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ORIGINAL ARTICLE

Improved specificity with ^{68}Ga PSMA PET/CT to detect clinically significant lesions "invisible" on multiparametric MRI of the prostate: a single institution comparative analysis with radical prostatectomy histology

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Abstract

Purpose Positron emission tomography (PET) for prostate-specific membrane antigen (PSMA) represents a promising method for prostate cancer diagnosis and staging. Comparisons of PSMA-based tumour characterisation to multiparametric MRI (mpMRI) are limited, hence this study sought to compare the diagnostic accuracy of ^{68}Ga-PSMA PET/CT to mpMRI against radical prostatectomy (RP) whole gland histopathology.

Methods A retrospective cohort study of consecutive patients who underwent pre-operative mpMRI and ^{68}Ga-PSMA PET/CT followed by a RP was performed. Standard clinical parameters were collected. "Per patient" and "per lesion" analyses for image-based detection according to RP histopathology were described using sensitivity, specificity and other measures of diagnostic accuracy.

Results Fifty-eight patients (median age 65.5 years, median PSA 7.35 ng/mL) underwent RP, resulting in a high-risk cohort (≥pT3 69%). Sensitivities for identification of index lesion, bilateral and multifocal disease were 90%, 21%, 19% for mpMRI and 93%, 42%, 34% for ^{68}Ga-PSMA PET/CT. Histology analyses revealed 88 cancer foci of Gleason grades 3 + 3 (4%), 3 + 4 (64%), 4 + 3 (19%), 4 + 4 (3%) and ≥ 4 + 5 (10%), of which ^{68}Ga-PSMA PET/CT correctly detected more foci (78%, AUC 0.817) than mpMRI (69%, AUC 0.729).

Conclusions ^{68}Ga-PSMA PET/CT may better reflect RP histopathology compared to mpMRI when considering multifocal and bilateral disease. These findings may influence surgical planning, targeted biopsy and focal therapy strategies and require further research.

Keywords Prostatic neoplasms · Positron-emission tomography · Magnetic resonance imaging · Glutamate carboxypeptidase II, human · Prostatectomy,

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Introduction

Prostate cancer detection, based on prostate-specific antigen (PSA) testing and digital rectal examination (DRE), remains controversial in contemporary urology practice. While over-treatment of indolent tumours has been reduced with enthusiastic adoption of active surveillance, imprecise under-detection of clinically significant disease leads to patient- and clinician-related anxiety while on active surveillance protocols. The use of multiparametric magnetic resonance imaging (mpMRI) has been shown to improve the detection of significant prostate cancer compared to standard template transrectal ultrasound (TRUS) biopsy techniques and also decreases the detection of insignificant prostate cancer [1, 2]. mpMRI also provides image guidance for targeted biopsy

and improved detection of anterior, apical or smaller lesions not detected using transrectal ultrasound (TRUS) guided prostate biopsy [3]. Furthermore, mpMRI has recently been applied more widely as a biopsy-triage tool. The recent PROMIS study demonstrated higher sensitivity of mpMRI (93%) compared to TRUS biopsy (48%) for clinically significant prostate cancer. If a mpMRI was performed before a prostate biopsy it was estimated that 27% of unnecessary biopsies could be avoided, 5% fewer clinically insignificant cancers would be diagnosed and an extra 18% clinically significant cancer would be identified [4].

Available evidence with mpMRI to detect clinically significant prostate cancer suggests both a high estimated sensitivity (0.96 for PI-RADS ≥3, 0.90 for PI-RADS ≥4) at the expense of specificity (0.29 for PI-RADS ≥3, 0.62 for PI-RADS ≥4) based on meta-analysis of five (PI-RADS ≥3) and ten (PI-RADS ≥4) studies [5]. Index lesion detection by mpMRI has been reported to have an accuracy of >90% when compared to RP histology and MRI/TRUS fusion biopsy; however, there are varied results with respect to accurate detection of multifocal disease [1, 6–8]. Other confounding factors include more difficulty in the diagnosis of transition zone tumours from benign prostatic hyperplasia [9]; however, it is anticipated that this will be overcome by the adoption of PI-RADS version 2 [10]. Also, small foci and disease within the central gland may not be easily identified using mpMRI [9].

Recently, ^{68}Ga prostate-specific membrane antigen (PSMA) PET/CT imaging has become increasingly used for defining the presence of metastatic disease, most commonly in those men with biochemical recurrence after curative treatment [11–14]. ^{68}Ga-PSMA PET/CT has the potential to improve the detection of prostate cancer compared with the limited sensitivity of traditional CT and whole body bone scan (WBBS) [15, 16] and choline-based PET/CT [17] due to the increased PSMA expression on the surface of a high proportion of malignant prostate cells, which further increases with grade and stage of disease [18].

Within the prostate, primary prostate cancer exhibits higher PSMA expression compared with normal prostatic cells [19]. However, use of ^{68}Ga-PSMA PET/CT in primary staging and evaluation with lesion concordance on whole specimen histology is limited [11, 20, 21]. Whole specimen analysis to date has indicated high sensitivity (87–97%) and specificity (87–90%) for primary diagnosis using a SUV_{max} cut off of ≥3–4 [20, 21]. However, when PSMA-based PET imaging was compared with mpMRI against whole specimen histology, sensitivity was reduced, but specificity is maintained [22–24]. To date, the largest study of 53 patients reported combined PSMA PET/MRI (AUC 0.88) was superior to mpMRI (0.73) or PET (0.83) alone [25].

The limitations of mpMRI in failing to detect clinically significant disease in all cases and smaller non-index lesions are well known and limit its application to replace biopsy in all men in initial workup of men suspected of prostate cancer. In this retrospective study, the primary endpoint was to evaluate ^{68}Ga-PSMA-PET/CT and mpMRI of the prostate for index lesion concordance and multifocal tumour detection. Secondary endpoints included comparative assessment of mpMRI and PET/CT PSMA scans to predict pathological stage and grade of primary prostate cancer in men undergoing RP with correlation to whole specimen histopathology.

Methods

The study received ethical approval from the Royal Brisbane and Women's Hospital (RBWH) Human Research Ethics Committee (Approval number HREC/17/QRBW/644).

Study population

A retrospective cohort study was performed at the RBWH, a tertiary urology unit, for 58 consecutive men between June 2014 and July 2017 who underwent mpMRI prior to transperineal prostate biopsy (per departmental protocol) and were subsequently staged using ^{68}Ga PSMA PET/CT prior to radical prostatectomy. No exclusions were applied based on time intervals between imaging, diagnosis or treatment modalities. Patients were excluded if they had been pre-treated with radiotherapy techniques. Clinical, imaging and histopathological data were confidentially obtained from patient records. Clinical risk was determined according to that determined by the European Association of Urology guidelines [26].

Imaging techniques

Prostate mpMRI was performed using a Siemens Skyra 3 Tesla system without endorectal coil. All mpMRI images were analysed by radiologists with experience in prostate mpMRI (average 15 reads per month individually, 19 reads per month for whole medical imaging department) and the treating urologist (50 reads per month between public and private practice). Prostate volume was recorded per the mpMRI estimate, as this is the volume used in our institution to estimate PSA density. PI-RADS 4 and 5 scans were considered a likely result, PI-RADS 3 was considered equivocal and PI-RADS 2 result was defined as an unlikely result.

The radiopharmaceutical used for the PET study was ^{68}Ga-PSMA-11 (ABX AG, Germany) manufactured at the Specialised PET Services Queensland Radiopharmaceutical Laboratory [27]. PET images were acquired 60 min after administration of 150 MBq ± 5% of ^{68}Ga-PSMA-11. All ^{68}Ga-PSMA-PET/CT imaging was undertaken using a Siemens Biograph mCT PET/CT scanner. Emission tomographic images were obtained from the skull vertex to the thighs. A low-dose CT scan was performed during tidal respiration for

attenuation correction and lesion localisation. Images were viewed and reported by visual qualitative analysis using the Siemens syngo.via viewing platform by two nuclear medicine specialists with significant experience in reading PSMA PET/CT scans Lesions were considered positive by the nuclear medicine specialist when there was focal uptake significantly above background prostatic uptake. Lesions were considered equivocal when there was focal uptake just above background uptake, or when uptake was less well defined.

Retrospective analysis of the PET images was performed in order to quantify the data for research purposes. Lesions seen on Ga^{68}-PSMA-PET/CT were also graded according to maximum standardized uptake values (SUV_{max}) and described as mildly avid ($SUV_{max} < 5$), moderately avid ($SUV_{max} > 5$) or intensely avid ($SUV_{max} > 10$). A three-point system was implemented to establish if prostate cancer was likely, equivocal or unlikely, similar to that described previously [25].

Comparison of mpMRI PI-RADS and Ga^{68}-PSMA-PET/CT Likert scales used in this study is outlined in Table 1.

Radical prostatectomy

All men underwent either a robot-assisted laparoscopic prostatectomy or open radical retropubic prostatectomy under general anaesthesia. The surgery was performed by a consultant urologist with involvement of senior registrar/trainee under close supervision. Before surgery, the surgeon reviewed the clinical details, ^{68}Ga PSMA PET/CT and mpMRI.

Histology examination

RP specimens underwent histopathology examination according to the International Society of Urological Pathology (ISUP) standard protocols by experienced uro-pathologists. Histopathology reports were structured according to the 2014 ISUP Gleason Grading guidelines [28].

Clinically significant disease was defined as Gleason 3 + 4 or greater [29], while other pathological characteristics (tumour grade/stage, presence of extraprostatic extension (EPE), seminal vesicle involvement and margin status) were recorded. Location and tumour volume of both dominant and non-dominant tumour nodules was recorded.

Table 1 Imaging performance

Overall / PET score	PI-RADS score	MRI	PSMA PET/CT
Likely / Positive	5	25	51
	4	26	
Equivocal	3	2	5
Unlikely / Negative	2	5	2
	1	0	

Assessing imaging and histopathological concordance

Lesion locations were determined according to the sextant-based descriptions included in the structured pathology reports (Supplementary Figure 1). Location of index tumours, defined as the tumour focus with highest Gleason score or greatest volume if two nodules were of the same Gleason score [30], was compared with location of suspicious lesions on mpMRI and ^{68}Ga PSMA PET/CT. Absolute concordance was defined as when all tumour foci on histopathology were identified as being likely on ^{68}Ga PSMA PET/CT or mpMRI. All lesions (likely or equivocal) described within the imaging reports for mpMRI and ^{68}Ga PSMA PET/CT were considered. Small lesions (<10 mm) noted in the histopathology report, but without description of grade, volume or location were excluded due to probable clinical insignificance on the basis of volume < 0.5 cc [31] and correlation with lower grade and Gleason score on RP [32], as well as inability to visualise on imaging due to limitations in image and tumour resolution [33].

Statistical analysis

Data were curated into dichotomous or categorical variables for most comparative analyses, except for continuous variables (PSA, PSA density, ADC value, SUVmax). Categorical variables were compared using Fisher's test, while continuous variables were compared with Mann-Whitney test (as most comparisons involved one or more datasets that were not normally distributed). Sensitivity analyses were performed using Diagnostic test (2 × 2 table) evaluation and sensitivities compared using McNemar's Chi-Square Test. Receiver operating characteristic analyses were performed to determine area under the curve (AUC), sensitivity, specificity at the optimal cut-point as determined by the Youden index. All statistical analysis was performed using MedCalc for Windows, Version 18 (MedCalc Software; Ostend, Belgium).

Results

Patient and pathological characteristics

In total, 58 men were included in this retrospective analysis. The patient demographics are included in Table 2. Most patients were of intermediate risk (77%), with a high median PSA density (0.196, interquartile range; IQR 0.146–0.278 ng/mL^2). Most RP specimen index lesions were of Gleason 3 + 4 (45%) or 4 + 3 (17%), increasing to 59% and 22%, respectively, if tertiary pattern 5 was included. However, a high prevalence of extracapsular extension and/or seminal vesicle invasion (69%) was present and contributed to a positive surgical margin rate of 27.5% (pT2 = 0; pT3a = 10,

Table 2 Demographic information

No. of patients	58	
Intermediate risk (%)	45 (77)	
High risk (%)	13 (23)	
Previous negative biopsy (%)	7 (12)	
Neoadjuvant androgen deprivation therapy	1	
Clinical demographics		
Age, years	65.5 (60–68)	
PSA value, ng/mL	7.35 (5.6–12)	
Prostate volume, mL	38 (30–50)	
PSA density	0.196 (0.146–0.278)	
Pathologic demographics		
Gleason Grade (%)	"Per Patient"	"Per Lesion"
3 + 3	0	2 (2)
3 + 3 + 4	0	2 (2)
3 + 4	26 (45)	48 (55)
3 + 4 + 5	8 (14)	8 (9)
4 + 3	10 (17)	13 (15)
4 + 3 + 5	3 (5)	3 (4)
3 + 5	1 (2)	1 (1)
4 + 4	1 (2)	2 (2)
≥4 + 5	9 (15)	9 (10)
Stage (%)		
pT2	18 (31)	
pT3a	31 (53.5)	
pT3b	9 (15.5)	
pT4	0	
Positive surgical margin (%)	16(27.5)	
pT2	0	
pT3a	10	
pT3b	6	

Expressed as median (IQR)

pT3b = 6). There was a median of 51.5 days (IQR 35.3–73.3) between prostate biopsy and ^{68}Ga-PSMA PET/CT.

Imaging diagnostic performance: "per patient"

As shown in Table 1, pre-biopsy mpMRI detected PI-RADS ≥3 lesions (likely or equivocal) in 53 (91.3%) men and concordant with the histopathology index lesion in 52 men (sensitivity 89.66%; 95% CI, 78.8–96.1). The five patients deemed PI-RADS 2 on mpMRI proceeded to biopsy, and subsequently RP, on the basis of ongoing clinical suspicion. ^{68}Ga-PSMA PET/CT demonstrated PSMA-avid disease (likely or equivocal) in 56 (96%) patients, identified the index lesion in 54 (93.1%) patients. An image comparison between mpMRI and ^{68}Ga-PSMA PET/CT is included as Fig. 1. Patients with non-PSMA avid tumours ($n = 2$) had Gleason 3 + 4 malignancy, low tumour volumes (0.98 cc and 0.27 cc) and had a significantly lower mean serum PSA (1.91 ng/mL; $p = 0.02$) than those with PSMA avid tumours (mean PSA 11.44 ng/mL). For patients in whom ^{68}Ga-PSMA PET/CT did not detect the index tumour (n = 2), one patient's index lesion was a 0.35 cc Gleason 4 + 3 tumour in which ^{68}Ga-PSMA PET/CT detected the non-index Gleason 3 + 4 (1.01 cc) nodule, while the other had Gleason 3 + 4 (tumour volume 0.72 cc, PSA 4.7 ng/mL) disease.

All tumour foci present with RP histology were identified by mpMRI for 37 patients (sensitivity 63.8%; 95% CI, 50.1–76%) and by ^{68}Ga-PSMA PET/CT for 42 patients (sensitivity 72.4%; 95% CI, 59.1–83.31%; $p = 0.27$). Multifocal disease was detected among 11 (18.9%) and 20 (38%; $p = 0.03$) patients, respectively.

^{68}Ga-PSMA PET/CT lesions were reported as likely for 51 men (negative due to: incorrect index lesion assignment $n = 2$, low SUV max $n = 5$). Lesions assigned as likely correlated with all RP tumour foci for 38 patients (sensitivity 65.5%; 95% CI, 51.9–77.5%).

When compared for clinical (PSA, PSA density), imaging (apparent diffusion coefficient; ADC, SUVmax) and histopathological (Gleason score) factors (Table 3), all groups were similar except that PI-RADS 5 lesions had lower ADC values

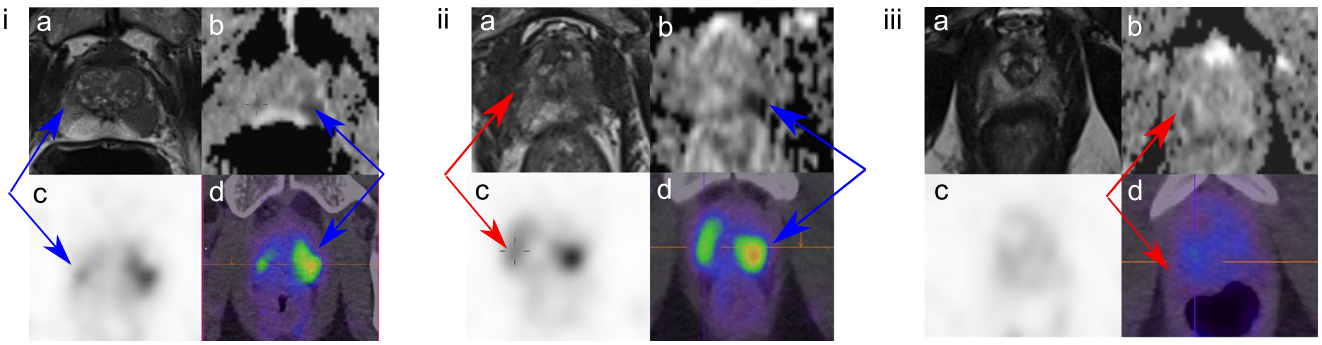

Fig. 1 Comparative imaging from three patients (**i** – **iii**) that demonstrate suspicious lesions seen on both mpMRI and ^{68}Ga-PSMA PET/CT (**i**), multifocal disease seen with ^{68}Ga-PSMA PET/CT and not mpMRI (**ii**) and index lesion seen on mpMRI but not convincingly detected on ^{68}Ga-PSMA PET/CT (**iii**). a - axial T2 weighted image; b – apparent diffusion coefficient (ADC) map derived from diffusion-weighted imaging viewed in axial section; c - ^{68}Ga-PSMA PET axial image; d - ^{68}Ga-PSMA PET fused with CT imaging. Blue arrow – concordant lesions; Red arrow – discordant lesions

Table 3 Comparison of mpMRI PI-RADS (a) and PSMA PET/CT (b) outcomes to clinical, imaging and histopathological parameters. Expressed as median (IQR), * $p < 0.05$; ** $p < 0.01$

a)							
		N	PSA (ng/mL)	PSA density (ng/mL/g)	ADC ($\mu m^2/s$)	PET matching lesions	SUVmax
OVERALL		58	7.35 (5.6–12)	0.1958 (0.1464–0.2778)	573 (446.25–669.5)	54	9.53 (6.3–14.32)
PI-RADS							
Likely	5	24	8.1 (6.2–14)	0.1903 (0.1511–0.379)	500 (367–620)**	23 = Likely 1 = Equivocal	9.04 (5.505–14.47)
	4	27	6.4 (5–11.75)	0.2 (0.1366–0.2642)	654 (540–715)	23 = Likely 2 = Equivocal 2 = Unlikely	10.01 (6.455–11.61)
			$P = 0.8633$	$P = 0.4386$	–		
Equivocal	3	2	6.9 (6–7.8)	0.1695 (0.1625–0.1765)	550	2 = Likely	9.41 (8.28–10.54)
			$P = 0.2453$	$P = 0.8571$	–		$P = 1.0000$
Unlikely	2	5	10 (7.35–12)	0.275 (0.1384–0.2955)	–	3 = Likely 2 = Equivocal	9.395 (5.835–18.785)
	1	0	–	–	–	–	–
b)							
PSMA PET/CT	N	PSA	PSA density	ADC	mpMRI matching lesions	SUVmax	
Likely / Positive	51	7.8 (5.85–13)	0.2 (0.1551–0.3119)	550 (432.5–654)	PIRADS 4 / 5 = 46 PIRADS 3 = 2 PIRADS 1 / 2 = 3	10.07 (6.65–14.33)	
		$P = 0.1768$	$P = 0.1863$	$P = 0.1027$		$P = 0.0165$	
Equivocal	5	6 (4.925–8.05)	0.1463 (0.1229–0.2137)	680 (647–694)	PIRADS 4/5 = 3 PIRADS 2 = 2	4.7 (4.07–5.28)	
		$P = 0.0952$	$P = 0.1905$	NS		–	
Unlikely / Negative	2	1.91 (0.92–2.90)*	0.0748 (0.0287–0.1208)*	730.5 (661–800)	PIRADS 4 = 2	–	
		***P* = 0.0208** (cf 2)	***P* = 0.0447**	P = 0.10		–	

($p = 0.009$) and likely ^{68}Ga-PSMA PET/CT lesions had higher SUVmax values ($p = 0.02$). Correlation analysis demonstrated a trend towards higher PSA and PSA density with lower ADC values, with an inverse trend observed for SUVmax, but these were not significant ($p > 0.05$; Supplementary Figure 2).

Imaging diagnostic performance: "Per lesion"

Among 58 RP specimens, 88 tumour foci were identified (Table 4), of which mpMRI detected 61 (PI-RADS ≥3) and ^{68}Ga-PSMA PET/CT detected 68 (likely or equivocal). Concordance among all modalities was present for 54 foci (61.3%). Fourteen lesions (15.9%) seen on ^{68}Ga-PSMA PET/CT were not seen on mpMRI. Seven lesions (7.9%) seen on mpMRI were not seen on ^{68}Ga-PSMA PET/CT. Sixteen lesions were identified by imaging (likely or equivocal) that did not correspond to tumour foci on histopathological analysis. Specifically, among "likely" lesions, one lesion identified on ^{68}Ga-PSMA PET/CT and two lesions on mpMRI did not correspond to tumour foci on histopathology. Among "equivocal" lesions, 12 lesions identified by ^{68}Ga-PSMA PET/CT and two identified by mpMRI did not correspond to tumour foci on histopathology. Significantly more false negatives occurred for mpMRI compared to ^{68}Ga-PSMA PET/CT interpretation (Table 4; $p = 0.04$). When ROC curves were compared (Table 4, Fig. 2), strict ^{68}Ga-PSMA PET/CT interpretation (lesions that were likely; AUC 0.817) was similar to mpMRI (PI-RADS≥3; AUC 0.729; $p > 0.05$) and mpMRI PI-RADS≥4 (AUC 0.776; $p > 0.05$). Consideration of clinically significant cancer, as defined by Gleason ≥3 + 4 resulted in slightly improved diagnostic accuracy for all methods except strict ^{68}Ga-PSMA PET/CT (likely only; AUC 0.810). All were superior to ^{68}Ga-PSMA PET/CT inclusive of both likely and equivocal lesions ($p < 0.05$ for both analyses).

Multifocal disease analysis

Among 58 patients, 26 demonstrated multifocal disease with RP histopathological analysis. mpMRI demonstrated multifocal disease in 17 cases, of which six cases were due to large solitary lesions on histopathology that appeared to be multifocal on mpMRI, resulting in 11 cases that were truly multifocal on both mpMRI and histopathology. When compared to RP histopathology, all tumour foci were concordant with mpMRI for six patients, while mpMRI failed to detect additional foci for five patients. ^{68}Ga-PSMA PET/CT detected 27 cases of multifocal disease, of which seven were due to large solitary lesions on histopathology that appeared to be multifocal on ^{68}Ga-PSMA PET/CT, resulting in 20 that were truly multifocal. "Likely" lesions on ^{68}Ga-PSMA PET/CT were concordant for all tumour foci on RP histopathology in eight cases ($p > 0.05$), which increased to 12 if likely and equivocal lesions were included ($p > 0.05$).

Table 4 **A**) Concordance between tumour foci (reported according to Gleason grade) according to histopathology compared to mpMRI and PSMA PET/CT lesions. Tertiary patterns were considered according to predominant Gleason patterns (e.g. 3 + 3 + 4 included in 3 + 3, 3 + 4 + 5 included in 3 + 4, 4 + 3 + 5 included in 4 + 3, 3 + 5 included in 4 + 4). **B**) Diagnostic accuracy according to ROC analysis of imaging modalities for detection of lesions for all cancer and clinically significant cancer (defined as Gleason grade ≥ 3 + 4)

A Histopathology		mpMRI			Ga^{68}PSMA PET/CT		
Gleason	*n*	Likely (Concordant)	Equivocal (Concordant)	Discordant	Likely (Concordant	Equivocal (Concordant)	Discordant
3 + 3	4	–		4	1		3
3 + 4	56	37		19	34	8	14
4 + 3	16	13	1	2	14		2
4 + 4	3	1	1	1	3		
≥4 + 5	9	8		1	9		
Total	88	59	2	27	61	8	19

B All cancer	mpMRI		^{68}Ga-PSMA PET/CT	
	PI-RADS ≥3	PI-RADS ≥4	Likely/equivocal	Likely only
AUC	0.729	0.776	0.510	0.817
95% CI	0.633 to 0.811	0.685 to 0.852	0.410 to 0.609	0.730 to 0.886
Sensitivity	69.3	67.1	78.4	69.3
Specificity	76.5	88	23.5	94.1
Clinically significant cancer (Gleason grade ≥ 3 + 4)				
AUC	0.768	0.804	0.571	0.810
95% CI	0.675 to 0.845	0.715 to 0.875	0.471 to 0.668	0.721 to 0.880
Sensitivity	72.6	70.2	81	71.4
Specificity	81	90.5	33.3	90.5

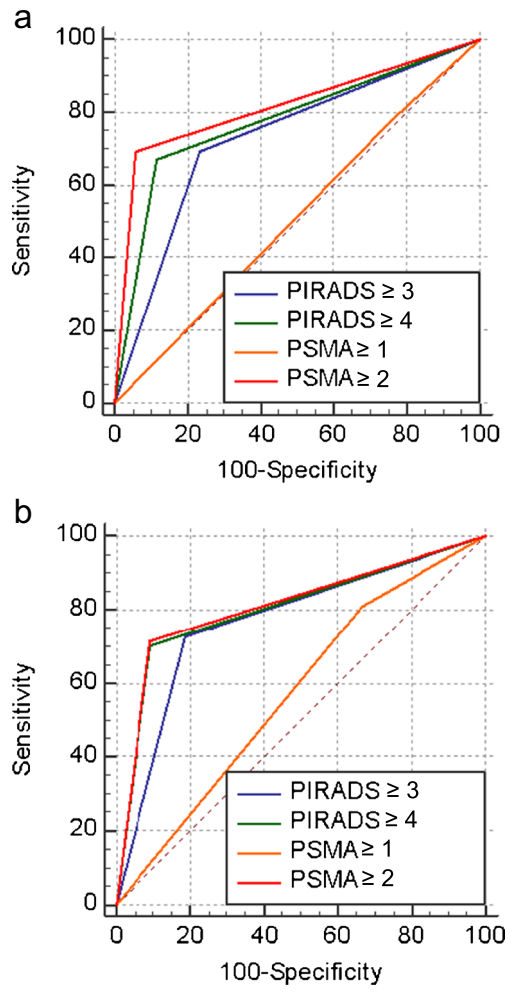

Fig. 2 Receiver Operating Characteristic analyses of mpMRI and ^{68}Ga-PSMA PET/CT using different confidence cut-offs (PIRADS ≥3 or ≥4; PSMA equivocal/likely (PSMA_1more) or likely only (PSMA_2more) considering all cancer (**a**) and clinically significant cancer (Gleason >3 + 3 and > 0.5 cc) (**b**)

Timing between imaging modalities

The median duration between mpMRI to RP, ^{68}Ga-PSMA PET/CT to RP and mpMRI to ^{68}Ga-PSMA PET/CT was 231 (180–322), 110 (83–161) and 103 (70–167) days, respectively. The effect of imaging delay between mpMRI and ^{68}Ga-PSMA PET/CT was considered with analysis of two groups, those who received both imaging modalities within 90 days ($n = 21$) and those after 90 days ($n = 37$). There were no significant differences between any variables (Table 5).

Specific cases

^{68}Ga-PSMA PET/CT detected nodules not apparent on mpMRI, one of which corresponded with a positive margin (non-dominant nodule): a contralateral 2.75 cc nodule of Gleason 3 + 4 disease was visible on ^{68}Ga-PSMA PET/CT, but not mpMRI (both of which detected the index lesion at 1.1 cc Gleason 4 + 5 tumour; Fig. 1). However, some disease may be missed by both modalities. Five patients with negative mpMRI (PI-RADS 2 overall), but likely PSMA PET/CT findings proceeded to RP. Of these, one case had Gleason 4 + 3 disease detected by biopsy that was upgraded to Gleason grade 4 + 5 disease (2.24 cc) on whole gland histology (Fig. 1). In contrast, mpMRI detected six lesions not seen on ^{68}Ga-PSMA PET/CT, including a 0.72 cc Gleason 3 + 4 tumour in which PSMA demonstrated low avidity in a separate area.

SUVmax analysis

When SUVmax was used to predict positive histopathology for tumour lesions, no significant differences were observed among different Gleason scores (Supplementary Table 1). SUVmax >6.3 resulted in 100% specificity for 60.1% sensitivity (AUC 0.788) for detection of overall cancer considering only likely or equivocal lesions, while 47.7% sensitivity (AUC 0.815) was observed if all false negatives were considered (Supplementary Figure 3). A trend of higher SUVmax being associated with a lower ADC was observed, however this was not significant ($p = 0.15$).

Discussion

This study represents, to our knowledge, the largest clinical study of primary prostate cancer characterisation using both mpMRI and ^{68}Ga-PSMA PET/CT compared to RP whole specimen histology. A significant strength of this study is that the data are sourced from routine investigations performed as part of standard clinical practice in our tertiary institution. Both mpMRI and ^{68}Ga-PSMA PET/CT exhibited excellent index lesion identification; however, ^{68}Ga-PSMA PET/CT detected more tumour foci (77.2 vs. 69.3%) and multifocal disease (22 vs. 12.5%) compared with mpMRI. Best diagnostic accuracy for tumour foci/lesions was obtained with ^{68}Ga-PSMA PET/CT (considering likely lesions only) compared with mpMRI or all ^{68}Ga-PSMA PET/CT lesions (inclusive of likely and equivocal). High accuracy for clinically significant disease was present, with 87% of detected foci at Gleason 3 + 4 or higher. Thus, ^{68}Ga-PSMA PET/CT may provide valuable additional information in primary staging for the treating urologist prior to treatment or diagnostic biopsy.

Our findings are similar to Eiber and colleagues, who reported on data from 53 patients who underwent ^{68}Ga-PSMA HBED-CC PET/MRI prior to prostatectomy [25]. However, our cohort represents higher risk disease (≥pT3a 69% versus 57%) with higher mpMRI accuracy (91% versus 66%), consistent with our pre-biopsy mpMRI-based model of prostate cancer diagnosis. Despite this, ^{68}Ga-PSMA PET/CT was the superior diagnostic modality and may be more discriminating

Table 5 Subgroup analysis with consideration for delay from mpMRI to ^{68}Ga-PSMA PET/CT of less than or greater than 90 days

	Total cohort	MRI – PSMA >90 days	MRI – PSMA <90 days	*p* value
No. of patients	58	37	21	
Intermediate risk (%)	45 (77)	29 (78.4)	16 (76.2)	1.0000
High risk (%)	13 (23)	8 (21.6)	5 (23.89)	1.0000
Previous negative biopsy (%)	7 (12)	6 (16.2)	1 (4.8)	0.4034
Neoadjuvant androgen deprivation therapy	1		1	
Clinical demographics				
Age, years	65.5 (60–68)	66 (63–68)	63 (58–69)	0.09
PSA value, ng/mL	7.35 (5.6–12)	6.9 (5–9.8)	7.8 (5.8–13)	0.467
Prostate volume, mL	38 (30–50)	40 (32–50)	35 (27–50)	0.369
PSA density	0.196 (0.146–0.278)	0.2 (0.15–0.29)	0.19 (0.15–0.27)	0.342
Pathologic demographics				
Gleason Grade (%)				
3 + 3	0	0	0	
3 + 4	34 (58.6)	19 (51.3)	15 (71.4)	0.1714
4 + 3	13 (22.4)	10 (27)	3 (14.2)	0.3380
4 + 4 or 3 + 5	2 (3.4)	2 (5.4)	0	0.5299
≥4 + 5	9 (15.5)	6 (16.2)	3 (14.2)	1.0000
Stage (%)				
pT2	18 (31)	14 (37.8)	4 (19)	0.1558
pT3a	31 (53.5)	18 (48.6)	13 (61.9)	0.4154
pT3b	9 (15.5)	5 (13.5)	4 (19)	0.7096
pT4	0			
Positive surgical margin (%)	16(27.5)	9 (24.3)	7 (33.3)	0.5460
pT2	0	0	0	
pT3a	10	6 (16.2)	4 (19)	1.0000
pT3b	6	3 (8.1)	3 (14.3)	0.6573

when applied in a traditional diagnostic pathway. Indeed, most of the limited studies comparing mpMRI of the prostate with ^{68}Ga-PSMA PET/CT report the latter to demonstrate a higher specificity and positive predictive value [24, 25]. The primary indication for ^{68}Ga-PSMA PET/CT in our institution is systemic staging after biopsy-confirmed prostate cancer diagnosis due to local experience and published evidence of superiority over traditional staging modalities (CT, WBBS) [16].

The benefits of ^{68}Ga-PSMA PET/CT compared with or in addition to mpMRI have several implications for contemporary urological practice. ^{68}Ga-PSMA PET/CT may be considered as a diagnostic study with ongoing suspicion of prostate cancer despite prior negative MRI or prostate biopsies. mpMRI-based targeting, whether performed "in bore" or with "cognitive fusion" [34], has emerged as a key component of localised prostate cancer diagnosis in some countries, on the basis of high quality evidence that targeted biopsy reduces over detection of insignificant disease and increases the detection of significant prostate cancer [2, 7]. Thus, incorporation of ^{68}Ga-PSMA PET/CT prior to biopsy may improve overall biopsy accuracy and disease characterisation on the basis of greater concordance between lesions seen on RP and ^{68}Ga-PSMA PET/CT compared to mpMRI.

^{68}Ga-PSMA PET/CT may provide additional information when considering a patient for focal therapy. The use of mpMRI to guide biopsy and focal therapy techniques has been reported internationally [35, 36]. However, the concern of multi-focal prostate cancer limits widespread use of focal therapy [37]. Our findings indicate that only 10% of men were eligible for focal therapy according to a consensus definition [38] on the basis of RP histopathology (38 bilateral disease, five Gleason score ≥ 4 + 3, 5 EPE present).

Furthermore, the decision to perform varying degrees of nerve-sparing during RP is based on multiple factors, however is contraindicated in patients at high risk of EPE [26]. The sensitivity of mpMRI in predicting EPE is unacceptably low (57% on meta-analysis) [39], while the accuracy of ^{68}Ga-PSMA PET/CT in predicting EPE is unclear. However, superior detection of bilateral and multifocal disease may influence the decision to perform

nerve-sparing surgery and is a further benefit for pre-operative use of ^{68}Ga-PSMA PET/CT. ^{68}Ga-PSMA PET/CT when used for localized staging also combines whole body functional imaging to detect distant metastases with initial diagnosis [40, 41] or biochemical recurrence [11, 12]. Cost-benefit comparison with an mpMRI/CT/WBBS approach is currently being assessed in prospective studies (Australia New Zealand Clinical Trials Registry identification numbers ACTRN12617000005358 and ACTRN12614000783628).

The limitations of this study include the retrospective, non-randomised nature and possible selection bias. Specifically, our cohort is limited to those undergoing radical prostatectomy and does not include patients referred for radiotherapy with androgen deprivation therapy. Inherent limitations include the translation of nuclear medicine specialist interpretation of ^{68}Ga-PSMA PET/CT to a quantitative scale (3-point Likert and SUVmax thresholds) for research purposes. However, we determined that a SUVmax >6.3 resulted in 100% specificity and 61% sensitivity. The comparison of histopathology with lesion location on imaging using histopathological report, omitting smaller lesions, as opposed to whole gland cross-sectional histopathological assessment which may potentially lead to interpretation errors. This approach was used to be clinically applicable and prioritise clinically significant disease, rather than consider all possible likely insignificant small foci within the RP specimen. It is likely this consideration contributed to the presence of falsely positive lesions seen on either imaging modality, which were significantly more abundant on ^{68}Ga-PSMA PET/CT. The time intervals between initial imaging (mpMRI) and definitive treatment (radical prostatectomy) may have contributed to discordant histopathology, affecting mpMRI diagnostic accuracy; however, this is likely to be minor given the traditionally slow growth of prostate cancer. The duration from biopsy to surgery were in accordance with our National Elective Surgery categorization guidelines. Subgroup analysis of time between mpMRI and ^{68}Ga-PSMA PET/CT did not demonstrate any significant differences in agreement with other studies between biopsy and surgery [42, 43], including those considering intermediate-risk cancer [44] that comprised the majority (approximately 80%) of our cohort.

In conclusion, ^{68}Ga-PSMA PET/CT is highly accurate for index lesion detection, as well as of tumour foci to characterise bilateral and multifocal disease. In addition to the benefit of ^{68}Ga-PSMA PET/CT in the detection of recurrent disease after primary prostate cancer treatment, there is a role for primary evaluation. Prospective studies are warranted to confirm diagnostic accuracy in other cohorts, determine which patients are expected to demonstrate non-avid tumours and assess cost-benefit of ^{68}Ga-PSMA PET/CT in altering primary management for localised disease.

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Compliance with ethical standards

Conflict of interest All authors declare to have no conflict of interest.

Ethical approval The study received ethical approval from the Royal Brisbane and Women's Hospital (RBWH) Human Research Ethics Committee (Approval number HREC/17/QRBW/644). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent An informed consent waiver was approved by the institutional ethics board for this retrospective study using pre-existing clinical data.

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