MOLECULAR IMAGING AND BIOLOGY
Mol Imaging Biol (2019) 21:799–807
DOI: 10.1007/s11307-018-01307-0

Published Online: 7 January 2019

REVIEW ARTICLE

A Review of Prostate-Specific Membrane Antigen (PSMA) Positron Emission Tomography (PET) in Renal Cell Carcinoma (RCC)

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Abstract

Metastatic renal cell carcinoma (mRCC) is a disease that portends poor prognosis despite an increasing number of novel systemic treatment options including new targeted therapies and immunotherapy. Ablative intervention directed at oligometastatic RCC has demonstrated survival benefit. Consequently, developing techniques for improved staging of mRCC on contemporary imaging modalities including X-ray computed tomography (CT), magnetic resonance imaging (MRI) and/or bone scan (BS) is a clinical priority. This is relevant for metastatic deposits too small to characterize or lymph nodes within physiological normality. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein highly expressed on prostate cancer epithelial cells. Recently, small molecules targeting the PSMA receptor, linked to radioactive isotopes have been developed for use with positron emission tomography (PET). Despite its nomenclature, PSMA has also been found to be expressed in the neovasculature of non-prostate cancers such as renal cell carcinoma (RCC) and hence PSMA PET/CT imaging has been proposed as an alternative staging modality. Preliminary small studies involving the use of PSMA PET/CT imaging in mRCC have been encouraging with evidence of improved staging sensitivity which has directly led to change in management in some cases. Given these early encouraging reports, we performed a comprehensive narrative review on the available evidence, including the scientific basis for PSMA expression in RCC, the role of PSMA PET/CT imaging with potential clinical implications in mRCC, its limitations and future opportunities.

Key words: Positron emission tomography, Prostate-specific membrane antigen, Gallium, Renal cell carcinoma, Metastasis

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Epidemiology and Issues with Renal Cell Carcinoma

Kidney cancer is the ninth and 14th most common cancer worldwide in men and women respectively, of which renal cell carcinoma (RCC) makes up greater than 90 % of these [1]. Approximately 20–30 % of patients with RCC present with metastatic disease [2, 3] whilst the incidence of post-operative RCC metastasis is much lower at less than 7 % at median follow-up between 1.5 to 5 years [4–6]. Metastatic RCC exhibits poor prognosis with a 5-year survival rate between 10 and 20 % and overall median survival of less than 1 year after diagnosis [7–9].

Staging and precise localization of tumour dissemination determines patient management and prognosis and hence prompt and accurate diagnosis is desirable. Traditionally, computed tomography (CT) with intravenous contrast agent has been the mainstay imaging modality in RCC staging. This is due to its widespread availability; however, definitive detection of small metastatic foci remains difficult [10]. Improved identification of metastases has significant clinical diagnostic and treatment relevance, especially in oligometastatic disease with the potential for definitive local therapy and subsequent better survival and prognosis [11].

Molecular Data Relating PSMA to RCC

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein. It has a unique three-part structure: an 18-amino-acid internal portion, a 25-amino-acid transmembrane portion and a 707-amino-acid external portion [12]. PSMA is encoded by a gene (Folate hydrolase 1; FOLH1) which is located on the short arm of chromosome 11 [13]. PSMA is significantly overexpressed in most prostate cancer cells associated with increasing tumour grade and stage [14, 15]. Subsequent initial clinical experience using PSMA PET/CT imaging has demonstrated superior sensitivity and specificity compared to standard of care (SOC) imaging in primary, metastatic and biochemically recurrent prostate cancer [16, 17].

Despite the specificity implied by its name, PSMA is physiologically widely expressed in numerous other tissues including kidney, liver, spleen, small and large bowel, rectum, bladder, thyroid gland and salivary gland [14, 18, 19]. PSMA has also been shown to be expressed in the neovasculature of many solid tumours including RCC [20, 21]. Consequently, the extracellular portion of the PSMA protein is a potential site for targeted imaging strategies.

The von Hippel-Lindau (VHL) gene, a tumour suppressor gene, was identified in the past few decades as an important step in renal carcinogenesis. Gene mutation or deletion of the VHL gene is most commonly seen in clear cell RCC (ccRCC), resulting in the overexpression of hypoxia-inducible factor (HIF). This overexpression subsequently leads to increased pro-angiogenic growth factors including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and platelet-derived growth factor [22]. These growth factors induce cell proliferation and angiogenesis. PSMA expression in the neovasculature of benign and malignant tumours including RCC has been previously identified, with a number of published histopathologic literature consistently reporting high PSMA expression rates in ccRCC [20, 21, 23–28]. Chang et al. found PSMA expression in the neovascular endothelial cells of 20 metastatic ccRCC lesions involving a number of different metastatic sites (Table 1) [21]. Baccala et al. also reported similar findings with positive PSMA staining in tumour-associated neovascular cells in 76.2 % of ccRCC, 31.2 % of chromophobe RCC, 52.6 % of renal oncocytoma and 21.4 % of transitional RCC. Interestingly, papillary RCC and angiomyolipoma (AML) were PSMA negative and PSMA expression did not correlate with the pathologic stage of ccRCC [20]. This is in contrast to findings of Spatz et al. where higher grade and stage ccRCC were associated with increased PSMA expression in tumour vessels, and increased PSMA staining intensity was associated with poorer overall survival [23]. Furthermore, there is conflicting data regarding PSMA expression in primary RCC [18, 29] with the majority of the literature findings supporting PSMA expression only in tumour-associated neovasculature [14, 21, 30]. Due to avid physiological renal uptake of PSMA tracers, primary RCCs are poorly visualized [20, 31, 32]. Overall, the translation of these immunohistochemical findings to clinical imaging diagnostics is unclear; however, early small studies (Table 2) have been encouraging with improved metastatic lesion detection *via* PSMA PET/CT for ccRCC.

Role of PSMA in RCC Imaging and Clinical Implications

The role of PSMA PET/CT imaging has been well-established in the staging of primary, metastatic and biochemically recurrent prostate cancer [16, 17, 42–44]. There has been an increasing interest in the role of PSMA PET/CT imaging in non-prostate malignancies [45, 46]. This is somewhat limited with regard to RCC specifically, with few reviews in the literature to date [47]. Clinically, there has been growing interest in the utilization of PSMA PET/CT for improved detection of metastatic lesions from RCC, especially that of ccRCC. ccRCC is the most common RCC (80–90 %) and is a highly vascularized [44] tumour with PSMA expression detected in tumour-associated vasculature [20, 21, 23–28, 34, 38]. A number of PSMA-directed ligands have been used thus far for PET imaging of mRCC (Table 2).

In 2014, Demirci et al. published the first case report utilizing Ga-68 labelled Glu-NH-CO-NH-Lys-(Ahx) ([^{68}Ga]Ga-PSMA-HBED-CC) PET/CT in the diagnosis of metastatic ccRCC [33]. They found that [^{68}Ga]Ga-PSMA-HBED-CC PET/CT had better radiotracer uptake for

Table 1. Summary of literature renal cell carcinoma-associated neovascular immunohistochemical staining

Study	Type	Year (study period)	Location	Number of patients/ nephrectomies	Objectives	Number and biopsy sites	Immunohistochemical agent	Immunohistochemical staining agents and results
Chang et al. [21]	R	2001	USA	20 patients	Assess expression of PSMA on tumour-associated neovasculature of met CaP and met ccRCC	22 CaP met lesions (7 bone, 4 LN, 2 liver, 1 lung, 8 soft tissue) 20 ccRCC met lesions (5 bone, 5 LN, 1 liver, 3 lung, 2 soft tissue, 3 brain, 1 adrenal gland)	Anti-PSMA mAb PM2 J004.5 Anti-PSMA mAb 7E11 Anti-endothelial cell mAb CD34	For ccRCC met lesion: – Anti-PSMA mAb PM2 J004.5 positive 20/20 specimens; – Anti-PSMA mAb 7E11 positive 15/20; – Anti-endothelial cell mAb D34 20/20 Metastatic CaP only 2 of 22 had neovasculature PSMA expression
Baccala et al. [20]	R	2007 (2003)	USA	109 RN or PN	Expression of PSMA in different primary renal tumours	169 lesions: 60 normal kidneys 21 ccRCC 20 pRCC 16 chRCC 19 oncocytoma 14 TCC 19 AML	Anti-PSMA mAb PM2 J004.5 Anti-endothelial cell mAb CD34	PSMA was expressed in the proximal tubules of the normal kidney and in the tumour-associated vasculature in the renal tumours. Positive PSMA staining was detected in: 76.2 % (16/21) of ccRCC 31.2 % (5/16) of chRCC 52.6 % (10/19) of oncocytoma 21.4 % (3/14) of TCC 0 % of pRCC and AML
Spatz et al. [23]	R	2017 (1992–2004)	Germany	257 patients	Find rationale for PSMA based imaging and investigate the prognostic role of vascular PSMA expression in patients with RCC	257 nephrectomies. 2 cores of non-necrotic tumour and 2 cores of adjacent normal tissues were extracted	Anti-endothelial cell mAb CD34	Of 30 patients with metastasis the primary tumour vessels were positive for PSMA in 29 (96.7 %) with ccRCC, of whom 60 % showed immunohistochemically moderate to highly reactive results. All 14 patients with ccRCC and LN metastases (pN1) showed positive PSMA results
Al-Ahmadie et al. [28]	R	2008	USA	75 nephrectomies	To determine whether PSMA is differentially expressed in the vessels associated with distinct types of renal epithelial neoplasms and whether it could be used as a marker of subtype.	75 nephrectomies. The staining pattern was assessed in tumour cells, tumour-associated vessels and adjacent normal kidney.	Anti-PSMA mAb 13D6 Anti-endothelial mAb CD31	In all cases, immunoreactivity was detected only in the tumour-associated neovasculature and not in tumour cells. ccRCC showed the most diffuse staining pattern, where 24/30 cases (80 %) had >50 % reactive vessels ChRCC (9/15; 60 %) Oncocytoma (5/15, 33 %). No diffuse staining was detected in any of the

Table 1. (continued)

Study	Type	Year (study period)	Location	Number of patients/ nephrectomies	Objectives	Number and biopsy sites	Immunohistochemical agent	Immunohistochemical staining agents and results
								pRCC and only focal staining was detected in 11 cases (11/15; 73 %)

AML, angiomyolipoma; CaP, prostate cancer; ccRCC, clear cell renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; LN, lymph node; met, metastatic; mAb, monoclonal antibody; pRCC, papillary renal cell carcinoma; P, prospective study; PN, partial nephrectomy; PSMA, prostate-specific membrane antigen; pRCC, papillary renal cell carcinoma; R, retrospective study; RN, radical nephrectomy; TCC, transitional cell carcinoma

multiple bone metastasis compared to 2-deoxy-2[^{18}F]fluoro-*D*-glucose ([^{18}F]FDG) PET/CT resulting in improved visual detectability [33]. In 2015, Rowe et al. compared PSMA-targeted F-18-labelled–low-molecular-weight PSMA ligand 2-(3{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid) also known as [^{18}F] DCFPyL PET/CT to conventional imaging (CT or MRI) in five patients and demonstrated superior sensitivity (95 *versus* 79 %) [34]. Unfortunately, histopathology confirmation was not performed in this study; however, this was offset by a later study which revealed PSMA expression in the majority of PSMA PET/CT positive and conventional CT-negative lesions in a rapid autopsy series [24]. In 2016, Rowe et al. reported a comparison of [^{18}F] FDG PET/CT and [^{18}F] DCFPyL PET/CT in a single patient with mRCC. [^{18}F] DCFPyL PET/CT demonstrated improved sensitivity and better radiotracer uptake in detecting occult lesions [35]. Rhee at al. investigated ten patients (eight patients with proven ccRCC) and found [^{68}Ga]Ga-PSMA-HBED-CC PET/CT had greater sensitivity (92 *versus* 69 %) and higher positive predictive value (97 *versus* 80 %) compared to conventional CT for detection of metastatic disease [26]. In this study, histopathological correlation was based on 36 tumour sites identified on either PSMA PET/CT or conventional CT. This improved staging ultimately led to a change in management of two patients, with the detection of small hepatic metastasis in one patient and superior delineation of IVC tumour in another. Both were subsequently excised. Siva et al. explored [^{68}Ga]Ga-PSMA-HBED-CC PET/CT and [^{18}F] FDG PET/CT in six cases of ccRCC with concordance in five patients whilst the former was able to detect two more lesions that led to a change in patient management [38].

PSMA is therefore a potential marker for the identification of tumour neoangiogenesis in ccRCC, even in small metastatic lesions. PSMA PET/CT may aid in improved early diagnosis and staging leading to subsequent interventions. It also has the extra added benefit of being able to be performed in patients with renal impairment or contrast allergy without risk of adverse events. These potential advantages may be limited to ccRCC, however, as non-clear cell metastasis is inconsistently detected. In a comparison between [^{18}F] DCFPyL PET/CT and conventional imaging (CT and/or MRI) in non-ccRCC, Yin et al. reported that only 10 of 73 (13.7 %) suspected metastatic lesions had definitive radiotracer uptake with no additional lesions identified through the use of molecular imaging [41].

Limitations and Future Opportunities

Currently, there are limitations for the clinical use of PSMA PET/CT imaging in RCC highlighted by the lack of large, well-designed clinical trials in the literature. PSMA PET/CT imaging has minimal value in evaluation of primary renal tumours. PSMA is expressed physiologically in the proximal tubules of normal kidneys and exhibits no increased

Table 2. Summary of literature utilizing PSMA-PET CT imaging for detection of metastatic RCC (mRCC)

Study	Type	Year	Location	Objectives	Number of patients	Median age (Q1,Q3)	Histology	Radiotracer/ligand	Comparative conventional imaging	Metastatic RCC lesion detection
Demirci et al. [33]	CR	2014	Turkey	Compare [^{68}Ga]Ga-PSMA-HBED-CC PET/CT and [^{18}F] FDG PET/CT for detection of mRCC	1	65	ccRCC	[^{68}Ga]Ga-PSMA-HBED-CC	[^{18}F] FDG PET/CT	[^{68}Ga]Ga-PSMA-HBED-CC provided improved radiotracer uptake in metastatic bone lesions (seventh cervical vertebrae and acromion left scapula SUVmax = 35 for PSMA, FDG = 7.2; sternum SUVmax = 28.3 for PSMA, FDG = 5.15; Right ischial tuberosity SUVmax = 34.1 for PSMA, FDG = 5.3)
Rowe et al. [34]	P	2015	USA	Evaluate the utility of [^{18}F] DCFPyL PET/CT in imaging 5 patients with metastatic ccRCC	5	58 (54–61)	10 ccRCC	[^{18}F]DCFPyL	Contrast-enhanced CT or MRI	[^{18}F] DCFPyL PET/CT ➔ 28 lesions were identified, 17 of which corresponded to sites of disease on conventional imaging; identified lesions not detected on CT/MRI (small LNs in mediastinum and RP, paraspinal muscle, perineal SC soft tissue, bone lesions) ➔ sensitivity 94.7 % CT/MRI ➔ 18 lesions were identified, able to detect one lesion that [^{18}F] DCFPyL was unable (6 mm metastatic liver lesion) ➔ sensitivity 78.9 %
Rowe et al. [35]	CR	2016	USA	Compare [^{18}F] DCFPyl PET/CT and [^{18}F] FDG PET/CT for detection of metastatic lesions in ccRCC	1	58	ccRCC	[^{18}F]DCFPyl	[^{18}F] FDG PET/CT	[^{18}F] DCFPyL PET/CT has improved sensitivity and better radiotracer uptake compared to [^{18}F] FDG PET/CT • Additional subtle uptake in left posterior ninth rib and left iliac bone found in [^{18}F] DCFPyL PET/CT • Right iliac lesion (SUVmax = 16.6 for [^{18}F] DCFPyL, 3.3 for [^{18}F]FDG); left iliac lesion (SUVmax = 13.9 for [^{18}F] DCFPyL, 4.0 for [^{18}F]FDG)
Rhee et al. [25]	P	2016	Australia	Evaluate the diagnostic potential OF [^{68}Ga] Ga-PSMA-HBED-CC PET/CT in detecting met renal tumour lesions	10	57 (45–69)	8 ccRCC 1 pRCC 1 unclassified	[^{68}Ga]Ga-PSMA-HBED-CC	CT ± MRI/US/BS	Detection of mRCC lesions: • Conventional sensitivity 68.6 %; PPV 80 %; • PSMA PET/CT sensitivity 92.11 %; PPV 97.22 %
Einspieler et al. [36]	CR	2016	Germany	–	1	78	–	[^{68}Ga]Ga-PSMA-HBED-CC	–	PSMA expression in mediastinal, RP and iliac LN with subsequent Bx LN ➔ RCC metastatic lesion

Table 2. (continued)

Study	Type	Year	Location	Objectives	Number of patients	Median age (Q1,Q3)	Histology	Radiotracer/ ligand	Comparative conventional imaging	Metastatic RCC lesion detection
Sawicki et al. [27]	R	2016	Germany	Evaluate the diagnostic potential of whole-body PET/CT using 68Ga-labelled PSMA ligand in histology proven RCC	6	72.3 (65–80)	Histology proven primary or metastatic/ recurrent RCC: 4 ccRCC 1 pRCC1 chRCC	[68Ga]Ga-PSMA-HBED-CC	–	22 lesions detected: • 21 malignant lesions – 5 primary RCCs in 5 patients however no significant differentiating uptake between normal parenchyma and tumour – 8/16 metastatic lesions in 2 ccRCC patients showed focal 68Ga-PSMA uptake • 1 benign lesion ➔ ectopic salivary tissue in left masseter
Sasikumar et al. [37]	CR	2016	India	–	1	80	ccRCC	[68Ga]Ga-PSMA-HBED-CC	[18F] FDG PET/CT	Intensely PSMA tracer concentrating lesions in left suprarenal region, mediastinal LN, lytic bone lesions, thyroid nodules, and mild abnormal tracer-avid lung nodules; FDG showed mild to no significant abnormal uptake in these lesions.
Siva et al. [38]	R	2017	Australia	To assess the utility of PSMA-PET/CT for diagnostic evaluation of isolated or limited metastases planned for local surgery or radiation + therapeutic response assessment post SABR	8	65 (50–78)	7 ccRCC 1 pRCC	[68Ga]Ga-PSMA-HBED-CC	[18F] FDG PET/CT	• 4 patients with ccRCC met lesions (lung, adrenal) ➔ intense PSMA avidity *versus* low-mod FDG avidity • 1 patient post ccRCC resection with adrenal met ➔ no uptake FDG or PSMA although histology positive • 1 patient with ccRCC GT met lesion ➔ avid FDG and PSMA uptake however greater FDG intensity • 1 patient bed recurrence pRCC ➔ FDG-avid, not avid on PSMA
Zacho et al. [39]	CR	2017	Denmark	–	1	75	–	[68Ga]Ga-PSMA-HBED-CC	–	3 PET avid lesions (RP LN and thyroid gland histology RCC; pelvic LN histology CaP)
Joshi et al. [40]	CR	2017	Australia	–	1	67	–	[68Ga]Ga-PSMA-HBED-CC	–	Detected 4 separate lesions in prostate, left thyroid, right kidney, left posterior iliac crest. Histology confirmed CaP (4 + 4), papillary carcinoma of thyroid, ccRCC and benign bone Bx
Yin et al. [41]	P	2018	USA	To investigate the utility of PSMA-targeted [18F] DCFPyl PET/CT for detection of metastatic lesion of non-	8	61 (54–66)	Histology proven non-clear cell RCC: 3 pRCC 2chRCC 2 unclassified 1 Xp11 translocation	[18F] DCFPyl	CT or MRI	73 metastatic lesions and 3 primary renal lesions were identified on conventional imaging. No lesions were identified on [18F] DCFPyl PET/CT without

Table 2. (continued)

Study	Type	Year	Location	Objectives	Number of patients	Median age (Q1,Q3)	Histology	Radiotracer/ligand	Comparative conventional imaging	Metastatic RCC lesion detection
				clear cell RCC						corresponding finding on conventional imaging. • Only 10 of 73 (13.7 %) suspected metastatic lesions were classified as having definitive radiotracer uptake • 14 (19.2 %) equivocal • 49 (67.1 %) no significant uptake

AML, angiomyolipoma; BS, bone scan; Bx, biopsy; CaP, prostate cancer; ccRCC, clear cell renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; CR, case report; CT, computed tomography; 18F-DCFPyl, 18F-labelled low-molecular weight PSMA ligand 2-(3{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid); 68Ga, gallium-68; GT, greater trochanter; LN, lymph node; mAb, monoclonal antibody; met, metastatic; mRCC, metastatic renal cell carcinoma; MRI, magnetic resonance imaging; pRCC, papillary renal cell carcinoma; P, prospective study; PET, positron emission tomography; PN, partial nephrectomy; PPV, positive predictive value; PSMA, Prostate-specific membrane antigen; pRCC, papillary renal cell carcinoma; RP, retro-peritoneal; R, retrospective study; RN, radical nephrectomy; SABR, stereotactic ablative body radiotherapy; SC, subcutaneous; SUVmax, maximum standardized uptake value; TCC, transitional cell carcinoma; US, ultrasound, USA, United States of America

expression in the primary tumour, compared to the normal surrounding renal parenchyma [20, 31, 32]. Other factors affecting specificity include wide PSMA expression across a number of normal organs (liver, spleen, salivary glands) [14, 18, 19], and expression in other solid organ tumours (*e.g.* bladder, colorectal, lung) [14, 48–50]. Other benign specific (sarcoidosis, tuberculosis) [51, 52] and non-specific conditions (regeneration, repair) [19, 53] can also lead to false positive imaging findings. Additionally, there is an inability to distinguish between benign and malignant renal tumour-associated neovasculature or RCC subtypes; however, PSMA ligand binding is more likely in ccRCC compared to pRCC or AML [20]. There is also conflicting evidence on the prognostic role of PSMA expression in the neovasculature of ccRCC [20, 23].

The small studies thus far, however, suggest that PSMA PET/CT imaging appears to facilitate improved detection of mRCC lesions especially in ccRCC. Studies have reported multiple biopsy proven metastatic ccRCC lesions, missed by conventional CT imaging indicating a potential role for more accurate staging of advanced and high-risk ccRCC [26]. This improved sensitivity in detection of metastatic ccRCC may significantly impact patient outcomes, especially with early detection of potentially curable oligometastatic disease [26].

PSMA PET/CT imaging could also be potentially utilized as a way of monitoring, assessing and/or predicting response to systemic neovasculature agents targeting angiogenesis in ccRCC. It may provide functional imaging feedback as a measure of the *in vivo* density of the neovascularity of metastatic lesions. Currently, no PSMA-targeted therapy exists although anti-angiogenesis agents VEGF and platelet-derived growth factor receptor (sunitinib, pazopanib) and isolated VEGF inhibitors (bevacizumab) have had varying degrees of success when used in clinical trials in advanced stage ccRCC [8, 54–56]. The potential therapeutic success and good tolerability of PSMA-targeted therapies in prostate cancer (with radionucleotides such as 177Lu-labelled PSMA) suggests promising potential further development. Further larger prospective trials are required in both diagnostic and treatment-related PSMA utilization [57, 58].

Currently, there are two clinical trials currently underway in the US investigating the role of PSMA imaging in RCC. The aim of one study is to evaluate and compare the diagnostic accuracy of PSMA-targeted [^{18}F] DCFPyL PET/CT with conventional imaging in 30 patients with various stages of mRCC [59]. The second trial is evaluating the feasibility and uptake of ^{68}Ga P16-093 PSMA PET/CT in 30 patients with known or suspected metastatic RCC or prostate cancer [60].

Conclusion

PSMA expression in the tumour neovasculature of RCC has been established especially for ccRCC. Although there is a sound scientific basis for the use of PSMA-PET/CT in detecting ccRCC metastatic foci, its translation into clinical practice is currently not routinely recommended. Early small studies involving PSMA PET/CT imaging have been encouraging with evidence of improved sensitivity compared to conventional imaging modalities. Further investigation is needed to confirm utility through larger studies in this clinical setting.

Funding Information. This research received no specific grant from any funding agency in public, commercial, or not-for-profit sectors. IV is supported by a Movember Clinician Scientist Award awarded through Prostate Cancer Foundation of Australia's Research Program.

Compliance with Ethical Standards

Conflict of Interest

All authors declare that there is no conflict of interest.

Human and Animal Rights

This article does not contain any studies with human participants or animals performed by any of the authors.

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