Non-prostate cancer tumours: incidence on $^{18}$F-DCFPyL PSMA PET/CT and uptake characteristics in 1445 patients

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Abstract

**Purpose** With increasing use of PSMA PET/CT in the staging and restaging of prostate cancer (PCa), the identification of non-prostate cancer tumours (NPCaT) has become an increasing clinical dilemma. Atypical presentations of PSMA expression in prostate cancer and expression in NPCaT are not well established. Understanding the normal and abnormal distribution of PSMA expression is essential in preparing clinically relevant reports and in guiding multidisciplinary discussion and decisions.

**Methods** Retrospective review of 1445 consecutive $^{18}$F-DCFPyL PSMA PET/CT studies by experienced radiologists and nuclear medicine physicians. Lesions indeterminate for PCa were identified. Correlation was made with patient records, biopsy results, and dedicated imaging. Lesions were then categorized into four groups: 1. Confirmed prostate cancer, metastases, 2. NPCaT 3. Benign, and 4. Indeterminate lesions.

**Results** 68/1445 patients had lesions atypical for prostate cancer metastases. These comprised 8/68 (11.8%) atypical prostate cancer metastases, 17/68 (25.0%) NPCaT, 29/68 (42.6%) indeterminate, and 14/68 (20.6%) benign. In the context of the entire cohort, these are adjusted to 8/1445 (0.6%), 17/1445 (1.2%), 29/1445 (2.0%), and 14/1445 (1.0%) respectively. With the exception of Renal Cell Carcinoma (RCC), NPCaT demonstrated no or low PSMA expression. A similar trend was also observed for indeterminate and benign lesions. Conversely, most atypical PCa metastases demonstrated intermediate or high PSMA expression.

**Conclusion** $^{18}$F-DCFPyL PSMA PET/CT detection of NPCaT is low. Lesions demonstrating intermediate to high PSMA expression were exclusively prostate cancer metastases, aside from RCC, and lesions detected in organs with high background expression.

**Keywords** $^{18}$F-DCFPyL · PET/CT · PSMA · Prostate cancer · Biochemical recurrence

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**Introduction**

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men and is the sixth leading cause of cancer death [1]. Imaging of prostate cancer both at initial staging and at recurrence has been revolutionized by the advent of positron emission tomography (PET) tracers targeted to prostate specific membrane antigen (PSMA) which have shown superiority in comparison with conventional imaging comprising CT and bone scintigraphy [2–4].

PSMA is a transmembrane glycoprotein with high expression in most prostate cancer cells although can be expressed in endothelial cells in non-prostate cancer tumours (NPCaT), particularly in the context of neovascularization [5]. There are several PSMA PET probes available, of which Gallium
68 probes are most widely used. Newer Fluorine 18 probes confer some advantages with longer half-life, opportunity for large scale batch production, and higher target to background resolution. ¹⁸F-DCFPyL is a commercially available PSMA PET probe used at our institutions.

This wide adoption of PSMA PET/CT with increasing availability of tracers has seen a substantial increase in its use which, along with expanding applications of PSMA in the realms of initial diagnosis, biochemical recurrence, and treatment follow-up, the identification of NPCaT is likely to increase accordingly. The physiological expression of PSMA, expression in benign pathology, and typical patterns of expression in prostate cancer are well documented [6]; however, atypical presentations of PSMA expression in benign pathology, and typical patterns of expression in prostate cancer are less established. Understanding the normal and abnormal distribution of PSMA expression is essential in preparing clinically relevant reports and in guiding multidisciplinary discussion and decisions.

Our multicenter international retrospective study is designed to detect the incidence and types of NPCaT detected on ¹⁸F-DCFPyL PSMA PET/CT in patients with PCa and describe their imaging characteristics. The primary outcome was the incidence of newly diagnosed NPCaT detected in this cohort. We also aimed to evaluate characteristics of atypical prostate cancer metastases and indeterminate lesions. Benign lesions outside the realms of abdominal incidentalomas and incidental lung nodules determined suitable for follow-up protocols were also examined.

Materials and methods

Study population

Retrospective multicenter international study using combined data from Pacific Radiology Canterbury, New Zealand (PRC) and St Vincent’s Hospital, Melbourne, Australia (STV). Institutional ethics approval has been granted for the maintenance of a prostate cancer database, from which the study data was derived. Our database includes consecutive patients who have had ¹⁸F-DCFPyL PET/CT between January 2016 and December 2020. Repeat studies for the same patient were excluded. For patients with multiple studies, only the first showing a suspected NPCaT was included. The patient cohort consisted of patients having a ¹⁸F-DCFPyL PET/CT for initial staging (35.6%), re-staging (5.1%), and biochemical failure post treatment (59.3%).

Case selection and imaging analysis

All imaging reports were reviewed to identify patients with suspected incidental NPCaT. Typical prostate cancer-related lesions were defined as PSMA expression greater than background in the expected distribution for prostate cancer within prostate/prostate bed, nodes, bone and visceral locations [6]. Typical sites of nodal involvement include obturator, iliac stations, and retroperitoneum. Although mesorectal nodes have been described as rare or atypical, these were included in the expected distribution as they are increasingly recognised. Distant nodal, liver, and thoracic metastases were also considered typical distributions. Although visceral metastases are described in the absence of nodal or bone involvement, extra-prostatic disease limited to these sites required clarification [6]. These studies were reviewed by either an experienced genitourinary radiologist with subspecialist PET/CT practice or an experienced genitourinary radiologist in consultation with an experienced nuclear medicine physician. Imaging features of the incidental lesions and standardized uptake values (SUVmax) were recorded and categorised according to PROMISE miPSMA expression score. Terminology used in this paper reflecting these guidelines were no expression (below blood pool, score 0), low expression (equal to or above blood pool and lower than liver, score 1), intermediate expression (equal to or above liver and lower than parotid gland, score 2) or high expression (equal to or above parotid gland, score 3) [7]. Histology reports were obtained from medical records and pathologic databases, follow-up imaging from the institutional PACS database, and clinical management from the patient’s medical records.

Non-avid incidental lung lesions were assessed by a chest radiologist with > 10 years’ experience. Those less than 10 mm with no PSMA expression and without features suggesting atypical adenomatous hyperplasia/adenocarcinoma spectrum which fitted adopted follow-up guidelines were excluded [8, 9]. Known lesions which had already been identified and investigated on prior imaging were also excluded. Abdominal ‘incidentalomas’ with no PSMA expression, including adrenal adenomas, liver and renal cysts, were assessed by a subspecialist abdominal radiologist with > 10 years’ experience and those fitting criteria for follow-up under ACR white paper for follow-up of incidentalomas were recorded but excluded from end point analysis [10–13].

Patient records were retrieved and subsequent biopsy results, dedicated imaging, multidisciplinary team meeting notes, follow-up clinic letters, and specialist consults were noted. Based on this information in combination with imaging characteristics, lesions were categorized broadly into four groups: 1. confirmed prostate cancer metastases: lesions either in an atypical distribution for PCa and/or considered possible NPCaT, subsequently determined as PCa lesion by histological or clinical confirmation; 2. NPCaT: lesions either in an atypical distribution for PCa and/or considered possible NPCaT, subsequently determined as NPCaT by
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Two hundred forty-three of these studies were excluded as

A total of 1445 studies were performed using 18F-DCFPyL

Results

Statistical analysis

PSMA and pathological findings were assessed using binomial
categorical data from unmatched groups compared with

Non-prostate cancer tumours

17/68 (25.0%) patients within our cohort had NPCaT. 2/17

(11.8%) lesions demonstrated intermediate to high hetero-
geneous PSMA expression and characteristic CT features of
renal cell carcinoma (RCC). The remaining 15/17 (88.2%)

lesions had no or low PSMA expression. Twelve of these

were classified as tumours with high malignant potential and
the remaining 3 as low malignant potential.

PSMA and pathological findings of NPCaT in our cohort
have been summarized in Table 2. 8/17 (47.1%) of these
patients were non-biopsy diagnoses. This was either based
on PSMA findings or subsequent imaging displaying char-
acteristic findings of non-prostate cancer; however, in some
patients, this diagnosis was made by multidisciplinary con-
sensus as further imaging or biopsy was not felt clinically
appropriate due to advanced patient age, performance status
or widespread metastatic malignancy.

9/17 (52.9%) patients had biopsy confirmation. Three
of these patients had lung lesions, all of which were

Imaging protocols and reconstruction

18F-DCFPyL for both centres was sourced from Cyclotek
(Melbourne, Australia and Wellington, New Zealand) pro-
duced by the same method described previously [14].

PRC: Patients were required to drink 1–2L of water prior
to their appointment and void immediately prior to scan-
ning. 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 itera-
tive reconstruction (50% ASiR). All patients at both centres
were administered 250 MBq (± 50 MBq) of 18F-DCFPyL
intravenously in accordance with reference standards out-
lined by the Australian Radiation Protection and Nuclear
Safety Agency (ARPANSA) [15]. Imaging was performed
at 120 min (± 10 min) after injection. 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.

STV: Patients were imaged on a GE Discovery 710
PET/CT (General Electric Medical Systems, Milwaukee
WI, USA). Otherwise the scanning protocol matched that
described above.

Confirmed prostate cancer metastases

5/8 (62.5%) of lesions subsequently confirmed as prostate
cancer metastases demonstrated intermediate to high PSMA
expression, 4 of which were lung metastases, with biopsy
confirmation, and one biopsy confirmed nodal metastasis.
The remaining 3/8 (37.5%) lesions were of low or no expres-
sion comprising two lung and one bone metastasis demon-
strating a range of PSMA expression from SUVmax of < 1
to 5.3 (Table 1).

Non-prostate cancer tumours

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acteristic findings of non-prostate cancer; however, in some
patients, this diagnosis was made by multidisciplinary con-
sensus as further imaging or biopsy was not felt clinically
appropriate due to advanced patient age, performance status
or widespread metastatic malignancy.

9/17 (52.9%) patients had biopsy confirmation. Three
of these patients had lung lesions, all of which were

they had lesions typical for prostate cancer or no detect-
able lesion. Two hundred two studies remained for further
analysis. Of these studies, 85 related to lung nodules and 49
to incidentalomas, fulfilling the exclusion criteria. Out of 49
 incidentalomas, 23/49 (46.9%) were hepatic cysts or heman-
giomas, 10/49 (20.4%) were adrenal adenomas, and 9/49
(18.4%) were renal cysts. The remaining 7/49 (14.3%) were
made up of pancreatic cysts, subcutaneous nodule, bone
island and incidental gastric mucosal thickening. A total of
68 studies were therefore included in our study (Fig. 1).

The remaining 68 lesions comprised 8/68 (11.8%) con-

firmed prostate cancer metastases, 17/68 (25.0%) NPCaT,
29/68 (42.6%) indeterminate, and 14/68 (20.6%) benign.
In the context of the entire cohort, these proportions are
adjusted to 8/1445 (0.6%), 17/1445 (1.2%), 29/1445 (2.0%)
and 14/1445 (1.0%) respectively.

Within our cohort, the number of false positives included
24/68 (35.3%) patients, who had avid lesions that were
proven to be benign either clinically or through biopsy. In
the context of the entire cohort, this adjusted to 24/1445
(1.7%) patients.

PSMA and pathological findings were assessed using bino-
mial categorical data from unmatched groups compared with
a chi-square test. Statistical analyses were conducted with
Jamovi software, version 1.2.22.0.

A total of 1445 studies were performed using 18F-DCFPyL
(PRC = 865 studies, STV = 580 studies). One thousand
two hundred forty-three of these studies were excluded as

Histological or clinical confirmation; 3. benign: lesions not
excluded by lung nodule or incidentaloma criteria either in
an atypical distribution for PCa and/or considered possible
NPCaT, subsequently determined as benign by histologi-
cal or clinical confirmation; and 4. indeterminate lesions:
lesions not excluded by lung nodule or incidentaloma criteria
either in an atypical distribution for PCa and/or considered
possible NPCaT, without definitive histological or clinical
confirmation. The lesions classified as indeterminate were
sub-classified as a. likely benign and b. likely malignant.
biopsy-proven primary lung cancer. Two patients had focal low PSMA expression within the colon, both of which had biopsy-proven colonic adenocarcinoma, one of which had additional biopsies confirming synchronous neuroendocrine tumor within the terminal ileum, occult on PET/CT.

Histopathological assessment of a breast lesion with low PSMA expression (SUVmax 2.8) was proven to be a recurrent ER positive grade 2 breast invasive carcinoma. The remaining three had histopathology consistent with clear cell RCC with no PSMA expression (SUVmax < 1), poorly differentiated pancreatic adenocarcinoma with low PSMA expression (SUVmax 4.8), and follicular lymphoma with low PSMA expression (SUVmax 3.5).

### Indeterminate lesions

25/29 indeterminate lesions demonstrated no or low PSMA expression. 3/29 demonstrated intermediate to high expression but were located in organs with high background expression (liver and spleen) or were secondary to significant inflammation (sinusitis). 1/29 cases demonstrated intermediate expression within the scrotum with repeat imaging demonstrating no interval change over a period of four years. 3/29 (10.3%) were considered most likely prostate cancer metastases without PSMA expression, 7/29 (24.1%) suspicious for NPCaT, and 19/29 (65.5%) were determined most likely benign (Table 3).

### Benign lesions

Most benign lesions were within the thyroid (6/14) and skin (4/14). 10/14 cases were biopsy proven and 4/14 cases were clinically proven benign lesions. All lesions except a scrotal lesion demonstrated no or low PSMA expression (Table 4).

### Discussion

This study represents the largest cohort to date assessing incidence of NPCaT detected by PSMA imaging and is the only study exclusively examining this incidence with $^{18}$F-DCFPyL PET/CT. PSMA imaging is considered highly...
| No | Age | Indication                        | PSA | Site      | Primary  | SUV | mPSMA Expression Score | Findings                                                                 | Clinical Rationale                                                                                      | Outcome                  |
|----|-----|-----------------------------------|-----|-----------|----------|-----|------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------|
| 1  | 74  | Biochemical persistence post RP   | 3.9 | Lung      | N/A      | 7.6 | 2                      | Solitary LLL nodule 13 mm. No evidence of PCa recurrence elsewhere. Multiple pleural plaques | Morphological appearances suggestive of lung adenocarcinoma lung in increased risk patient without PCa recurrence elsewhere | Biopsy                   |
| 2  | 66  | BF post RP                        | 0.53| Lung      | N/A      | 11.6| 2                      | Solitary 8 mm RUL lesion, no evidence of PCa recurrence elsewhere                                     | In context of no other sites of recurrence, primary lung cancer should be excluded                       | Wedge Resection          |
| 3  | 70  | BF post RP                        | 0.3 | Lung      | N/A      | 22.0| 3                      | High PSMA expression 10 mm LUL nodule. No prostate bed recurrence, equivocal expression in 4 mm left mesorectal node | Equivocal disease elsewhere. Primary lung cancer should be excluded                                      | Resolution of lesion on CT follow up on hormonal therapy                                               |
| 4  | 71  | Initial Staging                   | 11.6| Lung      | 8.5      | 11.5| 2                      | 21×12 mm RUL lobulated solititary nodule in a patient with pulmonary emphysema                      | No evidence of recurrence elsewhere and significant smoking related lung disease. Primary lung cancer should be excluded | Resection                |
| 5  | 77  | Initial Staging                   | 2.6 | Lung      | Bone     | 4.0 | 0                      | Multiple pulmonary nodules with no PSMA expression, but primary low expression. Low expression enlarged pelvic nodes and sclerotic bone lesions | DDx given as dedifferentiated neuro-endocrine tumour of prostate or metastases from bladder TCC       | Lung nodules reduced with Docetaxel and Goserelin                                                  |
| 6  | 60  | BF post RP                        | 3.9 | Lung      | N/A      | 1.0 | 0                      | Multiple new and enlarged pulmonary nodules with low expression, largest 12×14 mm RLL apical segment | DDx metastatic PCa versus other malignancy                                                              | VATS wedge resection      |
| 7  | 66  | BF post XRT                       | 24  | Node      | N/A      | 14.1| 3                      | High PSMA expression within left para-aortic and left pelvic nodes. *                               | Recent diagnosis of DLBCL confined to mediastinum. Considered most likely PCa but DLBCL should be excluded | Left para-aortic node excision                                                                         |
| 8  | 66  | Metastatic PCa on Zoladex, new right pelvic pain | 0.4 | Bone      | 45.6     | 5.3 | 1                      | Known multiple PCa bone metastases. New 73 mm expansile lytic right iliac lesion with predominant soft tissue mass, low PSMA expression | Dissimilar appearance to other bony metastases and previous pelvic RT for seminoma, exclude NPCaT | Bone biopsy               |

PSA prostate specific antigen, SUV standardized uptake value, RP radical prostatectomy, PCa prostate cancer, BCR biochemical recurrence, RT radiotherapy, RUL right upper lobe, PSMA prostate specific membrane antigen, LUL left upper lobe, CT computed tomography, DDx differential diagnosis, BPH benign prostatic hypertrophy, TCC transitional cell carcinoma, RLL right lower lobe, VATS video-assisted thoracoscopic surgery, DLBCL diffuse large B cell lymphoma

*Although this distribution of nodal involvement is typical for prostate cancer, the recent diagnosis of DLBCL led the MDM to consider a NPCaT, and therefore has been included in this group
| Age | Indication | Site | SUVmax | SUVmax \( \text{miPSMA} \) | SUVmax Expression Score | Findings | Outcome | Primary Pathology | Findings | Malig-nant Potential |
|-----|------------|------|--------|-----------------|------------------------|----------|---------|------------------|----------|-------------------|
| 1   | 77 BF      | Lung | 3.8    | 1               | 1                      | 29 mm LLL nodule             | Biopsy  | Primary lung adenocarcinoma | Biopsy in seminal vesicle and inguinal node | High |
| 2   | 79 BF      | Lung | 4.8    | 1               | 1                      | 54 mm right lower lobe      | Biopsy  | Non-small cell lung cancer  | Biopsy in pelvis and pelvic nodes | High |
| 3   | 73 BF      | Kidney | 2.8    | 1               | 1                      | 78 mm left renal lesion     | Biopsy  | Renal cell carcinoma | Biopsy in pre-sacral node | High |
| 4   | 95 Initial Staging | Breast | 1.9    | 1               | 1                      | 10 mm left upper outer lesion | Clinical | Invasive carcinoma of no special type | Biopsy in prostate gland | High |
| 5   | 71 BF      | Lung | 1.8    | 1               | 1                      | Left lower lobe mass        | Biopsy  | Non-small cell lung cancer | Biopsy in pelvic nodes and bone | High |
| 6   | 72 Initial Staging | Kidney | 5.2    | 1               | 1                      | Right renal lesion           | Clinical | Renal cell carcinoma | Biopsy in prostate gland | High |
| 7   | 66 BF      | Colon | 1.8    | 1               | 1                      | Distal transverse colon      | Biopsy  | Colonic adenocarcinoma | Biopsy in presacral node | High |
| 8   | 81 Initial Staging | Colon | 5.6    | 1               | 1                      | Ascending colon lesion       | Clinical | Colonic adenocarcinoma and terminal ileum neuroendocrine tumour | Biopsy in prostate gland | High |
| 9   | 63 BF      | Colon | 3.9    | 1               | 1                      | High Uptake in seminal node | Biopsy  | Colonic adenocarcinoma | Biopsy in seminal and inguinal nodes | High |
| 10  | 64 BF      | Brain | 0.0    | 0               | 0                      | 5 cm tubular structure in right temporal lobe | Clinical | Primary nerve sheath tumor | Biopsy in prostate gland | High |
| 11  | 64 Initial Staging | Pancreas | 4.8    | 1               | 1                      | 23 mm RLL nodule             | Biopsy  | Poorly differentiated neuroendocrine tumour | Biopsy in pelvic nodes and bone | High |
| 12  | 59 Initial Staging | Brain | 2.5    | 1               | 1                      | 24 x 15 mm circumscribed soft tissue lesion posterior to D3 | Biopsy  | Follicular Lymphoma (cervical node) | Biopsy in pelvic nodes and bone | High |
| 13  | 77 Initial Staging | Lung | 1.8    | 1               | 1                      | 24 x 15 mm circumscribed soft tissue lesion posterior to D3 | Biopsy  | Primary lung adenocarcinoma | Biopsy in pelvic nodes and bone | High |
| 14  | 73 Initial Staging | Kidney | 4.4    | 1               | 1                      | 15 mm left upper lobe nodule | Biopsy  | Likely renal cell | Biopsy in pelvic nodes and bone | High |
| 15  | 79 Initial Staging | Lymph Node, LUNG | 3.5    | 1               | 1                      | Not amenable to biopsy, likely renal cell | Clinical | Likely renal cell | Biopsy in pelvic nodes and bone | High |
| 16  | 70 BF      | Lung | 0.0    | 0               | 0                      | 15 mm left upper lobe nodule | Biopsy  | Likely renal cell | Biopsy in pelvic nodes and bone | High |
| 17  | 70 BF      | Kidney | 1.8    | 1               | 1                      | 24 x 15 mm circumscribed soft tissue lesion posterior to D3 | Biopsy  | Likely renal cell | Biopsy in pelvic nodes and bone | High |

**Note:** SUV = standardized uptake value, LLL = left lower lobe, RLL = right lower lobe, MRI = magnetic resonance imaging, D3 = duodenum (3rd segment), BF = biochemical failure.
Table 3  PSMA and pathological findings of patients with indeterminate lesions

| No | Age | Indication | Site | Primary SUV | SUV miPSMA Expression Score | Findings                                                                 | Clinical Rationale                                                                 |
|----|-----|------------|------|-------------|-----------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| 1  | 80  | Re-Staging | Node | 29.2        | 1.9                         | Low PSMA expression in left pelvic node. Uptake in left pelvic node.     | Known metastatic PCa with bony metastases but no other nodal disease and expression much lower than bone metastases. Further investigation not pursued due to lesions elsewhere and treated as PCa nodal metastasis |
| 2  | 69  | Initial Staging | Node | 19.2        | 2.4                         | Uptake in prostate and multiple bilateral prominent iliac nodes up to 12mm, much lower expression than primary. | No confirmation. Committed on ADT.                                                  |
| 3  | 76  | BCR post RP | Lung  | N/A         | 1.7                         | 11mm ground glass nodule within LUL.                                    | Likely synchronous primary lung Ca. Follow up CT in 3 months advised. No follow up at STV. |
| 4  | 95  | Initial Staging | Lung  | N/A         | 2.1                         | Uptake in prostate gland and 19mm spiculated lung nodule in RUL.        | Likely synchronous primary lung Ca. No follow up given age and comorbidities.     |
| 5  | 72  | BFpost RP   | Lung  | 49.8        | 4.2                         | Irregular 14mm pulmonary lesion RUL. Uptake in pelvic nodes.            | Likely primary lung adenocarcinoma. No follow up.                                   |
| 6  | 83  | Re-Staging | Lung  | 21.4        | 1.3                         | Uptake in prostate gland and 10mm RLL ground glass pulmonary nodule.   | Uncertain significance, possible lung primary. Stable on follow up CT (4 months). Ongoing follow up. |
| 7  | 65  | Initial Staging | Skin  | N/A         | 2.1                         | 10mm right thigh lesion.                                               | No evidence of primary or metastatic prostate cancer. No follow up as widespread metastases from separate neuroendocrine tumour |
| 8  | 75  | Re-Staging | Bladder | 42.9        | N/A*                        | Widespread uptake involving prostate, nodes and right VUJ lesion.       | Primary bladder tumour. No follow up, patient resident abroad and left New Zealand |
| 9  | 81  | Initial Staging | Lung  | 26.1        | 2.7                         | Uptake in prostate, pelvic nodes and low PSMA expression in 11mm nodule within RUL | Likely primary lung adenocarcinoma. No follow up given comorbidities and age.       |
| 10 | 73  | Initial Staging | Node  | 26.1        | 2.1                         | Uptake in prostate, pelvic nodes and low PSMA expression in 14mm mesenteric node | High expression in prostate and pelvic node considered typical for prostate cancer. Mesenteric node indeterminate. Commenced on ADT with pelvic Radiotherapy. Awaiting further follow up. |
| No | Age  | Indication       | Site    | Primary SUV | SUV  | SUV miPSMA Expression Score | Findings                                                                 | Clinical Rationale                                                                                       | Outcome                                                                                     |
|----|------|------------------|---------|-------------|------|----------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| 1  | 79   | BF post RP       | Lung    | 12.1        | 2.6  | 1 Uptake in prostate gland and low PSMA expression in LUL ground glass change | Likely inflammatory.                                                      | No follow up.                                                                                        |
| 2  | 72   | Initial Staging  | Lung    | 17          | 4.9  | 1 Uptake in prostate gland and low PSMA expression in LUL ground glass change | Likely inflammatory.                                                      | No follow up.                                                                                        |
| 3  | 84   | BF post RP       | Liver   | N/A         | 13.4 | 1 High PSMA expression within segment 4 of the liver.                     | Image noise versus liver metastasis, not solid organ disease elsewhere   | Not present on follow up PSMA with rising PSA. Most likely benign or artefact.                     |
| 4  | 77   | BF post RP       | Lung    | N/A         | 2.2  | 1 Low PSMA expression in 12mm LUL lung nodule[1]                          | Two sigmoid lesions FDG avid ?metastasis from bowel/ prostate or benign lesion | Follow up CT 2 years later showed no significant change in lesion.                                  |
| 5  | 69   | BF post RP       | Lung    | N/A         | 1.6  | 1 Minimal PSMA expression in 9mm irregular pulmonary nodule              | Solitary pelvic node recurrence. Indeterminate lung nodule              | No change on surveillance imaging for over 2 years.                                                |
| 6  | 76   | BF post RP       | Kidney  | N/A         | <1   | 0 30mm heterogeneous right retroperitoneal lesion abutting inferior pole of right kidney | Likely benign cyst or lymphatic lesion, exclude sarcoma.                | Non-enhancing on dedicated triple phase CT and unchanged over 13 months.                           |
| 7  | 79   | BF post RP       | Bone    | N/A         | <1   | 0 Low PSMA expression in sclerotic left temporal bone lesion.            | Likely benign lesion.                                                    | No further imaging. Remaining asymptomatic.                                                        |
| 8  | 69   | BF post RP       | Sinus   | N/A         | 7.5  | 2 Intermediate PSMA expression in left maxillary sinus mass.            | Likely inflammatory, exclude tumour.                                    | Follow up with ENT – CT/MRI demonstrating no suspicious lesion. Changes resolved on imaging 3 years later |
| 9  | 70   | Initial Staging  | Bone    | N/A         | <1   | 0 Sclerotic right saccal alar lesion with no PSMA expression.            | Indeterminate lesion, possibly benign.                                   | FDG PET/CT 2 weeks later demonstrated no activity. Changes resolved on imaging 3 months no change  |
| 10 | 56   | BF post RP       | Colon   | N/A         | <1   | 0 No PSMA expression within sigmoid colon.                              | Clinical and radiological evidence of diverticulitis.                   | Follow up over 18 months no change.                                                                |
| 11 | 83   | BF post RP       | Lung    | N/A         | <1   | 0 No PSMA expression within the lung.                                    | Likely rounded atelectasis.                                             | Resolved. Subsequent PSMA PET/CT no uptake.                                                        |
| 12 | 74   | BF post RP       | Larynx  | N/A         | <1   | 0 Uptake in seminal vesicle and solid nodule within right false vocal cord | Likely right laryngeal.                                                 | Resolved on subsequent CT.                                                                           |
| 13 | 67   | BF post RP       | Spleen  | N/A         | 13   | 3 Pelvic nodal recurrence with low PSMA expression.                     | Indeterminate splenic lesion.                                          | No progression with clinical surveillance.                                                         |
| 14 | 61   | BF post RP       | Retroperitoneal | N/A   | <1   | 0 Thin walled cystic retro-peritoneal lesion.                           | Most likely benign.                                                     | Patient underwent salvage radiotherapy. No specific follow up of retroperitoneal lesion.           |
| 15 | 63   | Initial Staging  | Lung    | 10.8        | 4.2  | 1 Uptake in prostate gland and 18mm pleural based nodule               | Likely benign.                                                          | Resolved on follow up CT 3 months later.                                                            |
| 16 | 50   | Initial Staging  | Skin    | N/A         | 3.2  | 1 Uptake in prostate gland and left paraspinal subcutaneous nodule with low PSMA expression. | Likely benign.                                                          | No change on follow up PSMA. Specific comment on follow up regarding skin lesion.                |
| 17 | 75   | BF post RP       | Lung    | N/A         | <1   | 0 No PSMA expression in a patchy opacity in LUL.                        | Likely inflammatory changes.                                            | Follow up CT in 6 weeks advised. No follow up at STV.                                              |
| 18 | 73   | BF post RP       | Thyroid | N/A         | 1.7  | 1 Indeterminate heterogeneous 24mm left thyroid nodule                   | Likely benign nodule.                                                   | No follow up.                                                                                     |
| 19 | 62   | Initial Staging  | Scrotum | 15.1        | 5.2  | 2 Bilateral scrotal extra-testicular nodules ? Epididymal metastases but no extra-prostatic disease elsewhere | Nodules not investigated. Patient proceeded to RP. BF 4 years later with repeat PSMA. No interval changes in scrotal nodules, considered benign | Patient undergone salvage radiotherapy. No specific follow up of scrotal lesion.                   |
| No | Age | Indication   | Site     | Primary SUV | SUV Expression Score | Findings                                                                 | Clinical Rationale                                                                 | Outcome                                             |
|----|-----|--------------|----------|-------------|----------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------|
| 1  | 65  | Initial Staging | Lung     | 8.9         | 1.6                  | 1 Uptake in prostate gland and 22 mm lesions within LUL                 | Suspected bronchogenic malignancy                                                  | Biopsy proven granuloma. Reduced in size on follow up imaging                        |
| 2  | 72  | BF post RP   | Lung     | 25.2        | 1.3                  | 0 Uptake in pelvic nodes and several pulmonary nodules (most significant 16 mm in RLL) | Suspected benign lesions given low PSMA expression                              | Wedge resection of RLL lesion confirming Hamartoma                                     |
| 3  | 77  | BF post RP   | Skin     | 6.5         | 4.5                  | 1 Uptake in abdominal nodes and low PSMA expression in subcutaneous nodules (3 mm and 8 mm) | Direct visualization suggested                                                  | Biopsy proven angiolipoma                                                                 |
| 4  | 72  | BF post RP   | Skin     | N/A         | 3.1                  | 1 Low PSMA expression in skin lesion lower right lateral abdomen        | Direct visualization suggested                                                  | Biopsy performed with non-specific findings, no malignancy                            |
| 5  | 65  | BF post RP   | Skin     | N/A         | 3.0                  | 1 18 mm subcutaneous right paraspinal lesion                             | Biopsy suggested                                                                | Biopsy proven hemangioma                                                                |
| 6  | 68  | Initial Staging | Breast   | 58.3        | 2.8                  | 1 Low PSMA expression in left breast                                     | Suspected gynaecomastia                                                         | Mammogram and biopsy performed confirming gynaecomastia                                |
| 7  | 65  | BCR post RP  | Skin     | N/A         | 1.7                  | 1 Uptake in pelvic nodes and 28 mm rounded lesion deep to skin in right lower back | Probable cyst                                                                   | Direct visualisation of lesions confirmed sebaceous cyst                               |
| 8  | 61  | BF post RP   | Thyroid   | N/A         | 2.7                  | 1 Multinodular thyroid enlargement causing tracheal narrowing            | Probable benign multinodular goitre                                              | Ultrasound confirmation of benign features                                             |
| 9  | 66  | BF post RT   | Thyroid   | 5.8         | 3.2                  | 1 Indeterminate heterogeneous left thyroid nodule with calcifications   | Ultrasound ± FNA suggested                                                      | Biopsy proven benign thyroid nodule                                                     |
| 10 | 57  | BF post RP   | Thyroid   | N/A         | 2.6                  | 1 38×28 mm ovoid homogeneous mass in lower pole of left thyroid lobe     | Ultrasound ± FNA suggested                                                      | Biopsy proven benign thyroid nodule                                                     |
| 11 | 69  | BF post RP   | Thyroid   | 5.5         | 3/1                  | No PSMA expression in a 40 mm nodule within the thyroid isthmus          | Ultrasound suggested                                                            | Ultrasound confirmation of benign features                                              |
| 12 | 66  | BF post RT   | Thyroid   | 3.5         | 4.6                  | 1 Indeterminate heterogeneous left thyroid nodule with calcifications   | Ultrasound ± FNA suggested                                                      | Biopsy proven benign thyroid nodule                                                     |
| 13 | 70  | BF post RP   | Thyroid   | N/A         | 2.3                  | 1 25 mm heterogeneous density nodule in right thyroid with calcifications | Ultrasound suggested                                                            | Ultrasound confirmation of benign features                                              |
| 14 | 58  | BF post RP   | Scrotum   | N/A         | 7.8                  | 2 Unilateral right scrotal extra-testicular nodule with PSMA expression | ? Epididymal metastases but no recurrence elsewhere                             | Orchidectomy pre-salvage, histology showed granulomatous epididymitis               |

*SUV standardized uptake value, LUL left upper lobe, BF biochemical failure, RP radical prostatectomy, RLL right lower lobe, PSMA prostate specific membrane antigen*
specific for prostate cancer although this specificity is only realized in combination with a comprehensive knowledge of the physiological and abnormal expression of PSMA. Physiological expression and distribution of typical prostate cancer related abnormal expression is well documented. [6]

Atypical PCa metastases are seen in less than 5% of cases but can affect most organs. Atypical metastases are rare in isolation and are often observed in the context of a typical pattern of disseminated metastatic PSMA expressing PCa. In addition, PCa metastases are described as focal with high PSMA expression whereas NPCaT expression is more likely to be low and non-focal [6, 16]. All lesions in our cohort categorized as PCa metastases were in expected sites for metastatic disease but NPCaT required exclusion due to their structural features or clinical presentation (Table 1). The majority of lesions confirmed to be PCa metastases demonstrated intermediate to high PSMA expression, with two cases of multiple lung lesions demonstrating no expression. This echoes the study by Damjanovic et al. which concluded that 27.5% of prostate cancer metastases demonstrated no PSMA expression. (Damjanovic 2018) Our study demonstrated that lesions with intermediate to high PSMA expression were more likely to be PCa metastases rather than NPCaT regardless of their CT morphology. All of the NPCaT in our group (except for two RCC cases) demonstrated no or low PSMA expression (SUV < 5). These findings correlate with literature describing PSMA expression in RCC [17, 18]. Although some cases in our cohort were not followed up due to factors including patient age, comorbidity, and extensive tumour burden, many lesions were subject to MDM discussion, clinical and radiological follow-up, and/or biopsy. This approach is valid and necessary in the clinical workup of these patients particularly in the context of advancing treatment options for patients with oligometastatic disease.

Numerous benign lesions are also known to express PSMA; however, from our cohort, the indeterminate and benign lesions largely demonstrated no or low PSMA expression (SUVmax < 5) [16, 19]. Pulmonary nodules in this patient cohort were common and the majority were assigned to follow-up based upon established guidelines [8, 9]. Lung nodules comprised the majority of the incidental potentially malignant group although these were larger (11–40 mm) with more complex imaging features and some demonstrated low PSMA expression. We found that lung nodules with intermediate or high PSMA expression were exclusively PCa metastases in our cohort whereas no biopsy-proven lung cancer demonstrated intermediate or high PSMA expression, despite PSMA expression in lung cancer described in the literature [20]. Our study has demonstrated that PCa metastases are substantially more frequent than NPCaT in the context of thoracic lesions with intermediate to high PSMA expression. These findings are further substantiated when considered in the context of existing structured reporting systems. For example, the European Association of Nuclear Medicine, including authors of both PROMISE data and PSMA-RADS, has recently provided guidelines for standardised reporting using E-PSMA five-point scale. The majority of the indeterminate and NPCaT lesions in our cohort comply with category 3 E-PSMA (indeterminate) lesions and the majority of benign lesions correspond to category 2 E-PSMA (likely benign). Furthermore, many lesions later confirmed to be PCa metastases arguably fell under E-PSMA 5, which would correctly allocate them to PCa metastases, but additional findings beyond this definition prompted clinical uncertainty, such as morphology, solitary site of disease, and other malignancy and predisposing factors for second primary [7, 21, 22].

The ability to differentiate PCa metastases from NPCaT is vital as further investigation can lead to morbidity, delays in therapy and incurs additional medical costs. In our cohort, 8% of patients with benign incidental findings underwent a biopsy as part of further investigation while of 19 patients with lung nodules over 10 mm, 13 (68%) were biopsied. Recognizing these patterns in context of established standardised reporting criteria can give PET/CT specialists the ability to make a confident diagnosis, thus avoiding escalating investigation, cost and therapeutic delays [7]. Importantly we would emphasise that guidelines and structured reporting systems allow for reduced variation of interpretation and clear communication however overall interpretation critically relies upon multiple factors and a multidisciplinary approach to diagnosis and management is paramount [7, 22].

The incidence of NPCaT in our PSMA cohort (1.7%) is substantially less than the incidence of significant incidental non-FDG avid findings on FDG PET/CT (22.6%) [23]. There are a number of potential reasons for this, including differing demographics, definitions of ‘major’ clinical significance, stricter evidence-based criteria used in our study, the use of subspecialist radiologists to exclude benign pathologies along with our exclusion of pre-existing known pathologies.

PSMA expression in NPCaT is more commonly associated with tumours which undergo neovascularization such as RCC, breast, glial tumours, gastrointestinal, pancreatic and lung tumours, all of which were represented in our cohort [24–29]. Further tumours reported to express PSMA not represented in our study include oral SCC, salivary ductal carcinoma, medullary thyroid carcinoma, small cell lung cancer, osteosarcoma, gynaecological malignancies, and adenoid cystic tumours [30, 31]. Such expression is variable but has significant clinical implications. PSMA imaging may provide an investigative tool for such tumours, with particular recent interest in clear cell RCC and in detection and characterisation of metastatic diseases [18, 32–35]. The potential for PSMA targeted radiopharmaceuticals in non-prostate tumours is vast and the degree of PSMA expression may prospectively
select treatment candidates and monitor response. Treatment monitoring, in particular drugs targeting neovascularization, e.g. bevacizumab and tyrosine kinase inhibitors, is a further potential application. PSMA expression in NPCaT may aid prognostication, for example, PSMA expression in non-metastatic triple negative breast cancer confers worse prognosis with higher relapse and reduced response to androgen receptor inhibition [25, 30]. In contrast, PSMA expression in non-small cell lung cancer (NSCLC) is associated with earlier stage tumours. It is noteworthy that these concepts remain in the realm of research and the full clinical impact of these applications is yet to be determined [24, 36].

This study benefited from a large number of consecutive patients in a multicenter international setting. A limitation of this study was its retrospective design. The largest impact of this was that many patients did not have histological confirmation and/or did not have conclusive follow up, leading to indeterminate findings in a cohort of patients. Selection of patients based on initial reports can introduce subjectivity and bias; however, the initial reports were generated by subspecialty trained experienced radiologists and nuclear medicine physicians. The imaging centers used different scanners albeit two consecutive generations of the same product, however this may have affected SUVmax measurements. Low numbers of individual non-prostate cancer tumours limit the ability to provide specific recommendations. There is always a degree of subjectivity when categorizing the significance of incidental findings and no perfect system exists although we have attempted to mitigate this by using experienced subspecialist radiologists and by considering the opinion of multidisciplinary meetings.

Conclusion

Our work is the largest study to date examining incidence of NPCaT detected by PSMA PET/CT and is the only study exclusively examining incidence in 18F-DCFPyL PET/CT. PSMA imaging of PCa is highly specific with the detection of PSMA expressing NPCaT exceedingly rare. NPCaT in our cohort generally demonstrated low or no PSMA expression. Although PSMA expression was noted in RCC, this was lower and less focal than typical PCa metastatic disease. We found that significant PSMA expressions at sites typical for prostate cancer metastases were exclusively PCa metastases rather than NPCaT.

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Declarations

Ethics approval Formal ethics review was waived under the New Zealand Health and Disability Ethics Committee exemption for minimal risk retrospective observational studies. Australian data was collected with an ethics approved prostate cancer database.

Consent to participate Not applicable.

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Conflict of interest The authors declare no competing interests.

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