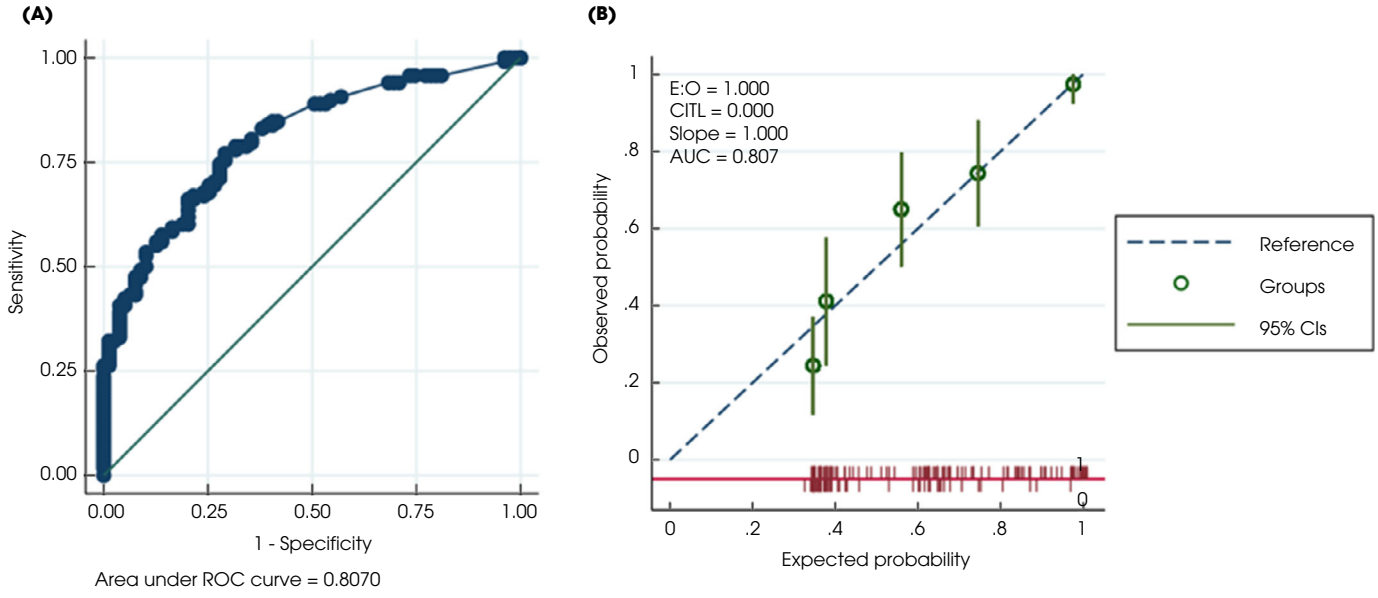
Extraprostatic, Intrapelvic Recurrence

Furthermore, 46 of 122 (37.7%) patients had a positive PSMA demonstrating extraprostatic but intrapelvic recurrent prostate cancer. Multivariable analysis revealed that having a higher PSA before PSMA scan (OR 0.88, 95% CI 0.79–0.99, $P = 0.029$) and ECE at the time of RP (OR 0.43, 95% CI 0.18–1.0, $P = 0.049$) were shown to be associated with lower odds of

Table 3 Localisation of lesions suggestive for prostate cancer on ^{18}F-DCFPyL PET/CT imaging stratified per PSA level.

Number of patients	PSA ≤0.2 ng/mL 11	PSA 0.2–0.49 ng/mL 90	PSA 0.5–0.99 ng/mL 37	PSA 1.0–1.99 ng/mL 27	PSA ≥2 ng/mL 49
PSMA PET/CT findings, *n/N* or *n* (%)					
No detectable cancer	9/11	57 (63.3)	14 (37.8)	3 (11.1)	3 (7.5)
Local recurrence of disease (miTr)	0/11	12 (13.3)	6 (16.2)	6 (22.2)	12 (30.0)
Locoregional lymph node metastases (miN1)	1/11	20 (22.2)	17 (46.0)	17 (63.0)	24 (60.0)
Distant lymph node metastases (miM1a)	0/11	2 (2.2)	2 (5.4)	5 (18.5)	7 (17.5)
Bone or visceral metastases (miM1b-M1c)	1/11	9 (10)	6 (16.2)	6 (22.2)	14 (35.0)
PSMA PET/CT findings, stratified per location; *n/N* or *n* (%)					
Inside the pelvis (miTr/miN1)	1/11	22 (24.4)	15 (40.5)	13 (48.1)	16 (40.0)
Outside the pelvis (≥miM1)	1/11	11 (12.2)	8 (21.6)	11 (40.7)	21 (52.5)
PSMA PET/CT Findings, disease outside the prostatic fossa (≥miN1); *n/N* or *n* (%)					
No	9/11	66 (73.3)	18 (48.6)	8 (29.6)	8 (20.0)
Yes	2/11	24 (26.7)	19 (51.4)	19 (70.4)	32 (80.0)

Fig. 3 Model performance for predicting prostate cancer. Area under ROC curve (**A**) shows model discrimination between events and non-event, while calibration plot (**B**) shows agreement between estimated (*x*-axis) and observed (*y*-axis) probability of events stratified by quintiles of risk. The reference line (dashed) shows a perfect calibration. The spike plot (red) at the bottom of the calibration plot represents the distribution of events – each spike represents one patient. Spikes above the red line represent patients with positive PSMA imaging and spikes below the line represent negative PSMA imaging.



extraprostatic intrapelvic disease. The model was of good fit (Hosmer–Lemeshow test, $P = 0.524$), but calibration and discrimination were poor (AUC 0.688) (Fig. S1).

Discussion

Our study is, to our knowledge, the first to evaluate PSA characteristics and pathological factors predicting ^{18}F-DCFPyL PET/CT positivity in BF following RP and to also investigate more specific factors to predict site of recurrence. Increasing PSA has been previously widely reported to correlate with positive PSMA imaging, which is well demonstrated in a recent meta-analysis specific to ^{68}Ga-PSMA [20] and the CONDOR trial (ClinicalTrials.gov Identifier: NCT03739684) data specific to ^{18}F-DCFPyL PET/CT [10], both studies not limited to RP and including patients following RRT. These findings correlate well with our study. In contrast to the recent meta-analysis, we found that Gleason score ≥8 and ISUP Grade Group ≥4 were significant in determining overall PSMA positivity in both uni- and multivariate regression. When recurrence was subcategorised

by location, we found that LVI and node positivity at RP reduced the odds of disease being limited to the pelvis. Patients with disease confined to the prostate bed had more recent PSA measurements and more recent RP and were less likely to have had SVI. Extraprostatic but intrapelvic recurrence was of reduced likelihood in those with ECE and at higher PSA levels.

Rauscher et al. [25] developed a pre-test nomogram to predict ^{68}Ga-PSMA positivity after RP. They included PSA score, ≥T3a disease (ECE and SVI), lymph node positivity, ISUP Grade Group ≥4 and ADT therapy in their predictive model, although the only significant predictors on multivariate analysis were of increasing PSA and ADT. Higher PSA level was strongly predictive of PSMA positivity in our group, both when applied in groups or as a continuous variable. We did not single out ADT as a factor to help predict PSMA positivity. The data in the literature are conflicting and confounding factors such as ADT administration in the higher-risk cohort and ADT flair effect reduce the reliability of this marker [28].

A further nomogram to predict PSMA positivity has been recently developed by Ceci et al. [29], using ^{68}Ga data and analysing diverse groups of BF including biochemical progression, first BCR, subsequent BCR after salvage, and castrate resistance. Significant factors used to construct their nomogram included ISUP Grade Group, PSA level at PSMA, PSAdt, ADT, and IBF. This study did not specifically analyse features of the RP specimens. We similarly found correlation with PSA at PSMA and ISUP Grade Group, although not with IBF. We also found some value in PSA kinetics, but these data were incomplete in a significant proportion of our cohort. In our cohort higher PSAvel was associated with increased odds of PSMA positivity; however, PSAdt did not demonstrate statistical significance. Retrospective data regarding PSA kinetics is challenging and often impacted by missing data. In order to calculate PSA kinetics using the MSKCC method a minimum of three PSA measurements is required [30]. Delay for repeated sampling may not be clinically appropriate in many patients.

Meijer et al. [28] also analysed PSMA positivity in 150 patients stratified by location as in our study, but differed by using a cohort of patients with biochemical persistence following robot-assisted RP that underwent either ^{68}Ga-PSMA or ^{18}F-DCFPyL PET/CT. In this study extraprostatic intrapelvic disease was predicted by post-treatment PSA level, ISUP Grade Group ≥4 and lymph node positivity. We saw a similar relationship to PSA in our cohort of extraprostatic intrapelvic disease, while lymph node positivity in our data set was significantly correlated with lower odds of pelvis-confined disease.

Pelvis-confined disease was also significantly less likely when LVI was present in our cohort. LVI has not been reported as a significant predictor in previous studies relating to PSMA positivity, although it is an established risk factor for BF following RP [31]. We found that it was not universally reported in pathological reports, as LVI reporting is a recommended but not required data point in structured reporting. Its varying inclusion in our cohort may skew these data [32].

Another interesting finding in our cohort was recurrent disease confined to the prostate bed correlating with more recent PSA and more recent RP. The reasons for this are speculative but may simply reflect earlier postoperative follow-up or PSA measurement allowing for earlier more localised disease detection. Another possibility is that these patients may have exhibited other risk factors for early recurrence and underwent more intensive surveillance.

Large studies have found multiple factors that predict PCSM, metastases-free survival and overall survival and at BF, preoperative PSA level, PSAdt, IBF, Gleason score, ECE, SVI, positive surgical margin, lymph node positivity are significant variables with which to construct a postoperative nomogram to predict PCSM [19,33]. Our results demonstrate additional factors that may influence positive PSMA PET/CT compared with previous studies and the predictive models thus generated showed good performance, although were less accurate in those with lower-risk disease.

Emmet et al. [34] showed PSMA PET/CT findings in those with BCR highly predictive of freedom from progression, particularly in patients with negative PSMA results or disease confined to the prostate bed, despite receiving less extensive RT and lower rates of additional androgen deprivation. The concept of 'PSMA-positive recurrence' as a unique entity in those with BF is of interest and may have distinct clinical implications in terms of treatment selection and long-term outcomes. Including PSMA in national data registries is likely to significantly contribute to further understanding of this entity, as well as mapping the impact of pending and established funding pathways for this modality in the global care of patients with prostate cancer [35].

Our study benefited from a relatively large sample size and a multicentre international combined database using a single PSMA probe. Multiple readers rather than a single expert are more representative of real clinical practice. Limitations were of retrospective design and lack of histopathological correlation with the ^{18}F-DCFPyL PET/CT findings. Pathological correlation was not undertaken due to ethical, comorbid, and technical factors, and this is in line with multiple other studies. The data suggest a very high positive predictive value of PSMA in BF [12] and although false-positive findings may have impacted our results; these are infrequent in the literature and our acceptance of positivity is

in keeping with current clinical practice. Approximately 4% of primary prostate tumours will not demonstrate PSMA expression, which is also a limitation of the study [36]. The retrospective multisite nature of the study contributed to data gaps where some variables were not documented. This resulted in smaller cohorts for some groups, most notably nodal status at RP.

Conclusion

Our study is the first, to our knowledge, to evaluate PSA and pathological factors predicting ^{18}F-DCFPyL PET/CT positivity in BF and to also examine more specific factors to predict a site of recurrence. Our results echo larger cohorts focussing on postoperative patients, those imaged with ^{68}Ga and those concerning biochemical persistence. Nomograms that include risk factors for 'PSMA-positive recurrence' in the BF population may increase the detection of patients with disease confined to the prostate bed or pelvis who have a greater probability of prolonged disease-free survival. Further prospective data will be required to develop and fortify such models.

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Disclosure of Interests

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Ethics Approval

Ethics was waived under New Zealand Health and Disability Ethics Committee exemption criteria for minimal risk de-identified retrospective observational studies [21,22]. Formal ethics was obtained at STV for a PSMA-PET Prostate Cancer Registry (STV Local Ref. No.: 195/19). Under such provision, patients are not contacted individually for consent; however, consent for retrospective de-identified images to be used for research was built into the general imaging consent forms.

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Data Availability Statement

At request.

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Abbreviations: ADT, androgen-deprivation therapy; ARPANSA, Australian Radiation Protection and Nuclear Safety Agency; AUC, area under the ROC curve; BCR, biochemical recurrence; BF, biochemical failure; ECE, extracapsular extension; IBF, time interval from RP to BF; IQR, interquartile range; ISUP, International Society of Urological Pathology; LVI, lymphovascular invasion; MSKCC, Memorial Sloan-Kettering Cancer Center; OR, odds ratio; PCSM, postoperative prostate cancer-specific mortality; PET, positron emission tomography; PNI, perineural invasion; PRC, Pacific Radiology Canterbury, New Zealand; PSAdt, PSA-doubling time; PSAvel, PSA velocity; PSMA, prostate-specific membrane antigen; ROC, receiver operating characteristic; RP, radical prostatectomy; (R)RT, (radical) radiotherapy; STV, St. Vincent's Hospital, Melbourne, Australia; SVI, seminal vesicle involvement.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Model performance for predicting prostate cancer isolated to prostate bed (**A** and **B**), extraprostatic but intrapelvic prostate cancer (**C** and **D**) and prostate cancer limited to the pelvis (**E** and **F**).