European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:2038–2046
https://doi.org/10.1007/s00259-020-05143-9

ORIGINAL ARTICLE

[18F]DCFPyL PET/CT in detection and localization of recurrent prostate cancer following prostatectomy including low PSA < 0.5 ng/mL

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Received: 13 September 2020 / Accepted: 29 November 2020 / Published online: 5 January 2021

Abstract

Purpose The primary aim of this retrospective multicenter analysis was to assess the performance of PSMA PET/CT using [18F]DCFPyL in the detection and localization of recurrent prostate cancer post radical prostatectomy (RP). Particular reference is given to low PSA groups < 0.5 ng/mL to aid discussion around the inclusion of this group in PSMA guidelines and funding pathways.

Methods Retrospective analysis of combined PSMA database patients from centers in Australia and New Zealand. Two hundred twenty-two patients presenting with recurrence post RP were stratified into five PSA groups (ng/mL): 0–0.19, 0.2–0.49, 0.5–0.99, 1–1.99, and ≥ 2. Lesions detected by [18F]DCFPyL PET/CT were recorded as local recurrence, locoregional nodes, and metastases.

Results Of 222 patients, 155 (69.8%) had evidence of abnormal uptake suggestive of recurrent prostate cancer. The detection efficacies for [18F]DCFPyL PET/CT were 91.7% (44/48) for PSA levels ≥ 2 ng/mL, 82.1% (23/28) for PSA levels 1–1.99 ng/mL, 62.8% (27/43) for PSA levels 0.5–0.99 ng/mL, 58.7% (54/92) for PSA levels 0.2–0.49 ng/mL, and 63.6% (7/11) for PSA levels ≤ 0.2 ng/mL. In those with PSA < 0.5 ng/mL, 47.6% (49/103) had detectable lesions, 71.4% (35/49) had disease confined to the pelvis, 22.4% (11/49) had prostate bed recurrence, 49.0% (24/49) had pelvic lymph nodes, and 28.6% (14/49) had extra pelvic disease.

Conclusion [18F]DCFPyL PET/CT has a high detection rate in recurrence following RP even at low PSA levels with similar detection levels in the PSA subgroups < 0.5 ng/mL. Employing rigid PSA thresholds when constructing guidelines for PSMA PET/CT funding eligibility may result in a significant number of patients below such thresholds having delayed or inappropriate treatment.

Keywords [18F]DCFPyL · PET/CT · PSMA · Prostate cancer · Biochemical recurrence

This article is part of the Topical Collection on Oncology - Genitourinary

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Introduction

Prostate cancer (PC) is the most commonly diagnosed cancer and is the second highest cause of all cancer deaths in Australia [1, 2]. Standard of care for patients eligible for curative intent treatment is radical prostatectomy (RP) or radiotherapy; however, over one-third will develop biochemical recurrence [3]. A proportion of these will progress to metastatic disease without prompt therapy. Post RP patients with recurrence may be eligible for salvage radiotherapy to achieve cure. Accurate staging pre-salvage radiotherapy is paramount to guide patient selection, radiation target volumes, and ultimately biochemical control.

The prerequisite of this approach is to have an accurate diagnostic modality with high sensitivity and specificity. The diagnostic yield of conventional imaging techniques, for example, bone scan, CT, and MRI, however is low, particularly in asymptomatic patients and at lower prostate-specific antigen (PSA) levels [4–8]. Bone scintigraphy has less than 5% positivity in PSA < 40 ng/mL and no positive cases below 7 ng/mL in a systematic review. CT also demonstrates low positivity in recurrence, reported as 11–14% [9, 10]. Pooled MRI sensitivity and specificity for prostate bed recurrence has been reported as 82–84% and 85–87%, respectively [11]. Also up to 80% of involved pelvic lymph nodes are below 8 mm and therefore below threshold for standard imaging and therefore dependent upon more subjective morphologic features for characterization [12]. Clinical nomograms are in use to stratify patients into risk groups for recurrence, for example, Partin tables, the Memorial Sloan Kettering Cancer Centre nomogram, and Cancer of the Prostate Risk Assessment Score; however, these cannot reliably predict site and extent of disease [13–17].

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein expressed in approximately 95% of prostatic adenocarcinomas. Positron emission tomography (PET) targeting PSMA has established value in the assessment of patients with PSA recurrence who have undergone curative intent treatment with significant impact on management [7, 18, 19]. There are several PSMA PET probes available. Gallium-68 (^{68}Ga) probes are widely used and can be manufactured on site without the need for a cyclotron. Fluorine-18 (^{18}F) probes confer some advantage in longer half-life and opportunity for large-scale batch production. Improved spatial resolution can be achieved using short-range positron emitters such as ^{18}F compared with long range such as ^{68}Ga [20–23]. 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. [^{18}F]DCFPyL PET/CT in recurrent prostate cancer is currently less prevalent in the international literature than ^{68}Ga-PSMA PET/CT; however, there is a growing evidence base with several noteworthy studies focusing on this tracer recently published [24]. In addition there is some evidence to suggest that [^{18}F]DCFPyL PET/CT may be more sensitive in the lower PSA groups [25–32].

Recommendation for the performance of PSMA PET in recurrence in national and international guidelines is variable. Recommendation varies from no recommendation [33, 34], performance above a threshold PSA level [33, 35], performance following negative or equivocal conventional imaging [36], performance in all patients considered for salvage therapy [37], or a combination thereof. PSMA PET in recurrence is not currently publicly funded in Australia and is not universally publicly funded in New Zealand.

This retrospective study will examine the performance of [^{18}F]DCFPyL PET/CT in the detection and localization of disease recurrence in patients who have undergone prostatectomy and have biochemical recurrence.

Materials and methods

Study population

This is a retrospective multicenter 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. Formal ethics review was waived under New Zealand and Australian Health and Disability Ethics Committees exemption for minimal risk de-identified retrospective observational studies. Under such provisions, patients are not contacted individually for consent; however, both departments have consent for retrospective de-identified images to be used for research built into general imaging consent forms. Included were patients post prostatectomy (± adjuvant RT) presenting with recurrence, defined as those who achieve an undetectable PSA after radical prostatectomy with a subsequent detectable PSA level that increases on two or more subsequent samples [34]. All included patients had a PSA within 62 days of the [^{18}F]DCFPyL PET/CT. Those who had already undergone salvage RT were excluded as were patients with castrate-resistant metastatic disease and those with other primary malignancies (not including non-melanoma skin cancers). Patients were stratified into five PSA groups (ng/mL); 0–0.19, 0.2–0.49, 0.5–0.99, 1–1.99, and ≥ 2.

Radiosynthesis, quality control, and application of [^{18}F]DCFPyL PET/CT

[18F]DCFPyL for both centers was sourced from Cyclotek (Melbourne, Australia, and Wellington, New Zealand) and produced by the same method described below.

[^{18}F]DCFPyL is produced from the precursor 5-((S)-5-carboxy-5-(3-((S)-1,3-dicarboxypropyl)ureido)pentylcarbamoyl)-N,N,N-trimethylpyridin-2-aminium 2,2,2-trifluroacetate in a one-step labeling procedure with [^{18}F]fluoride. The product is synthesized using an automated radiosynthesizer contained within a shielded isolator cabinet maintained to grade C standards. Sterilization and dispensing of the drug product occur in a grade A shielded isolator. Together with formulation, the sterilization and filling of the vial containing injectable drug product is a continuous process whereby the drug substance is never isolated or detained.

Immediately upon completion of the radiosynthesis reaction, the mixture is purified by HPLC and formulated in a phosphate

buffered saline solution containing 20 mg sodium ascorbate and up to 100 mg of ethanol per 1 mL. A sample is removed for quality control analysis, bacterial endotoxin, and sterility testing.

Product batch consists of approximately 20 mL of formulated drug product contained in a sterile 25-mL vial. The drug product is dispensed into multi-dose vials and released for transport to the imaging site. Final use is quarantined pending completion of required quality control analysis, bacterial endotoxin, and sterility testing.

All patients at both centers were administered 250 MBq (± 50 MBq) of [^{18}F]DCFPyL produced intravenously in accordance with reference standards outlined by the Australian Radiation Protection and Nuclear Safety Agency [38]. Imaging was performed at 120 min (± 10 min) after injection.

Imaging protocols and reconstruction

Both centers imaged patients using the same protocol. Patients were required to drink 1–2 L of water prior to their appointment and void immediately prior to scanning. No diuretics were administered. PRC patients were imaged on a GE Discovery 690 PET/CT, whereas STV patients were imaged on a GE Discovery 710 PET/CT (General Electric Medical Systems, Milwaukee, WI, USA). Low-dose attenuation correction CT images were acquired and reconstructed to 3.75 mm slice thickness with increment of 3.27 mm using iterative reconstruction (50% ASiR). 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 β value of 400. Sharp IR function was applied with no z-axis filter. PET images were reconstructed on a 256 matrix.

Image analysis

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

At St Vincents Hospital, all images were reviewed by a nuclear medicine physician or radiologist with nuclear medicine accreditation.

Focal uptake higher than background consistent with sites of recurrent prostate cancer were considered suspicious for malignancy as described in previous studies [30, 39, 40]. Findings were recorded as prostate bed local recurrence, locoregional nodal involvement (subdivided into unilateral or bilateral pelvic nodes), and metastases (non-regional nodes, bone, or other) (Fig. S1–3).

Statistical analysis

Positive [^{18}F]DCFPyL PET/CT were stratified according to PSA subgroup by total positive studies, local recurrence, locoregional nodes, and metastases.

The detection rates were plotted against PSA level (ng/mL). Mann-Whitney *U* tests were used to evaluate differences in PSA levels between groups with and without PSMA positivity. The χ^2 test was used to compare proportions. A level of 5% was used to confer statistical significance. Statistical analyses were conducted with Jamovi software, version 1.2.22.0.

Results

Study population

A total of 222 patients, with a median age of 71 years (range 49–89 years), were included in this retrospective multicenter study ($n = 143$ PRC, $n = 79$ STV). Patient characteristics are summarized in Table 1.

The mean age was significantly higher in patients with positive [^{18}F]DCFPyL PET/CT findings (70.9 ± 7.27 vs. 67.9 ± 6.99, $p = 0.004$). A total of 25 patients (11.3%) received adjuvant radiotherapy post prostatectomy.

Radiosynthesis and quality control of [^{18}F]DCFPyL PET/CT

The final product [^{18}F]DCFPyL has a concentration of 29.6–7733 MBq/mL@EOS as a sterile, non-pyrogenic PET tracer in a solution containing 20 mg sodium ascorbate and 0.027 mL ethanol absolute, per 1 mL phosphate buffered saline. [^{18}F]DCFPyL was obtained with a typical average radiochemical yield of 25 ± 5% (non-decayed corrected) after a total synthesis time not exceeding 60 min. The radiochemical purity of [^{18}F]DCFPyL is ≥ 95% as [^{18}F]DCFPyL (based on HPLC analysis of the crude product). The solution has a pH between 4.5 to 8.5 and a chemical purity of ≤ 100 μg/mL. The

Table 1 Baseline clinical characteristics of study cohort

Characteristic	Number (*n*, %)
Number of patients, total	222 (100%)
Age (years), median ± range	71 (49–89)
PSA, μg/L or ng/mL	
< 0.2	11 (5.0%)
0.2–0.49	90 (41.4%)
0.5–0.99	43 (19.4%)
1.0–1.99	28 (12.6%)
> 2	48 (21.6%)
PSA, median (range)	0.51 (0.08–58.9)
Further treatment	
Adjuvant radiotherapy, total (%)	25 (11.3%)
Androgen deprivation therapy (ADT)	16 (7.2%)

solution is tested for bacterial endotoxin < 17.5EU/mL, radionuclide purity ≥ 99.9% after 24 h, and sterility.

[^{18}F]DCFPyL PET/CT lesion detection vs. PSA level

Of the 222 patients, 155 (69.8%) had evidence of pathological uptake suggesting recurrent PC. The detection efficacies for [^{18}F]DCFPyL PET/CT were 91.7% (44/48) for PSA levels ≥ 2 ng/mL, 82.1% (23/28) for PSA levels 1–1.99 ng/mL, 62.8% (27/43) for PSA levels 0.5–0.99 ng/mL, 58.7% (54/92) for PSA levels 0.2–0.49 ng/mL, and 63.6% (7/11) for PSA levels ≤ 0.2 ng/mL (Fig. 1).

Statistical significance was achieved with respect to [^{18}F]DCFPyL PET/CT positivity versus PSA levels stratified by these groups ($p < 0.001$). Furthermore, the mean PSA level was significantly higher in patients with positive [^{18}F]DCFPyL PET/CT findings than in those with negative findings (2.77 ± 5.9 vs. 0.62 ± 0.73, $p = 0.003$).

PSA level vs. location of recurrence

Lesions demonstrating increased PSMA expression stratified by PSA group are shown in Table 2 and Fig. 2.

The frequency of local recurrence increased with rising PSA levels and was evident in 9.1% (1/11) at PSA level < 0.2 ng/mL, 10.9% (10/92) at PSA levels 0.2–0.49 ng/mL, 16.3% (7/43) at PSA levels 0.5–0.99 ng/mL, 17.9% (5/28) at PSA levels 1–1.99 ng/mL, and 31.3% (15/48) at PSA level > 2 ng/mL. Locoregional pelvic lymph node metastases were present in 18.2% (2/11) at PSA levels < 0.2 ng/mL, 23.9% (22/92) at PSA levels 0.2–0.49 ng/mL, 44.2% (19/43) at PSA levels 0.5–0.99 ng/mL, 53.6% (15/28) at PSA levels 1–1.99 ng/mL, and 56.3% (27/48) at PSA > 2 ng/mL. There was an increase in any location metastases ranging from 18.2% (2/11) at PSA levels < 0.2 ng/mL, 13.0% (12/92) at PSA levels 0.2–0.49 ng/mL, 23.3% (10/43) at PSA levels 0.5–0.99 ng/mL, 39.3% (11/28) at PSA levels 1–1.99 ng/mL, and 47.9% (23/48) with PSA > 2 ng/mL. Findings indicating bony metastases increased with increasing PSA levels; however, visceral lesions were uncommon in all patient groups.

Lesion location with PSA level < 0.5 ng/mL

46.4% (103/222) of patients had a PSA level < 0.5 ng/mL, and of these, 47.6% (49/103) had detectable lesions. Sites of recurrence are shown in Fig. 3 and Table 3. 10.7% (11/103) had local recurrence, 23.3% (24/103) had pelvic nodal metastases, and 13.6% (14/103) had extra pelvic metastases. Of those with detectable lesions, 71.4% (35/49) had disease within the pelvis that could be targeted by radiotherapy, but only 22.4% (11/49) had disease in the standard prostate bed field only. Conversely 28.6% (14/49) had extra pelvic disease.

PSA group vs. ISUP grade

The majority of cases were ISUP grade 2 (37.7%) or ISUP grade 3 (28.7%) at radical prostatectomy. ISUP grade 1 (3.3%), ISUP grade 4 (13.1%), and ISUP grade 5 (17.2%) made up the remainder. There was no statistical difference identified when ISUP grade was grouped by PSA level ($p = 0.084$).

Discussion

Accurate detection and localization of recurrent prostate cancer following prostatectomy is essential to guide management, prevent delayed or unnecessary treatment, and improve survival outcomes [41]. Conventional imaging including CT, MRI, and bone scintigraphy is limited in detecting recurrence particularly at low PSA values with both a low sensitivity and limited specificity [7, 9, 18]. PSMA targeted PET/CT has revolutionized the investigation of this patient group with validated high sensitivity and specificity for prostate cancer recurrence, even in low volume disease and at low PSA levels [7, 18]. Several PSMA probes are commercially available.

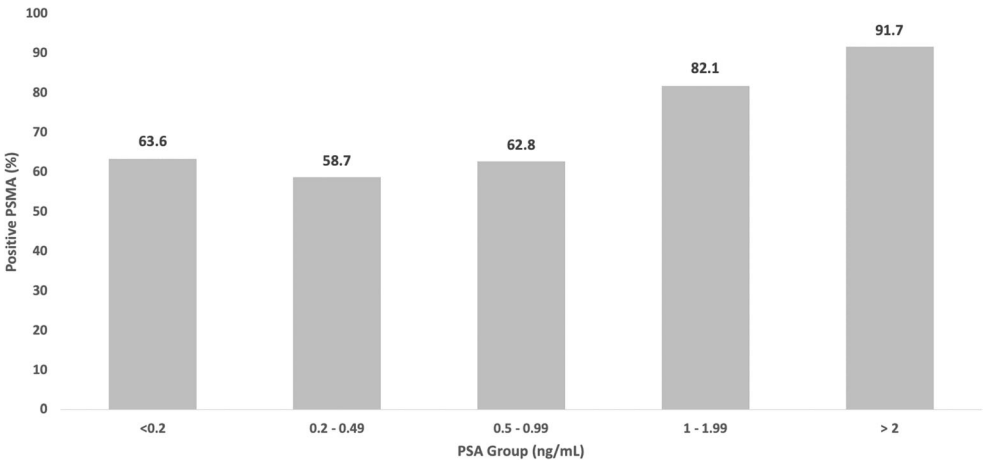

Fig. 1 Detection efficacies for [^{18}F]DCFPyL PET/CT stratified by PSA group

Table 2 Site of disease recurrence stratified by PSA group

	< 0.2	0.2–0.49	0.5–0.99	1–1.99	≥ 2
Total number	11	92	43	28	48
Positive PSMA	7 (63.6%)	54 (58.7%)	27 (62.8%)	23 (82.1%)	44 (91.7%)
Local recurrence	1 (9.1%)	10 (10.9%)	7 (16.3%)	5 (17.9%)	15 (31.3%)
Locoregional nodes—any	2 (18.2%)	22 (23.9%)	19 (44.2%)	15 (53.6%)	27 (56.3%)
Locoregional Nodes—unilateral	1 (9.1%)	20 (21.7%)	15 (34.9%)	12 (42.9%)	24 (50.0%)
Locoregional Nodes—bilateral	1 (9.1%)	2 (2.2%)	4 (9.3%)	3 (10.7%)	3 (6.3%)
Metastases—any	2 (18.2%)	12 (13.0%)	10 (23.3%)	11 (39.3%)	23 (47.9%)
Metastases—non-regional nodes	0 (0%)	4 (4.3%)	3 (7.0%)	6 (21.4%)	18 (37.5%)
Metastases—bone	2 (18.2%)	8 (8.7%)	5 (11.6%)	6 (21.4%)	11 (22.9%)
Metastases—other	0 (0%)	3 (3.3%)	3 (7.0%)	1 (3.6%)	0 (0%)

[^{18}F]DCFPyL, used in this study, has been validated as at least equivalent to the ^{68}Ga probes which are more prevalent in the literature [26, 27, 42].

The lesion detection rates in our cohort are similar to previous studies using either ^{68}Ga and [^{18}F]DCFPyL although many studies do not include a large number of patients with lower PSA values. The low PSA group is of particular significance as salvage radiotherapy is most effective when given at PSA levels < 0.5 ng/mL [43, 44]. King [45] showed a significant correlation between PSA at time of salvage radiotherapy and recurrence free survival, with a 2.6% decrease in recurrence free survival for each 0.1 ng/mL incremental increase in PSA, thus recommending that treatment should be performed at the lowest possible PSA level.

In our cohort, 46.4% (103/222) of patients had PSA < 0.5 ng/mL, and of these, 59.2% had positive [^{18}F]DCFPyL PET/CT. Subgroup analysis showed that 63.6% (7/11) PSA < 0.2 ng/mL and 58.7% (54/92) PSA 0.2–0.49 ng/mL had lesions detected on [^{18}F]DCFPyL PET/CT. Comparison of our results to a large meta-analysis of ^{68}Ga-PSMA PET/CT by Perera et al. [46] suggested higher lesion detection rate in our cohort. This meta-analysis demonstrated 33% and 45% positive PSMA studies in PSA groups < 0.2 and 0.2–0.49 ng/mL, respectively. These results are similar to a large multicenter prospective study investigating ^{68}Ga-PSMA PET/CT with a detection rate of 38% in PSA < 0.5 ng/mL [47]. Whether this is attributable to difference in tracer or inherent differences in the cohort is not possible to establish on the basis of our data.

Recent retrospective studies examining [^{18}F]DCFPyL have lower numbers than our study but show similar results. These include Wondergem et al. [32] which demonstrated 59% (17/29) positivity with PSA < 0.5 ng/mL with 39% of this cohort having disease beyond the prostate bed. Markowski et al. [28] included 46 patients with PSA < 0.5 ng/mL with a positivity rate of 56.5%. Prospective studies examining [^{18}F]DCFPyL

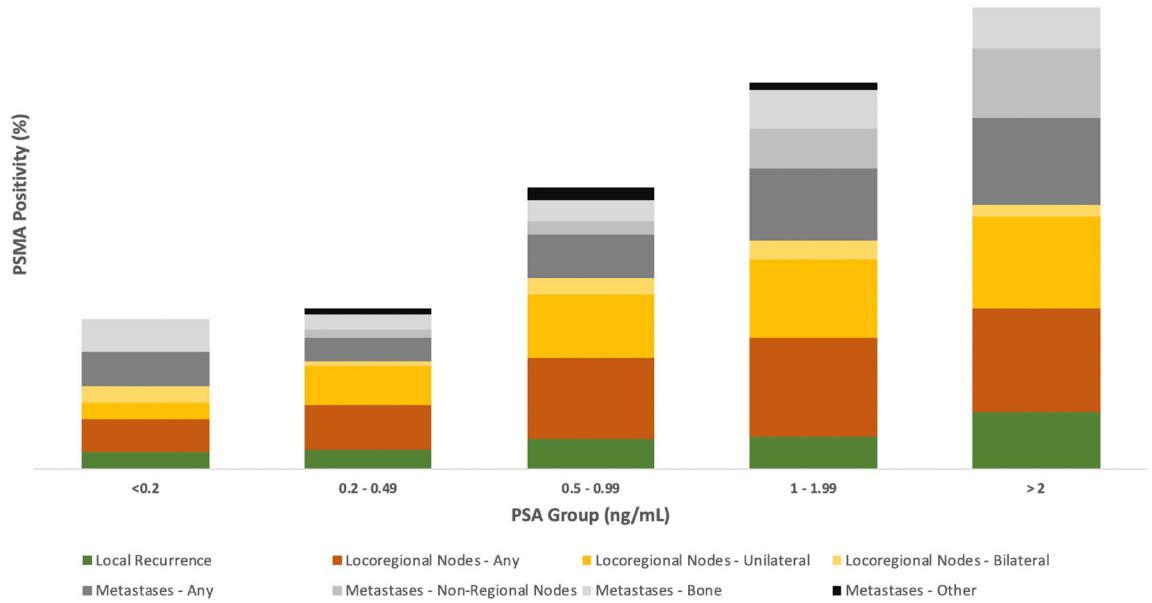

Fig. 2 Lesions demonstrating increased PSMA expression stratified by PSA group

Table 3 Site of disease recurrence stratified for patients with [^{18}F]DCFPyL PET/CT PSA < 0.5 ng/mL and > 0.5 ng/mL

	< 0.5	> 0.5
Total number	103	119
Positive PSMA	61 (59.2%)	94 (79.0%)
Local recurrence	11 (10.7%)	27 (22.7%)
Locoregional nodes	24 (23.3%)	61 (51.3%)
Metastases	14 (13.6%)	44 (37.0%)

have recently published similar results. Song et al. [31] included 8 patients with PSA < 0.5 ng/mL of which 50% had a positive PSMA, whereas Rowe et al. [30] included 22 patients with PSA 0.2–1 ng/mL of which 59.1% were positive. It is reassuring that our study with a larger subset of ultralow PSA recurrence patients supports these findings.

Management changes driven by PSMA PET/CT were not the focus of our study; however, significant impact on management has been widely reported [18, 19, 31, 48–50]. A retrospective study by Schmidt-Hegemann et al. [51] reported no difference in recurrence free survival between PSMA PET/CT positive and negative groups suggesting that PSMA PET/CT imaging successfully enabled tailoring of management options such as inclusion of pelvic lymph nodes in the radiation field if PSMA PET/CT node positive. PSMA PET/CT may have a pivotal role not only in targeting treatment in locoregional recurrence but also in selecting patients for targeted treatment of oligometastatic disease [52–55]. Furthermore, negative PSMA PET/CT can predict higher salvage response rates [49].

Accurate disease localization therefore has a significant impact on radiotherapy management. Landmark trials of adjuvant radiotherapy only treated the prostate bed, and more recent trials on early salvage radiotherapy treated the same target volume [56]. Patients who biochemically progress after prostate bed radiotherapy fail in the lymph nodes, which supports the case for addition of pelvic lymph node radiation to the prostate bed [57]. Our data clearly demonstrate increasing rates of pelvic and extra pelvic disease with increasing PSA levels. In our cohort, 59.2% (61/103) of all patients with PSA <0.5 had a positive [^{18}F]DCFPyL PET/CT. Of this group, only 22.4% had disease in the standard prostate bed field only. An additional 49% had nodal disease confined to the pelvis, and an additional 28.6% had extra pelvic disease. Therefore, within this group with detectable lesions, 71.4% (35/49) had disease confined to the pelvis that could potentially be incorporated into radiotherapy target volumes. Conversely a considerable proportion of those with lesions detected at PSA < 0.5 ng/mL had extra pelvic disease (28.6%). In this group, salvage radiotherapy alone will not achieve biochemical control, and management can be altered to either (1) omit radiotherapy and offer systemic therapy or (2) allow targeting of oligometastatic disease with stereotactic radiotherapy [58].`

Similar lesion detection rates were seen in both our < 0.5 PSA subgroups (< 0.2 63.6%, 0.2–0.49 58.7%) which suggests that using a cutoff threshold within this group is arbitrary and of little value in terms of patient selection for imaging pathways. Despite increasing evidence for the utility of PSMA PET/CT in recurrence, there is no consistency in its recommendation in international guidelines and from funders [33, 34, 36, 37]. Currently there is no universal public funding available for this indication in Australasia. Some public and private funding groups provide access to PSMA PET/CT above a PSA threshold, for example, > 0.5 ng/mL in some areas of New Zealand; however, significant early treatable disease may be missed with this approach. Earlier salvage

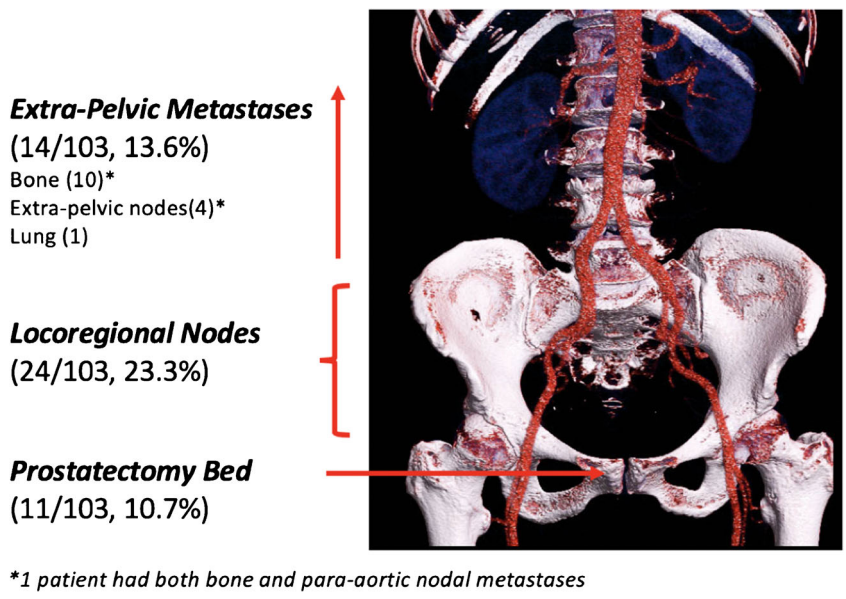

Fig. 3 Sites of recurrence in patients with PSA < 0.5ng/mL

radiotherapy with lower pretreatment PSA (< 0.2) results in improved biochemical free survival and decreasing the PSA threshold for PSMA PET/CT will encourage earlier referral for radiotherapy with the benefit of detecting disease with a superior imaging modality [44]. Many of the studies that have been conducted evaluating PSMA PET/CT in recurrence exclude patients with low PSAs although clearly a role does exist, which can be further explored in future prospective trials [23, 29, 59].

Limitations of our study are its retrospective design and lack of histopathological correlation. Lack of histopathological correlation is a common issue in retrospective research particularly in the biochemical failure population. These patients generally do not have biopsy confirmation in Australia and NZ unless further characterization is essential, for example, when disease pattern is not compatible with prostate cancer and/or a second primary is possible. Without histopathological correlation, we were unable to ascertain our false-positive or false-negative rate; however, a recent large study using 68Ga-PSMA PET/CT or PET/MRI demonstrated that such results in post prostatectomy patients are very rare with < 1% (2/217) falsely positive prostate bed lesions in this group. This study demonstrated higher rates of false positives in the post-radiotherapy group but overall low rates [60]. Our method of interpreting PSMA studies as positive is commonly used in the literature and clinical practice; however, for the purposes of future studies from this database, we will use miTNM classification described by the prostate cancer molecular imaging standardized evaluation (PROMISE) investigators which are considered more comprehensive and reproducible [30, 31, 40, 61]. Our study benefited from overall high sample size and large proportion of patients with a PSA under 0.5 ng/mL, although there are limited numbers of patients in the PSA < 0.2 ng/mL cohort. Use of a multicenter international combined database has limitations in terms of homogeneity of acquisition and reporting practices; however, both centers used the same tracer produced by the same company under the same conditions. The imaging protocols used were also concordant. This multicenter structure allowed for reduction in population bias and for image analysis by multiple radiologists and physicians rather than a single expert, therefore more representative of real clinical practice. A final limitation of our study is that it lacks detail on change in management by PSMA PET/CT and the resultant impact on disease outcomes.

Conclusion

Our study is, to our knowledge, the largest to date examining [18F]DCFPyL PET/CT in biochemical failure with particular reference to patients with PSA < 0.5 ng/mL. Our data demonstrate that this tracer has high overall detection rates in biochemically detected recurrent prostate cancer, which markedly increases with rising PSA. We found that over one half of patients with PSA < 0.5 ng/mL have detectable disease with this high rate of detection continuing into the ultralow PSA group, the majority of whom have potentially salvageable disease within the pelvis and a significant proportion have disease outside the standard prostate bed radiation field. Furthermore, patients with PSA ≥ 0.5 have increasingly higher rates of extra pelvic disease, not appropriate for salvage radiotherapy limited to the prostate bed. PSMA therefore has an important role in the work up of patients with recurrence in terms of treatment selection and treatment intent. Our findings suggest that using PSA thresholds to exclude patients from funding pathways opens potential for a substantial number of patients below such thresholds having delayed or inappropriate treatment, potentially missing the treatment window in which to achieve biochemical control.

We would recommend validating these findings with a prospective study which aims to examine the impact on management decisions in this cohort. In this regard, we await data from the current IMPPORT trial [62].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-020-05143-9.

Acknowledgments We wish to thank Ms. Daisy O'Connor and Ms. Chelseigh Fransch from Pacific Radiology, Christchurch, Canterbury, New Zealand.

Funding AstraZeneca have provided tracers without cost to a small number of patients with financial hardship at St. Vincent's Hospital; however, no authors have any role or relationship with AstraZeneca.

Data availability At request

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval Formal ethics review was waived under New Zealand and Australian Health and Disability Ethics Committee with an exemption granted for minimal risk de-identified retrospective observational studies. Under such provisions, patients are not contacted individually for consent; however, both departments have consent for retrospective de-identified images to be used for research built into general imaging consent forms.

Consent to participate Not applicable

Consent for publication Not applicable

Code availability Not applicable

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