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ORIGINAL ARTICLE

The use of ^{68}Ga-PET/CT PSMA in the staging of primary and suspected recurrent renal cell carcinoma

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Abstract

Purpose The role of ^{68}Ga-PSMA PET/CT in the staging of prostate cancer is well known. PSMA is also overexpressed in the neovasculature of other tumours including renal cell carcinoma (RCC), suggesting there may be a role for the use of ^{68}Ga-PSMA PET/CT. Thus far, there has been limited literature documenting the use of ^{68}Ga-PSMA PET/CT in the investigation and management decisions of RCC.

Methods This was a retrospective case series of patients who received a ^{68}Ga-PSMA PET/CT scan for staging or restaging of RCC between July 2016 and December 2018. Primary outcome measure was to identify whether ^{68}Ga-PSMA PET/CT changed management compared to standard diagnostic CT imaging. Analysis was based on four categories: (1) identification of new disease, (2) refuting disease on CT imaging, (3) identification of synchronous primaries, and (4) concordance with CT imaging.

Results 38 ^{68}Ga-PSMA PET/CT scans met inclusion criteria. Primary staging scans were performed in 16 patients, of which 75% showed avid primary lesions, with the majority of clear cell subtype. Management was changed in 43.8% of patients. CT agreed with ^{68}Ga-PSMA PET/CT in 37.5% of cases. Restaging scans were performed in 22 patients. 40.9% of patients had management changed by results of ^{68}Ga- PSMA PET/CT. CT agreed with ^{68}Ga- PSMA PET/CT in 36.4% of cases. Management was predominantly changed due to the identification of new sites of suspected metastases, as well as the detection of synchronous primaries.

Conclusions ^{68}Ga-PSMA PET/CT directly changed management in 42.1% of cases. Strongest detection rates occurred in those patients with clear cell RCC. The results of this study suggest there may be merit in the use of the modality in the staging of RCC. Further analysis, both with respect to histological confirmation, efficacy and cost-benefit, is required to determine whether there is a role for routine ^{68}Ga-PSMA PET/CT imaging.

Keywords ^{68}Ga-PSMA PET/CT · Renal cell carcinoma cancer · Staging · Restaging

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Introduction

The locoregional and metastatic staging of primary and recurrent renal cell carcinoma (RCC) has traditionally been performed with Computed Tomography (CT) of the abdomen and chest [1]. Radionuclide bone scans are reserved for patients with symptomatic bone pain, while Magnetic Resonance Imaging (MRI) or duplex Ultrasound Scan (USS) is indicated for those patients with suspected Inferior Vena Cava (IVC) involvement [2]. Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) has occasionally been used, however its utility in local staging is limited by the excretion of FDG through the kidneys, resulting in high background renal activity on PET imaging and difficulties in imaging interpretation [1].

In recent times, with the growing role of prostate-specific membrane antigen (PSMA) PET in the management of prostate cancer, there has been interest in exploring its utilisation in other cancers, with RCC purported to be a potential target for the modality. This interest has increased following studies by Campbell et al. [3] and Baccala et al. [4], who found overexpression of PSMA in the neovasculature of RCC, opening the door for the protein to be used as a possible target for imaging. Despite these findings, the uptake of PSMA PET/CT in the management of RCC has been slow, with a paucity of research investigating the appropriate role of the modality. In a recent systematic review performed by Evangelista et al., only 13 studies were found analysing the role of PSMA PET/CT in the staging of RCC [5]. There appear to be two main PSMA radioligands identified in the literature as possible targets for further investigation: 18-Fluorine-DCFPyL (^{18}F-DCFPyL-PSMA) and 68-Gallium (^{68}Ga-PSMA). Of the 13 studies identified by Evangelista, eight related to ^{68}Ga-PSMA and included a total of 29 patients, with most of the studies found to be single case reports of low evidence quality [3]. With such limited data, the present study represents the largest dataset in the literature of patients receiving ^{68}Ga- PSMA PET/CT scans for staging of primary or recurrent RCC. The aim was to retrospectively examine the effectiveness of ^{68}Ga- PSMA PET/CT in identifying disease missed by conventional imaging and subsequently changing management.

Methods

Patients

Ethics approval was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee ref.: HREC/18/QRBW/395. The need for individual patient consent was waived as per the Ethics Committee. This was a retrospective single tertiary institution case series between July 2016 and December 2018. To meet inclusion criteria, patients must have received a ^{68}Ga-PSMA PET/CT scan for either primary staging of RCC or restaging of suspected recurrent disease. Patients who did not receive a separate diagnostic CT scan prior to ^{68}Ga-PSMA PET/CT scan were excluded from the study. Outpatient and inpatient notes, discharge summaries and pathology reports of all patients receiving ^{68}Ga-PSMA PET/CT scans were examined. The primary objective was to determine whether ^{68}Ga-PSMA PET/CT scanning changed management of patients.

Statistical analysis

To help determine whether or not ^{68}Ga-PSMA PET/CT resulted in change of management compared to conventional imaging, scan results were divided into 4 categories:

1. Did ^{68}Ga-PSMA PET/CT identify new disease not apparent on conventional imaging?
2. Did ^{68}Ga-PSMA PET/CT refute disease found on conventional imaging?
3. Did ^{68}Ga-PSMA PET/CT identify synchronous primary malignancies not apparent on conventional imaging?
4. Did ^{68}Ga-PSMA PET/CT agree with conventional imaging?

Data was presented as percentages of the total respective subcohorts. Histological confirmation of suspected disease was reported for all categories.

Imaging protocol

The ^{68}Ga-PSMA PET/CT scans were performed on a Siemens Biograph mCT PET/CT scanner. The minimum uptake time was 45–60 min following administration of an average injected dose of 150 MBq ± 5% of 200 MBq ^{68}Ga-PSMA-11. Emission tomographic images were obtained from the skull vertex to upper thighs. A low-dose CT scan was performed during tidal respiration for attenuation correction and lesion localisation.

Image analysis

Each ^{68}Ga-PSMA PET/CT scan was double-read by two experienced nuclear medicine specialists and the diagnostic CT scans were read by an experienced diagnostic radiologist, as per routine protocol at our institution. The ^{68}Ga-PSMA PET/CT and diagnostic CT scans were reported separately, before results were combined. Scans requiring further clarification were discussed at the Royal Brisbane and Women's Hospital Multidisciplinary Urology Meeting. For diagnosis of a metastasis, concordant moderate or intense PSMA uptake in a CT-visualised anatomical lesion was required. This included PSMA uptake in an enlarged lymph node, lytic bone lesion

or solid organ as identified with CT. Local recurrence was defined as a moderate or intense PSMA avid lesion within the kidney or within the renal bed with an SUVmax ≥2 [6].

Results

38 ^{68}Ga-PSMA PET/CT scans met criteria for inclusion in analysis which were performed in 35 different patients. The median age was 64 years (range 38–86 years). A total of 29 scans were performed in females, while nine scans were performed in males. There were 51 instances of avid disease in the 38 scans. Avid disease was primarily located in visceral organs, and soft tissue (68.6%, 35/51). Locations included the primary renal lesions, adrenal glands, brain, lungs and prostate. Suspected local recurrence was detected in 7.8% of instances (4/51). Avid lymph nodes and suspected bony disease occurred in 11.8% (6/51) each.

Primary staging

Sixteen scans were included for analysis (Table 1). Six patients in the primary staging cohort did not have histology available at time of submission. Two patients died of unrelated pathology prior to investigation of their lesions. The other four patients have primary lesions which are under surveillance (2 patients) or are awaiting surgery (2 patients) at time of submission. Diagnosis of suspected RCC in those patients without histological confirmation was made based on CT criteria for renal masses, with enhancement, heterogeneity of contents and size criteria applied [7].

Renal lesions were PSMA avid in 12 scans (75%, Fig. 1). Of the 12 patients with avid primary disease, nephrectomy or biopsy of the lesion diagnosed clear cell RCC in seven patients (87.5%) and oncocytoma in one patient (12.5%). Of the four scans where lesions identified on diagnostic CT were not visualised on PET/CT, one patient had papillary RCC while another had clear cell RCC. As mentioned, histology was not available for the remaining two patients with the patients dying of unrelated disease prior to further investigation.

Of the 16 patients who received ^{68}Ga-PSMA PET/CT scans for primary staging, management was changed in seven patients (43.8%) as a direct result of the imaging findings (Table 2). ^{68}Ga-PSMA PET/CT identified new disease in two cases (12.5%), refuted diseases in six cases (37.5%) and identified new synchronous primaries in three cases (18.8%), though management was not changed in all cases. ^{68}Ga-PSMA PET/CT agreed with CT imaging in six scans (37.5%), with management unchanged.

^{68}Ga-PSMA PET/CT identified new metastatic disease not present on standard CT in two patients with management changed in both of these patients. Histopathology of metastases was available for one patient, who had a cerebral metastatic deposit which was excised and confirmed metastatic ccRCC. Importantly, traditional staging of RCC currently does not extend to include the brain, as was the case in this patient. Extensive local disease was identified in the other patient, with ^{68}Ga-PSMA PET/CT suspicious for nodal spread of disease not seen on diagnostic CT. Prior to the ^{68}Ga-PSMA PET/CT, curative surgery to excise the local recurrence was being considered for this patient. Nodes were not biopsied to confirm diagnosis. However, together with the suspicion of nodal disease, the extensive locally advanced nature of disease confirmed on ^{68}Ga-PSMA PET/CT and the patient's poor functional status, management was reconsidered and palliative chemotherapy was offered.

^{68}Ga-PSMA PET/CT refuted CT scan findings in six separate cases, with management changed in three of these cases (Fig. 2). Histology of suspicious lesions on CT was available in three of the six patients. However, of the three patients where management was changed, histology was not available for the CT suspicious nodes which were non-avid on PSMA

Table 1 Primary staging demographics

Demographic	Value
Total scans	16
Median age	70 (38–86)
PSMA-avid primary lesions	12 (75%)
	- 7 × ccRCC
	- 1 × oncocytoma
	- 4 × unknown (lesions under surveillance or awaiting treatment at time of publication)
PSMA non-avid primary lesions	4 (25%)
	- 1 × ccRCC
	- 1 × papillary RCC
	- 2 × unknown (patients died of unrelated pathology prior to management)

PSMA prostate-specific membrane antigen, *RCC* renal cell carcinoma

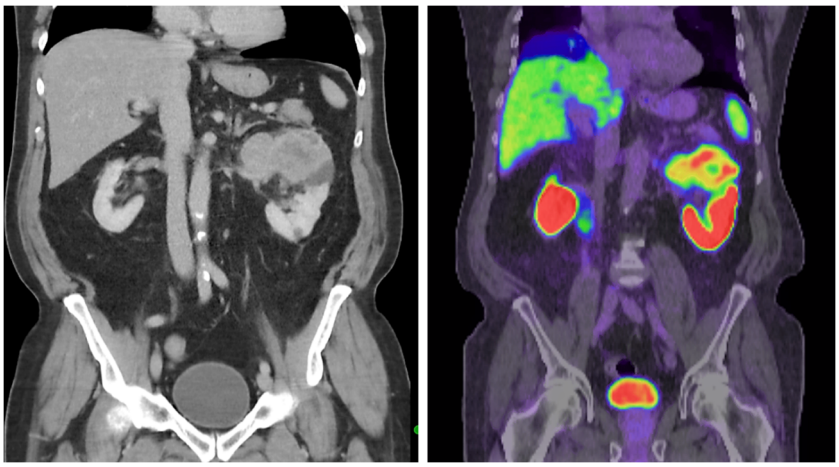

Fig. 1 Prostate-specific membrane antigen (PSMA) PET avid left upper pole renal lesion; Patient P16

PET/CT. Clinical follow-up of these patients with restaging imaging has shown these nodes to be stable. In all three cases, ^{68}Ga-PSMA PET/CT refuted nodal disease identified on CT imaging and thus downgraded disease, allowing the respective patients to proceed through to surgical management of the primary renal lesions. Two of these patients were found to have clear cell RCC, while the third patient is awaiting surgery. Nodal disease was discordant between CT and ^{68}Ga-PSMA PET/CT in a separate case, however an adrenal metastasis on CT was confirmed as avid on ^{68}Ga-PSMA PET/CT and thus the original plan for cytoreductive nephrectomy and subsequent commencement of systemic therapy was not changed. The primary renal lesion was not visualised on ^{68}Ga-PSMA PET/CT in a separate patient, with biopsy confirming papillary RCC. Investigations were unable to be completed on the final patient who died prior to management of their primary renal lesion; however, lung nodules on CT which were non-avid on ^{68}Ga-PSMA PET/CT were shown to be interstitial pneumonitis on biopsy.

Synchronous primaries were detected in three patients as a result of ^{68}Ga-PSMA PET/CT (Fig. 3). Biopsy-proven prostate primaries were identified in two patients. Biopsy-proven lung adenocarcinoma was identified in the third patient. Management was changed in all three cases as a result of detection of synchronous primaries.

In six cases, ^{68}Ga-PSMA PET/CT agreed with disease identified on conventional imaging. In four patients, both CT and ^{68}Ga-PSMA PET/CT confirmed no metastases. In the remaining two patients, CT and ^{68}Ga-PSMA PET/CT identified discrete neck lesions. Biopsy confirmed metastatic melanoma in one patient, and diffuse large B cell lymphoma in the other.

Table 2 Primary staging and change in management

Parameter	Identify new disease	Refute disease	Synchronous primaries	Agree with CT
Number of cases	2 (12.5%)	6 (37.5%)	3 (18.8%)	6 (37.5%)
Histological confirmation of disease	1	3	3	2
Change in management	2 (histology available 1/2) *Patient P6:* Identification of cerebral met. Proceeded through to excision of met. *Patient P9:* Identification of nodal metastatic disease meant patient was not a candidate for surgery and received palliative chemotherapy.	3 (histology available 0/3) *Patient P12*[a]*:* No PSMA-uptake in enlarged porta hepatis nodes which met CT size criteria. Proceeded to partial nephrectomy. *Patient P13:* No PSMA-uptake in enlarged para-aortic nodes which met CT size criteria. Proceeded to radical nephrectomy. *Patient P16:* No PSMA-uptake in sclerotic skeletal lesion. Awaiting partial nephrectomy.	3 (histology available 3/3) *Patient P2:* Synchronous prostate primary, biopsy-proven adenocarcinoma. Proceeded to radical prostatectomy. *Patient P3:* Synchronous lung primary, biopsy-proven adenocarcinoma. Proceeded to chemo-radiation. *Patient P12*[a]*:* Synchronous primary prostate. Prostate lesion under surveillance.	0

Management changed in 7/16 patients (43.8%)

PSMA prostate-specific membrane antigen

[a] P12 belonged to two groups

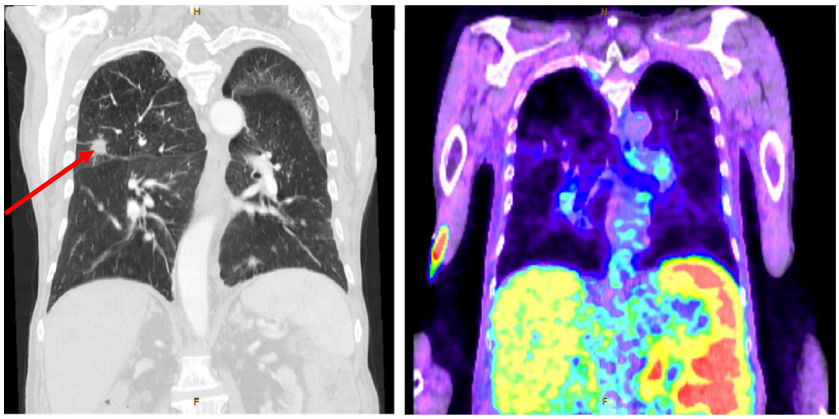

Fig. 2 PSMA PET refutes suspected lung metastasis on CT with biopsy showing interstitial pneumonitis; Patient P1

Restaging

Twenty-two scans met inclusion criteria (Table 3). Management was changed in nine patients (40.9%) as a direct result of ^{68}Ga-PSMA PET/CT (Table 4). ^{68}Ga-PSMA PET/CT identified new disease in nine cases (40.9%), refuted diseases in seven cases (31.8%) and identified new synchronous primaries in four cases (18.2%), though management was not changed in all cases. In 8/22 (36.4%) scans, ^{68}Ga-PSMA PET/CT agreed with CT and management was unchanged. Scans were performed to restage patients with known clear cell RCC in 20/22 (90.9%), with the other two patients having chromophobe RCC and transitional cell carcinoma respectively.

^{68}Ga-PSMA PET/CT identified suspected recurrence not identified on diagnostic CT scan in nine separate instances (Fig. 4). Management was changed in four cases as a result of the identification of new sites of suspected recurrence. Though additional sites of suspected recurrence were identified in the remaining five cases, the original decision to commence systemic therapy based on the results of the CT was not changed. Histological confirmation of recurrence was available in four patients, with treatment changed in two of these cases. In the remaining five patients without histological confirmation of disease, management was changed in two patients. The decision to change management in these patients was supported with both patients showing clinical and radiological improvement following the commencement of treatment for suspected RCC recurrence. In addition to distant sites of metastases, ^{68}Ga-PSMA PET/CT also identified local recurrence in two scans which were not appreciable on CT. In one of these cases, the extensive nature of the local disease precluded surgery and systemic therapy was commenced.

In seven instances, ^{68}Ga-PSMA PET/CT refuted disease suspected on conventional imaging. In all seven cases, suspicious lesions on CT imaging were found to be non-avid on ^{68}Ga-PSMA PET/CT. Biopsies were not performed on any of the non-avid lesions to confirm benign histology. ^{68}Ga-PSMA PET/CT refuted nodal disease in the majority of cases, with liver lesions found to be non-avid in two other cases and the absence of suspected local recurrence in a further case. Management was changed in five of seven cases. In the first instance where management was not changed, a patient with a

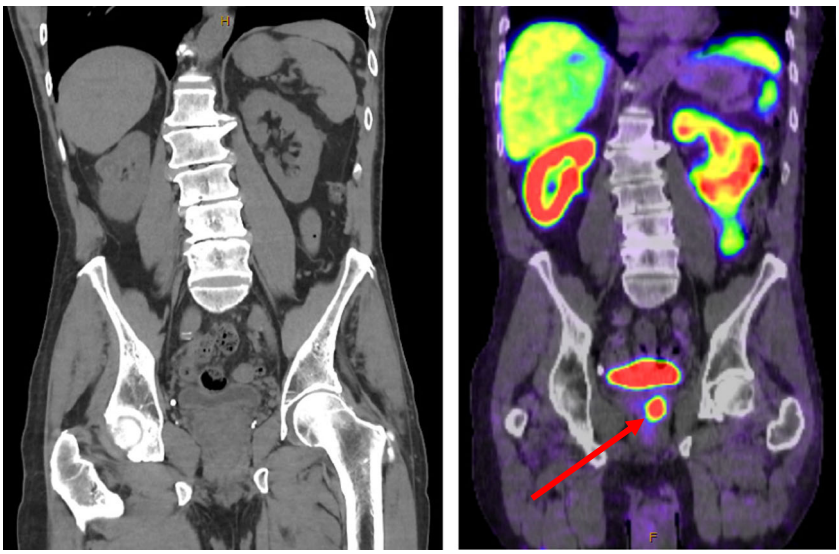

Fig. 3 PSMA PET/CT identifies a synchronous prostatic adenocarcinoma confirmed on biopsy; Patient P2

Table 3 Restaging demographics

Demographic	Value
Total scans	22
Median age	62 (range, 47–77)
Histology of original primary renal lesion	Clear cell RCC – 20
	Chromophobe RCC – 1
	Transitional cell carcinoma (TCC) – 1

RCC renal cell carcinoma

non-avid lung nodule was commenced on treatment in spite of the ^{68}Ga-PSMA PET/CT refuting conventional imaging. The nodule was found to resolve on interval imaging. In the second instance, despite ^{68}Ga-PSMA PET/CT refuting suspected metastatic disease on conventional imaging, it confirmed other sites of disease and thus the initial decision to commence systemic therapy was not modified.

Synchronous primary malignancies were identified in four patients, with incidental PSMA uptake in the prostate gland in all four patients. Two of the patients received biopsies of the prostatic lesions confirming adenocarcinoma, with the other two lesions under surveillance. The original treatment plan for these patients was changed, with all four prostatic lesions now part of management. In two of these cases, identification of a prostate primary malignancy was complicated by the presence of PSMA uptake in other sites concerning metastatic spread. The treatment question in this situation became whether the newly diagnosed sites were (1) new primaries, (2) metastatic disease of RCC origin or (3) prostatic metastases. In one situation, PSMA-avid adrenal glands were proven to be RCC on

Table 4 Restaging - change in management

Parameter	Identify new disease	Refute disease	Synchronous primaries	Agree with CT
Number of cases	9 (40.9%)	7 (31.8%)	4 (18.2%)	8 (36.4%)
Histological confirmation of disease	4	0	2	2
Change in Management	5 (histology available 2/5) *Patient R2:* Identification of extensive metastatic disease meant patient was not an operative candidate. Commenced on tyrosine kinase inhibitors (TKI), received radiotherapy to cerebral met. *Patient R3:* Extensive local recurrence not amenable to surgery. Commenced on TKI. *Patient R11*[a]*:* Multiple sites of metastatic disease not identified on CT. Diagnostic dilemma as PSMA PET/CT also identified synchronous primary. Commenced on TKI and androgen deprivation therapy (ADT) for treatment of both RCC and prostate cancer. *Patient R12:* Identification of new primary renal lesion in remaining kidney, biopsy-proven high-grade TCC not detected on CT. Proceeded to palliative radiotherapy. *Patient R19:* Identification of multiple soft-tissue and skeletal biopsy-proven metastases not detected on CT. Proceeded to palliative radiotherapy.	2 (histology available 0/2) *Patient R10:* Prominent retroperitoneal nodes on CT found to be non-avid. Treatment was avoided and patient is under surveillance. *Patient R15*[a]*:* soft tissue mass in renal bed shown to be not PSMA-avid. Patient avoided local therapy of renal bed, remains on TKI for known metastatic disease to adrenal gland.	4 (histology available 2/4) *Patient R4:* Synchronous prostate primary, biopsy-proven prostate adenocarcinoma. Under surveillance. *Patient R11*[a]*:* Synchronous prostate primary, biopsy-proven prostate adenocarcinoma. Under surveillance. *Patient R15*[a]*:* Prostate avidity, suspected prostate primary. Low PSA, under surveillance. *Patient R22:* Prostate avidity, suspected prostate primary. Low PSA, under surveillance.	0

Management changed in 9/22 patients (40.9%)

PSMA prostate-specific membrane antigen

[a] P11 and P15 belonged to more than one group

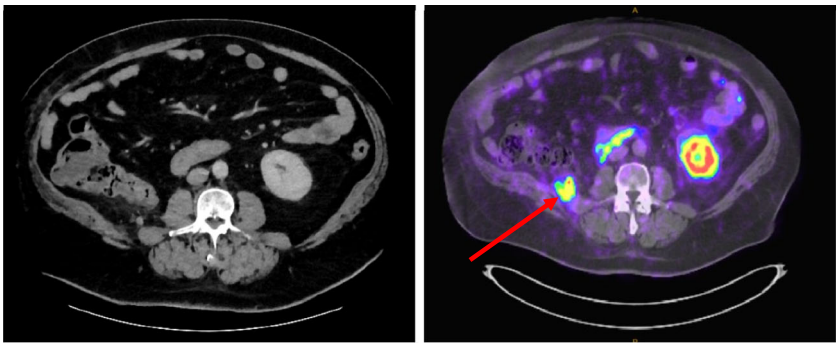

Fig. 4 PSMA PET identifies local recurrence not easily detectable on CT; Patient R3

biopsy and systemic therapy was commenced. In the other case, the patient received palliative systemic treatment for both outcomes, with tyrosine kinase inhibitors administered to manage potential RCC metastatic disease, and androgen-deprivation therapy (ADT) commenced for prostatic disease.

In eight cases, ^{68}Ga-PSMA PET/CT agreed with findings on CT. In six cases, surveillance imaging showed no new recurrence and management was continued. In the remaining two cases, lesions identified on CT and ^{68}Ga-PSMA PET/CT were biopsied and shown to be metastatic deposits.

Discussion

The literature is relatively sparse with only a handful of published case reports and case series investigating a role for ^{68}Ga-PSMA PET/CT in RCC staging [5, 8–11]. Our aim was to determine the effectiveness of ^{68}Ga-PSMA PET/CT in guiding management decisions compared to conventional imaging, with our primary goal to identify and examine cases where management was directly changed. A total of 43.8% of primary staging PSMA PET/CT scans and 40.9% of restaging PSMA PET/CT scans resulted in a change in management. Considering the absence of prospective studies and the fact that this small retrospective study of 38 patients is the largest dataset in the literature, the quality of evidence exploring the role of ^{68}Ga-PSMA PET/CT in RCC staging is very limited and broad conclusions regarding utility cannot be drawn. However, what is clear from these results is that further research regarding the utility of ^{68}Ga-PSMA PET/CT in the investigation of RCC is warranted.

FDG PET has previously been used in the evaluation of recurrent and metastatic RCC with variable utility due to biological characteristics of the tumour [12]. As shown by Evangelista et al., there exist only a few papers in the literature comparing FDG PET with ^{68}Ga-PSMA PET/CT and other new radioligands. With the evidence largely comprising case reports, it is not possible to make over-arching claims regarding the usefulness of ^{68}Ga-PSMA PET/CT over FDG PET. However, Demerci et al. and Sasikumar et al. both provided examples of cases where ^{68}Ga-PSMA PET/CT outperformed FDG PET in the detection of metastatic disease, with FDG PET appearing to miss soft tissue lesions [8, 11]. The largest series comparing the two modalities was performed by Siva et al., who described eight patients who showed ^{68}Ga-PSMA PET/CT was better able to detect all sites of metastatic disease compared to FDG PET [13]. In all studies, histopathological confirmation of metastatic disease was unpredictable, as with our series. What appears clear though is that the histopathology of the primary renal lesion is critical in determining the effectiveness of the imaging modality.

FDG, a glucose analogue, is taken up and retained by tissues with high metabolic activity including brain, kidney and lungs cells, as well as most types of malignant tumours [7]. It is known that FDG avidity is variable in RCC. Takahashi et al. showed high-grade RCC having higher metabolism than low-grade lesions, and thus being more FDG-avid [14]. Lower grade, well-differentiated, non-metabolically active RCC can have relatively low FDG avidity similar to background renal parenchyma and can therefore be missed if careful attention is not paid [7]. When combined with physiologic renal excretion of FDG, assessment of primary disease can be difficult [5, 12, 15]. With ^{68}Ga-PSMA similarly excreted through the kidneys [5, 15], challenges exist for this modality as well. Peripheral lesions away from renal excretion are usually much easier to visualise, with lesions near the renal sinus remaining a diagnostic challenge. While both FDG and ^{68}Ga-PSMA are renally excreted, making primary staging of RCCs in the kidneys more difficult, the higher uptake of ^{68}Ga-PSMA in clear cell renal carcinomas [12] makes them more readily visualised within the kidneys, and may enable more accurate local staging.

Typically, management decisions were changed in our study based on the identification of new metastatic disease on ^{68}Ga-PSMA PET/CT, with aggressive local treatment giving way for the commencement of systemic therapy. PSMA PET/CT was particularly useful in the identification of locally recurrent disease initially missed on diagnostic CT imaging, with PSMA-avid disease more readily identifiable. Lesions on conventional imaging suspicious for metastatic disease were occasionally refuted on ^{68}Ga-PSMA PET/CT, allowing for the patient to proceed to definitive local therapy. The detection of

synchronous primaries was predominantly characterised by the incidental identification of prostatic lesions, with the majority proven malignant on prostate biopsy.

The results of this study support those of Rhee et al. [16] who investigated the role of ^{68}Ga-PSMA PET/CT in primary staging of RCC. In their cohort of ten men, histological correlation was performed on lesions identified by diagnostic CT and PSMA PET/CT. PSMA PET was found to have 92.1% sensitivity and 97.2% PPV with no false-negative lesions, while CT showed sensitivity and PPV of 68.6% and 80.0%, respectively, with 11 false-negative lesions. Similar to our results, management was changed in two of ten patients. Primary lesions were PSMA PET-avid in all patients. ccRCC was confirmed in eight of ten patients, with one patient having unclassified disease and the final patient having papillary RCC. The single patient with primary papillary RCC was found to have non-avid disease. Of the patients with avid-primary disease and available histology, all seven patients were found to have ccRCC in our cohort. Our findings are consistent with the literature, with PSMA shown to be expressed in 80–100% of ccRCC, while other subtypes of RCC including chromophobe and papillary have significantly lower expression (30–60% and 0%, respectively) [4, 17–19].

Sawicki and colleagues' [20] study of ^{68}Ga-PSMA PET/CT staging in six patients with primary renal cell carcinoma also found promising results. Metastatic disease was identified in two patients with ccRCC with a mean SUVmax of 9.9. Multiple sub-centimetre pulmonary metastases were not identified on ^{68}Ga-PSMA PET/CT, with diagnostic CT surveillance required to identify these lesions at 4 weeks post initial scan. PSMA PET scans have well-documented difficulty in identifying small lesions, with normal respiration reducing detection of lung lesions [20]. Hybrid imaging with CT imaging appears to have compensated for this in Sawicki's study, with pulmonary lesions detected on CT and appropriately monitored. Primary tumours were shown to have varying avidity, with ccRCC the most clearly identifiable tumour type, which agrees with our results. None of the primary renal tumours were found to have higher PSMA uptake relative to adjacent physiologic radiourine activity [4]. As such, Sawicki et al. concluded ^{68}Ga-PSMA PET/CT has limited role in the local staging of disease, with diagnostic CT remaining gold standard for this purpose. We would tend to agree with this assessment for the primary staging of disease, with ^{68}Ga-PSMA PET/CT proving most useful in the identification and clarification of suspected metastatic disease.

There are always limitations to a retrospective study. The major flaw, as with other similar studies, is the lack of consistent histological correlation. Primary histology was not available for six of 16 patients, with suspected sites of metastatic disease biopsied inconsistently. A good example is the identification of two hepatic lesions on CT which were non-avid on PSMA PET/CT. Both hepatic lesions were not biopsied, and we are not able to definitively rule out metastasis. Fortunately, in both situations, other information was available to make clinical decisions regarding the commencement of systemic therapy. Ideally, regions of ^{68}Ga-PSMA PET/CT positivity would undergo targeted biopsy to determine the accuracy of the imaging modality in detecting metastatic disease and local recurrence. Histological correlation of ^{68}Ga-PSMA PET/CT-avid disease has been performed previously, but predominantly in the setting of prostate cancer. Further prospective data with histological correlation is required to determine the accuracy of ^{68}Ga-PSMA PET/CT in detecting recurrent and metastatic disease. Additionally, larger cohorts are required to clarify the differences in primary detection of the various RCC subtypes. Our study, together with Rhee et al. and Sawicki et al. suggest ^{68}Ga-PSMA PET/CT has a role in the investigation of the clear cell subtype, with imaging in other subtypes proving less effective.

Conclusion

With the paucity of research examining the utility of ^{68}Ga-PSMA PET/CT in the management of RCC, this retrospective series of 38 patients represents the largest dataset in the literature for the staging and restaging of disease. ^{68}Ga-PSMA PET/CT was shown to change management in 43.8% of primary staging and 40.9% of restaging cases. It appears that the strongest detection rates occur in those patients with clear cell RCC; however, the accuracy for the detection of the various histological variations of RCC needs further clarification with prospective data. The results of this study suggest there may be merit in the use of PSMA PET/CT in the staging of RCC. However, as this study has shown, there is very limited data in the literature regarding the utility of ^{68}Ga-PSMA PET/CT in RCC staging, with the overall quality of evidence low. Further analysis, both with respect to efficacy, histological confirmation of avid disease, and cost-benefit, is required to determine whether there is a role for routine ^{68}Ga-PSMA PET/CT imaging in all patients with suspected RCC or recurrent disease.

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Authors' contributions SR collected data and wrote the manuscript. RE and JY provided expert opinion regarding renal cell carcinoma. SK provided extensive information regarding ^{68}Ga-PSMA PET/CT. All authors read and approved the final manuscript.

Data availability The dataset used during the present study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Ethics approval and approval to publish Ethics approval was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee ref.: HREC/18/QRBW/395 (ERM: 42076).

Conflict of interest The authors have no conflicts of interest to declare.

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