Non-Prostate Cancer Tumours: Incidence on ^{18}f-Dcfpyl Psma Pet/Ct and Psma Expression Characteristics in 1445 Patients.

Elisa Perry
Pacific Radiology Group Inc
Arpit Talwar (talwar.arpit@gmail.com)
St Vincent's Hospital Melbourne Pty Ltd https://orcid.org/0000-0002-7187-3074
Sanjana Sharma
St Vincent's Hospital Melbourne Pty Ltd
Daisy O'Connor
Pacific Radiology Group Inc
Lih-Ming Wong
St Vincent's Hospital Melbourne Pty Ltd
Kim Taubman
St Vincent's Hospital Melbourne Pty Ltd
Tom R Sutherland
St Vincent's Hospital Melbourne Pty Ltd

Research Article

Keywords: 18F-DCFPyL, PET/CT. PSMA, Prostate Cancer, Biochemical recurrence

Posted Date: September 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-883330/v1

Abstract

Purpose

Prostate cancer (PCa) imaging has been revolutionized by Positron emission tomography (PET) tracers targeted to prostate specific membrane antigen (PSMA). Identification and characterization of non-PCa tumors has become an increasing clinical dilemma with growing use. The primary aim of this retrospective multicenter analysis was to determine atypical PSMA expression in PCa and expression in non-PCa tumors to aid providing clinically relevant reports and guiding multidisciplinary discussion.

Methods

Retrospective multicenter study examining 1445 consecutive ^{18}F-DCFPyL PSMA PET/CT between 2016-2020. Referrals were from public and private, secondary and tertiary referral centres serving New Zealand and Melbourne. Repeat studies were excluded. Lesions atypical for PCa were categorized into four groups: 1. Atypical PCa metastases 2. Non-PCa tumors 3. Benign and 4. Indeterminate.

Results

67 patients had lesions atypical for PCa metastases; 11.9% atypical prostate cancer metastases, 25.4% non-PCa tumors, 40.3% indeterminate, 10.4% benign. With the exception of Renal Cell Carcinoma (RCC), the non-PCa tumors, indeterminate and benign lesions demonstrated low PSMA expression. Most atypical PCa metastases demonstrated significant expression. Limitations included retrospective design and lack of histopathological correlation/follow up in some.

Conclusions: Non-PCa tumor detection is low. Lesions demonstrating significant PSMA expression were almost exclusively PCa metastases. Differentiation of atypical PCa metastases from second primary malignancies is vital to avoid unnecessary investigation, delayed therapy and additional costs.

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men and is the sixth leading cause of cancer death, with significant world-wide variation relating to screening availability and management options. [1] Imaging of prostate cancer both at initial staging and at recurrence has been revolutionized by the advent of PET tracers targeted to prostate specific membrane antigen (PSMA) which have shown superiority in comparison with conventional imaging comprising CT and bone scan. [2-4]

PSMA is a transmembrane glycoprotein with high expression in most prostate cancer cells although also can sometimes be expressed in endothelial cells in non-prostate cancer tumor 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. ^{18}F-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 non-prostate cancer tumors is likely to continue. The physiological

expression of PSMA and typical patterns of expression in prostate cancer is well documented however atypical presentations of PSMA expression in prostate cancer and expression in non-prostate cancer tumors is 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 non-prostate cancer tumors detected on ^{18}F-DCFPyL PSMA PET/CT in patients with primary prostate cancer and describe their imaging characteristics. The primary outcome was the incidence of new diagnosis non-prostate cancer tumors detected in this cohort. The proportion and types of tumors demonstrating avidity was assessed and correlated with the indication for the examination. In tumors that were not further investigated, the reasons for these were explored.

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 all patients who have had ^{18}F-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 non-prostate cancer was included.

Case Selection and Imaging Analysis

All imaging reports were reviewed to identify patients with suspected incidental non-prostate cancer related tumors. Typical prostate cancer related tumors were defined as PSMA expression greater than background in the expected distribution for prostate cancer within prostate, nodes, bone and visceral locations. 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 SUV were recorded. 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 10mm without PSMA expression or features suggesting atypical adenomatous hyperplasia/adenocarcinoma spectrum which fitted adopted follow up guidelines were excluded. [6, 7] Known lesions which had already been identified and investigated on prior imaging were also excluded.

Abdominal 'incidentalomas' without PSMA expression, including non-avid adrenal adenomas, low attenuation 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 excluded. [8] Further lesions that had definitive benign diagnoses on subsequent dedicated imaging were also excluded.

Of the remaining lesions, patient records were retrieved and further biopsy results, dedicated imaging, multidisciplinary team meeting notes, follow up clinic letters and specialist consults were noted. Based on this information, lesions were categorized broadly into four groups: 1. Atypical prostate cancer metastases 2. Non-Prostate Cancer tumors 3. Benign and 4. Indeterminate lesions.

Groups 1-3 were subdivided into those with biopsy confirmation and those clinically determined. The lesions classified as indeterminate were sub classified as a. likely benign, b. likely non-prostate cancer tumor and c. likely prostate cancer metastasis.

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 as previously described. [9]

PRC: Patients were required to drink 1-2L of water prior to their appointment and void immediately prior to 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 3.75mm slice thickness with an increment of 3.27mm using iterative reconstruction (50% ASiR). PET images were acquired at 3.5min/bed through the pelvis and 3.0min/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.

Decision Aid

Following collation and analysis of all results a decision support algorithm was constructed to guide management of findings within the chest and abdomen. Management guidance beyond these two body regions was not performed due to low numbers limiting the ability to make general recommendations.

Results

A total of 1445 studies were performed using ^{18}F-DCFPyL (PRC = 865 studies, STV = 580 studies). 1237 of these studies were excluded as they had lesions typical for prostate cancer or no detectable lesion. 208 studies remained for further analysis. Of these studies, 85 related to lung nodules and 56 to incidentalomas, fulfilling the exclusion criteria. A total of 67 studies were therefore included in our study. (Figure 1)

Of these 67 lesions, 8/67 (11.9%) were atypical prostate cancer metastases, 17/67 (25.4%) were other non-prostate cancer tumors, 27/67 (40.3%) were indeterminate and 7/67 (10.4%) were benign. In the context of the entire cohort these proportions are adjusted to 8/1445 (0.55%), 17/1445 (1.18%), 27/1445 (1.9%) and 7/1445 (0.5%) respectively.

Atypical Prostate Cancer Metastases

4/8 (50%) of lesions identified as being atypical for prostate cancer metastases demonstrated significant PSMA expression, all of which were suspected to be primary lung cancer, however all were biopsy confirmed PCa lung metastases. The remaining 4/8 (50%) lesions were two lung, one bone and one nodal metastasis, demonstrating a range of PSMA expression from SUV of <1 to 22. (Table 1)

Non-Prostate Cancer Tumors

17/68 (25.0%) of patients within our cohort had clinical suspicion or biopsy proven non-prostate cancer tumors. 2/17 (11.8%) lesions demonstrated significant heterogeneous PSMA expression and characteristic CT features of renal cell carcinoma (RCC). The remaining 15/17 (88.2%) lesions had low PSMA expression (SUVmax <5). 12 of these were classified as tumors with high malignant potential and the remaining 3 as low malignant potential.

PSMA and pathological findings of non-prostate tumors 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 characteristic findings of non-prostate cancer, however in some patients this diagnosis was made by multidisciplinary consensus as further imaging or biopsy was not felt clinically appropriate due to advanced patient age, performance status or widespread metastatic malignancy.

The remaining 9/17 (52.9%) patients proceeded to biopsy. Three of these patients had lung lesions (mean SUVmax 3.7), all of which were biopsy-proven primary lung cancer. Two patients had focal low PSMA expression within the colon (mean SUVmax 4.2), 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.

Four other non-prostate cancer tumors were also biopsy proven. 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 (SUVmax < 1), poorly differentiated pancreatic adenocarcinoma (SUVmax 4.8) and follicular lymphoma (SUVmax 3.5).

No hepatic malignancies were diagnosed with all liver findings representing simple hepatic cysts, hemangiomas and a hydatid cyst.

Indeterminate Lesions

25/27 indeterminate lesions did not demonstrate significant PSMA expression. 2/27 demonstrated expression but were located in organs with high background expression (liver and spleen). 3/27 (11.1%) were considered most likely prostate cancer metastases without PSMA expression, 7/27 (25.9%) suspicious for non-prostate cancer tumors and 17/27 (63.0%) were determined most likely benign.

Benign Lesions

Of the six-biopsy proven and one clinically-proven benign lesions none demonstrated significant PSMA expression.

Decision Aid

The above findings were amalgamated and presented in a flow diagram. (Figure 2)

Discussion

This study represents the largest cohort to date assessing incidence of non-prostate cancer tumors detected by PSMA imaging and is the only study exclusively examining this incidence with ^{18}F-DCFPyL PET/CT. PSMA imaging is considered highly 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 is well documented and is most notable in the lacrimal glands, salivary glands, liver, kidneys and spleen with less marked variable expression in the vocal cords, intestine and parasympathetic ganglia. Numerous benign lesions are also known to express PSMA however from our cohort the 24 benign lesions were largely non-avid or demonstrated low PSMA expression (SUVmax < 5). [10, 11]

Typical sites of PSMA expression in prostate cancer are prostate/prostate bed, lymph nodes, most commonly pelvic and retroperitoneal, and bone metastases. [9, 12] Less common but expected sites of metastasis are liver and thorax (including lymph nodes, lungs and pleura). [13] Atypical 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 prostate cancer. In addition, prostate cancer metastases are described as focal with intense PSMA expression whereas non-prostate cancer tumor uptake is more likely to be lower intensity and non-focal. [10, 13] All lesions in our cohort which were categorized as atypical for metastatic prostate cancer but later demonstrated to be prostate cancer metastases were in expected sites for metastatic disease but of low PSMA expression (four cases) or demonstrated intense expression and required differentiation from a primary lung tumor (four cases) due to their structural features. (Table 1) Our study demonstrated that lesions considered atypical metastatic prostate cancer with significant PSMA expression were more likely to be prostate cancer metastases rather than second primaries regardless of their CT morphology. All of the non-prostate cancer tumors in our group (except for two RCC cases) demonstrated low PSMA expression (SUV<5). These findings correlate with literature describing PSMA expression in RCC. [14] Although some cases in our cohort were not followed up due to factors including patient age, comorbidity, extensive tumor 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 work up of these patients particularly in the context of advancing treatment options for patients with oligometastatic disease.

Pulmonary nodules in this patient cohort are common and the majority were assigned to follow-up based upon established guidelines. [6, 7] Lung nodules comprised the majority of the incidental potentially malignant group although these were larger (11-40mm) with more complex imaging features and some demonstrated mild PSMA expression. We found that lung nodules with significant PSMA expression were exclusively prostate cancer metastases in our cohort whereas no biopsy proven lung cancer demonstrated significant PSMA expression, despite PSMA expression in lung cancer described in the literature. [15]

The ability to differentiate atypical prostate cancer metastases from second primary malignancies 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 10mm, 13 (68%) experienced further investigation. Our study has demonstrated that atypical prostate cancer metastases are substantially more frequent than second primaries in the context of thoracic lesions with increased PSMA expression. Recognizing this can give PET/CT specialists the ability to make a confident diagnosis, thus avoiding escalating investigation, cost and therapeutic delays.

The incidence of significant non-prostate cancer tumors in our PSMA cohort (4.2%) is substantially less than the incidence of significant incidental non-FDG avid findings on FDG PET/CT (22.6%). [16] There are a number of potential reasons for this, including differing demographics, definitions of ‘major’ clinical significance, with 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 non-prostate cancer tumors is more commonly associated with tumors which undergo neovascularization such as RCC, breast, glial tumors, gastrointestinal, pancreatic and lung tumors, all of which were represented in our cohort. [17-22] Such expression is variable but has significant clinical implications. PSMA imaging may provide an investigative tool for such tumors and this application in RCC is under investigation, although preliminary studies suggest most value would be for clear cell subtypes. [23-25] The potential for treatments targeting PSMA in non-prostate tumors is vast and the degree of PSMA expression may help to prospectively select treatment candidates and monitor response. A further application is of 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. [18] In contrast PSMA expression in NSCLC is associated with earlier stage tumors. 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. [17, 26]

This study benefited from large numbers and a multicenter international database. Limitations include its retrospective design and not all patients having histopathological confirmation. Low numbers of individual non-prostate cancer tumors 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 non-prostate cancer tumors detected by PSMA imaging and is the only study exclusively examining this incidence in ^{18}F-DCFPyL PET/CT. PSMA imaging prostate cancer is highly specific with the detection of non-prostate cancer tumors exceedingly rare. Non-prostate cancer tumors in our cohort generally demonstrated low or no significant PSMA expression. Although PSMA expression was noted in RCC this was lower and less focal than typical prostate cancer metastatic disease. We found that significant PSMA expression at sites typical for prostate cancer metastases were exclusively prostate cancer metastases rather than second primaries.

Declarations

Funding
No funding declaration.

Conflicts of Interest/Competing Interests

EP – Research grant has previously been received from GE Healthcare.

KT – Research grant has previously been received from GE Healthcare.

TS – paid lecture for Bayer and paid workshops for Siemens.

Availability of data and material

Data are available for bona fide researchers who request it from the authors.

Code availability

Not applicable

Ethics Approval

Institutional ethics approval has been granted for the maintenance of a prostate cancer database, from which the study data was derived.

Consent to participate

Not applicable

Consent for publication

Not applicable

Acknowledgements

None.

References

1. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent global patterns in prostate cancer incidence and mortality rates. *European urology.* 2020;77(1):38-52.
2. Morris MJ, Rowe SP, Gorin MA, Saperstein L, Pouliot F, Josephson D, et al. Diagnostic Performance of 18F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study. Clinical Cancer Research. 2021.
3. Pienta KJ, Gorin MA, Rowe SP, Carroll PR, Pouliot F, Probst S, et al. A Phase 2/3 Prospective Multicenter Study of the Diagnostic Accuracy of Prostate Specific Membrane Antigen PET/CT with 18F-DCFPyL in Prostate Cancer Patients (OSPREY). The Journal of Urology. 2021:10.1097/JU. 0000000000001698.
4. Tanaka T, Yang M, Froemming AT, Bryce AH, Inai R, Kanazawa S, et al. Current Imaging Techniques for and Imaging Spectrum of Prostate Cancer Recurrence and Metastasis: A Pictorial Review. RadioGraphics. 2020:190121-. doi:10.1148/rg.2020190121.
5. Conway RE, Rojas C, Alt J, Nováková Z, Richardson SM, Rodrick TC, et al. Prostate-specific membrane antigen (PSMA)-mediated laminin proteolysis generates a pro-angiogenic peptide. Angiogenesis. 2016;19:487-500.
6. Baldwin DR, Callister ME. The British Thoracic Society guidelines on the investigation and management of pulmonary nodules. Thorax. 2015;70:794-8.

7. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung AN, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284:228-43.
8. Mayo-Smith WW, Song JH, Boland GL, Francis IR, Israel GM, Mazzaglia PJ, et al. Management of incidental adrenal masses: a white paper of the ACR Incidental Findings Committee. Journal of the American College of Radiology. 2017;14:1038-44.
9. Perry E, Talwar A, Taubman K, Ng M, Wong L-M, Booth R, et al. [18 F] DCFPyL PET/CT in detection and localization of recurrent prostate cancer following prostatectomy including low PSA< 0.5 ng/mL. European Journal of Nuclear Medicine and Molecular Imaging. 2021;48:2038-46.
10. Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-specific membrane antigen PET: clinical utility in prostate cancer, normal patterns, pearls, and pitfalls. Radiographics. 2018;38:200-17.
11. Kirchner J, Schaarschmidt BM, Sawicki LM, Heusch P, Hautzel H, Ermert J, et al. Evaluation of practical interpretation hurdles in 68Ga-PSMA PET/CT in 55 patients: physiological tracer distribution and incidental tracer uptake. Clinical nuclear medicine. 2017;42:e322-e7.
12. Koschel S, Taubman K, Sutherland T, Yap K, Chao M, Guerrieri M, et al. Patterns of disease detection using [18 F] DCFPyL PET/CT imaging in patients with detectable PSA post prostatectomy being considered for salvage radiotherapy: a prospective trial. European Journal of Nuclear Medicine and Molecular Imaging. 2021:1-11.
13. Barbosa FG, Queiroz MA, Nunes RF, Viana PC, Marin JFG, Cerri GG, et al. Revisiting prostate cancer recurrence with PSMA PET: atlas of typical and atypical patterns of spread. Radiographics. 2019;39:186-212.
14. Pozzessere C, Bassanelli M, Ceribelli A, Rasul S, Li S, Prior JO, et al. Renal cell carcinoma: the oncologist asks, can PSMA PET/CT answer? Current urology reports. 2019;20:1-10.
15. Schmidt LH, Heitkötter B, Schulze AB, Schliemann C, Steinestel K, Trautmann M, et al. Prostate specific membrane antigen (PSMA) expression in non-small cell lung cancer. PLoS One. 2017;12:e0186280.
16. Sheldon JA, Yap KK, Taubman KL, Schlicht SM. Prevalence of non 18F-fluorodeoxyglucose-avid incidental findings of clinical significance on whole body positron emission tomography/computed tomography: A review of 500 consecutive cases. Journal of medical imaging and radiation oncology. 2018;62:194-202.
17. Farag M, Bolton D, Lawrentschuk N. Prostate-specific membrane antigen for the surgical oncologist: interpreting expression beyond the prostate. ANZ journal of surgery. 2020;90:715-8.
18. Kasimir-Bauer S, Keup C, Hoffmann O, Hauch S, Kimmig R, Bittner A-K. Circulating tumor cells expressing the prostate specific membrane antigen (PSMA) indicate worse outcome in primary, non-metastatic triple-negative breast cancer. Frontiers in oncology. 2020;10:1658.
19. Malik D, Kumar R, Mittal BR, Singh H, Bhattacharya A, Singh SK. 68Ga-labeled PSMA uptake in nonprostatic malignancies: has the time come to remove “PS” from PSMA? Clinical nuclear medicine. 2018;43:529-32.
20. Patel DN, Karsh LI, Daskivich TJ. Next-generation imaging in localized high-risk prostate cancer. Nature Publishing Group; 2021.
21. Shetty D, Patel D, Le K, Bui C, Mansberg R. Pitfalls in gallium-68 PSMA PET/CT interpretation—a pictorial review. Tomography. 2018;4:182-93.

22. Stoykow C, Huber-Schumacher S, Almanasreh N, Jilg C, Ruf J. Strong PSMA Radioligand Uptake by Rectal Carcinoma: Who Put the" S" in PSMA? Clinical nuclear medicine. 2017;42:225-6.
23. Chang SS, Reuter VE, Heston W, Gaudin PB. Metastatic renal cell carcinoma neovasculature expresses prostate-specific membrane antigen. Urology. 2001;57:801-5.
24. Rhee H, Blazak J, Tham CM, Ng KL, Shepherd B, Lawson M, et al. Pilot study: use of gallium-68 PSMA PET for detection of metastatic lesions in patients with renal tumour. EJNMMI research. 2016;6:1-6.
25. Yin Y, Campbell SP, Markowski MC, Pierorazio PM, Pomper MG, Allaf ME, et al. Inconsistent detection of sites of metastatic non-clear cell renal cell carcinoma with PSMA-targeted [18 F] DCFPyL PET/CT. Molecular Imaging and Biology. 2019;21:567-73.
26. Backhaus P, Noto B, Avramovic N, Grubert LS, Huss S, Boegemann M, et al. Targeting PSMA by radioligands in non-prostate disease—current status and future perspectives. European journal of nuclear medicine and molecular imaging. 2018;45:860-77.
27. Berland LL, Silverman SG, Gore RM, Mayo-Smith WW, Megibow AJ, Yee J, et al. Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee. Journal of the American College of Radiology. 2010;7:754-73.

Tables

Table 1

Characteristics of Atypical Prostate Cancer Metastases

No.	Age	Indication	PSA	Site	SUV	Findings	Clinical Rationale	Outcome
1	74	Biochemical persistence post RP	3.9	Lung	7.6	Solitary LLL nodule 13mm. No evidence of local or nodal recurrence. Multiple pleural plaques	Morphological appearances suggestive of lung adenocarcinoma lung in increased risk patient without PCa recurrence elsewhere.	Biopsy.
2	66	BCR post RP and salvage XRT	0.53	Lung	11.6	Solitary 8mm RUL lesion, no disease elsewhere.	In context of no other sites of recurrence, primary lung cancer should be excluded.	Wedge Resection.
3	70	BCR post RP	0.3	Lung	22.0	Marked PSMA expression 10mm LUL nodule. No prostate bed recurrence, equivocal expression in 4mm left mesorectal node.	Equivocal disease elsewhere. New primary should be excluded.	Resolution of lesion on CT follow up on hormonal therapy.
4	71	Initial Staging	11.6	Lung	11.5	21x12mm RUL lobulated solitary nodule in a patient with emphysema.	Solitary and significant history of smoking.	Resection.
5	77	Initial Staging	2.6	Lung Bone Node	< 1.0 6.2 4.0	Multiple pulmonary nodules with minimal PSMA expression, but primary low expression. Enlarged pelvic nodes with minimal expression. Mild bone expression.	DDx given as dedifferentiated neuro-endocrine tumour of prostate or BPH and metastases from bladder TCC.	Lung nodules reduced with Docetaxel and Goserelin.
6	60	BCR post RP and salvage XRT	3.9	Lung	1.0	Multiple new and enlarged pulmonary nodules with minimal expression, largest 12x14mm RLL apical segment.	DDx metastatic PCa versus other malignancy.	VATS wedge resection.

No.	Age	Indication	PSA	Site	SUV	Findings	Clinical Rationale	Outcome
7	66	BCR post XRT	24	Node	14.1	Increased 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	6.8	Known multiple PCa bone metastases. New 73mm expansile destructive right iliac lesion with predominant soft tissue mass, mild PSA expression.	Dissimilar appearance to other bony metastases and previous pelvic XRT for seminoma, exclude non-prostate cancer tumour.	Bone biopsy.

PSA = prostate specific antigen, SUV = standardized uptake value, RP = Radical prostatectomy, LLL = left lower lobe, PCa = prostate cancer, BCR = biochemical recurrence, XRT = 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

Table 2

PSMA and pathological findings of patients with non-prostate cancer tumors.

	Age	Site	Expression	SUV	Findings	Outcome	Pathology
1.	77	Lung	Low	3.8	29mm LLL nodule.	Biopsy	Primary lung adenocarcinoma
2.	79	Lung	Low	4.8	RLL mass.	Biopsy	Non-small cell lung cancer.
3.	73	Kidney	Low	< 1	34mm right renal lesion.	Biopsy	Renal cell carcinoma.
4.	95	Kidney	High	19.9	78mm left renal lesion.	Clinical	Renal cell carcinoma.
5.	71	Breast	Low	2.8	10mm left upper outer lesion.	Biopsy	Invasive carcinoma of no special type.
6.	72	Pituitary	Low	1.8	Pituitary enlargement.	Clinical	Subsequent MRI – pituitary macroadenoma.
7.	66	Colon	Low	4.4	Distal transverse colon lesion.	Biopsy	Colonic adenocarcinoma.
8.	81	Colon	Low	3.9	Ascending colon lesion.	Biopsy	Colonic adenocarcinoma and terminal ileum neuroendocrine tumour.
9.	63	Colon	Low	< 1	5cm tubular structure in right iliac fossa.	Clinical	Appendix mucocele.
10.	64	Brain	Low	< 1	Right posterior temporal lesion.	Clinical	Subsequent MRI – Meningioma.
11.	64	Pancreas	Low	4.8	Dilated pancreatic and bile ducts.	Biopsy	Poorly differentiated pancreatic adenocarcinoma.
12.	59	Brain	Low	4.5	Intracranial lesion.	Clinical	Subsequent MRI – Glioblastoma.
13.	77	Lung	Low	2.5	23mm RLL nodule.	Biopsy	Primary lung adenocarcinoma.
14.	73	Kidney	Low	4	Left upper pole lesion.	Clinical	Not investigated due to pre-existing widespread metastatic malignancy.
15.	79	Lymph Node	Low	3.5	24 x 14mm circumscribed soft tissue lesion posterior to D3.	Biopsy	Follicular Lymphoma (cervical node)

	Age	Site	Expression	SUV	Findings	Outcome	Pathology
16.	70	Lung	Low	4.7	15mm left upper lobe nodule.	Clinical	Not amenable to biopsy. Likely lung cancer.
17.	70	Kidney	High	10	Left renal mass.	Clinical	Characteristic for renal cell carcinoma.

SUV = standardized uptake value, LLL = left lower lobe, RLL = right lower lobe, MRI = magnetic resonance imaging, D3 = duodenum (3^{rd} segment)

Table 3. PSMA and pathological findings of patients with indeterminate lesions.

	No	Age	Indication	Site	SUV	Findings	Clinical Rationale	Outcome
MALIGNANT	1	80	Re-Staging	Node	1.9	Minimal PSMA expression 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	2.4	Multiple bilateral prominent iliac nodes up to 12mm, much lower expression than primary.	No confirmation.	Commenced on ADT.
	3	76	BCR post RP	Lung	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	2.1	19mm spiculated lung nodule in RUL.	Likely synchronous primary lung Ca.	No follow up given age and comorbidities.
	5	72	BF post RP	Lung	4.2	Irregular 14mm pulmonary lesion RUL	Likely primary lung adenocarcinoma	No follow up.
	6	83	Re-Staging	Lung	1.3	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	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	N/A*	Right VUJ lesion.	Primary bladder tumour.	No follow up, patient resident abroad and left New Zealand
	9	81	Initial Staging	Lung	2.7	Low PSMA expression in 11mm nodule within RUL	Likely primary lung adenocarcinoma.	No follow up given comorbidities and age.

	No	Age	Indication	Site	SUV	Findings	Clinical Rationale	Outcome
	10	73	Initial Staging	Node	2.1	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.
BENIGN	1	79	BF post RP	Lung	2.6	Low PSMA expression in LUL ground glass change	Likely inflammatory.	No follow up.
	2	72	Initial Staging	Lung	4.9	Low PSMA expression in LUL ground glass change	Likely inflammatory.	No follow up.
	3	84	BCR post RP	Liver	13.4	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	BCR post RP	Lung	2.2	Minimal PSMA expression in 12mm RUL lung nodule	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	BCR post RP	Lung	1.6	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	BCR post RP	Kidney	< 1	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	BCR post RP	Bone	< 1	Low PSMA expression in left temporal bone.	Likely benign lesion.	No further imaging. Remained asymptomatic.

No	Age	Indication	Site	SUV	Findings	Clinical Rationale	Outcome
8	69	BCR post RP	Sinus	7.5	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	< 1	Right sacral alar lesion without significant expression, significant expression in primary	Indeterminate lesion, possibly benign.	FDG PET/CT 2 weeks later demonstrated no avidity. Follow up over 18 months no change
10		BCR post RP	Colon	< 1	Minimal PSMA expression within sigmoid colon.	Clinical and radiological evidence of diverticulitis.	Resolved. Subsequent PSMA PET/CT no uptake.
11		BCRP post RP	Lung	< 1	Minimal PSMA expression within the lung.	Likely rounded atelectasis.	Resolved on subsequent CT.
12		BCRP post RP	Larynx	< 1	Solid nodule within right false vocal cord.	Likely right laryngocele.	No progression with clinical surveillance.
13	67	BCR post RP	Spleen	13	Pelvic nodal recurrence with mild expression. 7mm hypodense splenic lesion	Indeterminate splenic lesion	Not suitable and patient reluctant for active treatment. Patient remains well over 4 years of clinic follow up.
14	61	BCR post RP	Retro-peritoneal	< 1	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	4.2	18mm pleural based nodule	Likely benign.	Resolved on follow up CT 3 months later.

No	Age	Indication	Site	SUV	Findings	Clinical Rationale	Outcome
16	50	Initial Staging	Skin	3.2	Left paraspinal subcutaneous nodule with minimal PSMA expression.	Likely benign.	No change on follow up PSMA. No specific comment on follow up regarding skin lesion.
17	75	BCR post RP	Lung	< 1	Non-avid patchy opacity in LUL.	Likely inflammatory changes.	Follow up CT in 6 weeks advised. No follow up at STV.

*Unable to accurately assess due to bladder excretion.

SUV: standardized uptake value, PSMA: prostate specific membrane antigen, PCa: prostate cancer, ADT: androgen deprivation therapy, BCR: biochemical recurrence, RP: radical prostatectomy, LUL: left upper lobe, Ca: cancer, CT: computed tomography, STV: St. Vincent's Hospital Melbourne, RUL: right upper lobe, RLL: right lower lobe, VUJ: vesicoureteric junction, PSA: prostate specific antigen, FDG: fluorodeoxyglucose, ENT: ear nose and throat, MRI: magnetic resonance imaging

Table 4

PSMA and pathological findings of patients with biopsy or clinically proven benign lesions

No.	Age	Indication	Site	SUV	Findings	Clinical Rationale	Outcome
1	65	Initial Staging	Lung	1.6	22mm lesions within LUL	Suspected bronchogenic malignancy	Biopsy proven granuloma. Reduced in size on follow up imaging.
2	72	BF post RP	Lung	1.3	Several pulmonary nodules (most significant 16mm in RLL)	Suspected benign lesions given low PSMA expression	Wedge resection of RLL lesion confirming Hamartoma.
3	77	BF post RP	Skin	4.5	Mild PSMA expression in subcutaneous nodules (3mm and 8mm)	Direct visualization suggested.	Biopsy proven angiolipoma.
4	72	BF post RP	Skin	3.1	Mild 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	3.0	18mm subcutaneous right paraspinal lesion.	Biopsy suggested.	Biopsy proven hemangioma.
6	68	Initial Staging	Breast	3.0	Low PSMA expression in left breast.	Suspected gynaecomastia	Mammogram and biopsy performed confirming gynaecomastia.
7	65	BCR post RP	Skin	1.7	28mm rounded lesion deep to skin in right lower back.	Probable cyst.	Direct visualisation of lesions confirmed sebaceous cyst.

SUV: standardized uptake value, LUL: left upper lobe, BF: biochemical failure, RP: radical prostatectomy, RLL: right lower lobe, PSMA: prostate specific membrane antigen.

Figures

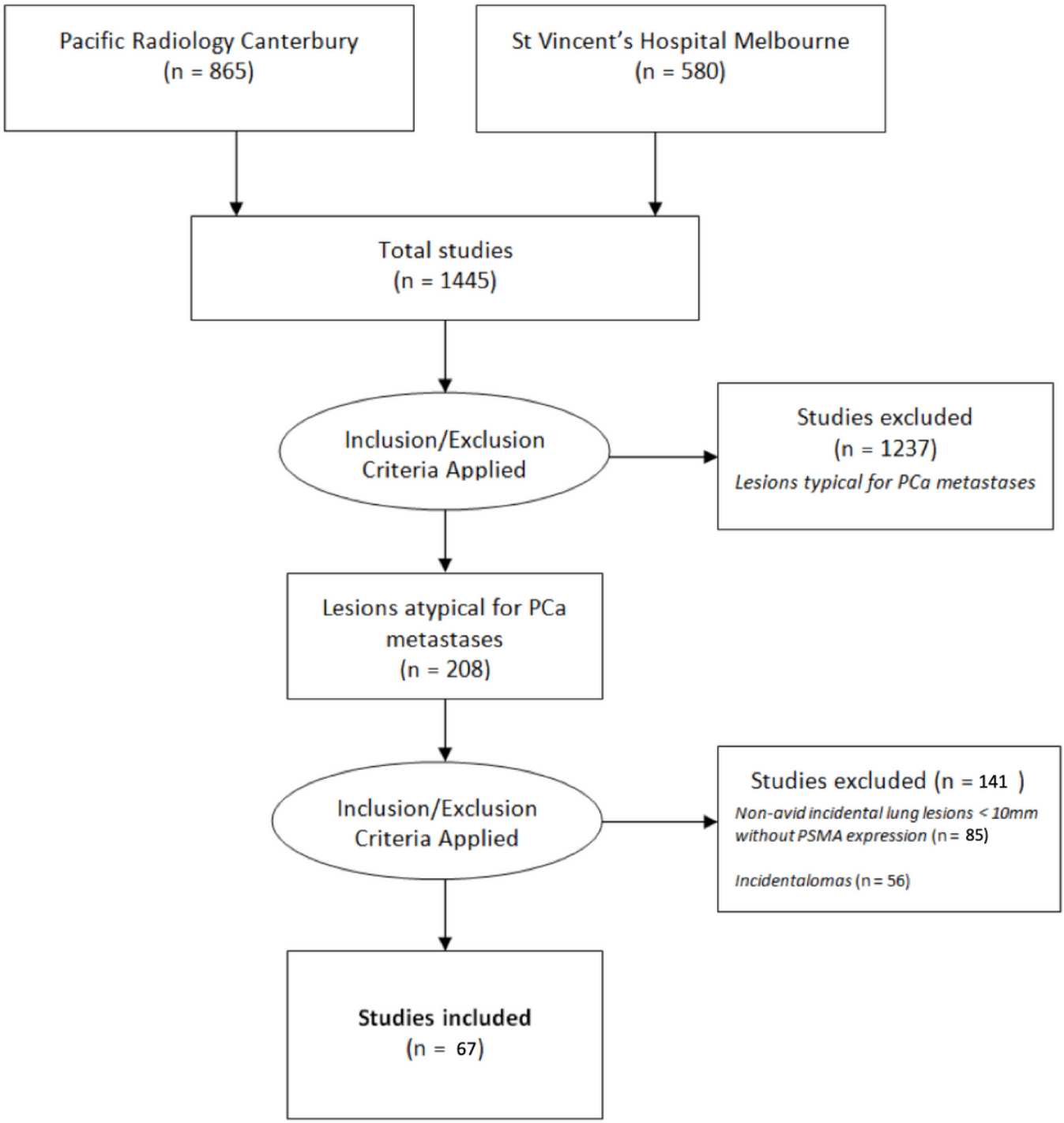

Figure 1

Flow diagram for inclusion and exclusion of studies. PCa = prostate cancer, PSMA = prostate specific membrane antigen.

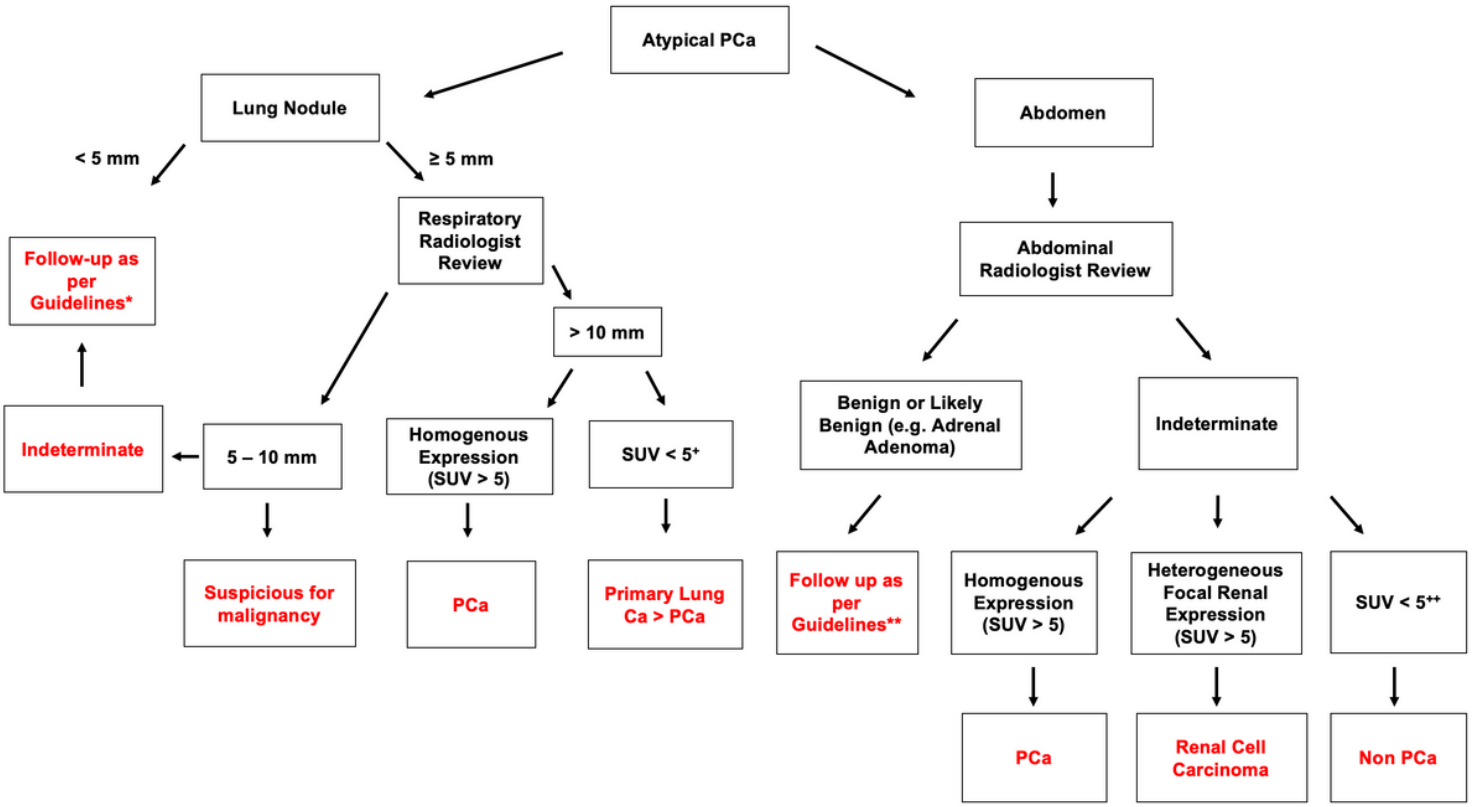

Figure 2

Flow Diagram Decision Aid generated from 1445 studies. This is a schematic representation of our findings and does not constitute a formal guideline. * British Thoracic Society guidelines/Fleischner Guidelines [7] ** White paper of the ACR Incidental Findings Committee [27] + unless the primary PCa has SUV<5 ++Not enough cases to make a formal recommendation. SUV=standardized uptake value, PCa=Prostate cancer.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- EJNMMISupplementary.docx