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ORIGINAL ARTICLE

# $^{68}$Ga-PSMA PET/CT better characterises localised prostate cancer after MRI and transperineal prostate biopsy: Is $^{68}$Ga-PSMA PET/CT guided biopsy the future?

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## Abstract

**Background** 68Ga prostate specific membrane antigen PET/CT (68Ga-PSMA PET/CT) may be superior to multiparametric MRI (mpMRI) for localisation of prostate cancer tumour foci, however the concordance and differences between 68Ga-PSMA PET/CT and mpMRI when applied to all biopsied patients and potential benefit in patients with negative mpMRI is unclear.

**Methods** Retrospective analysis of patients undergoing mpMRI, prostate biopsy and 68Ga-PSMA PET/CT over a 3-year period. Diagnostic performance of 68Ga-PSMA PET/CT and mpMRI were assessed using biopsy histopathology for the entire cohort and radical prostatectomy specimen in a subset of patients. Lesion concordance and additional detection of each modality were determined, including in a dedicated cohort of patients with mpMRI PIRADS 2 scans.

**Results** A total of 144 patients were included in the study. Index lesion/foci detection was similar between 68Ga-PSMA PET/CT and mpMRI (sensitivity 83.1% vs 90.1%; $p = 0.267$), however lesions missed by mpMRI were larger (1.66 $cm^3$ vs 0.72 $cm^3$; $p = 0.034$). Lesion detection rates were similar across the biopsy histopathology and radical prostatectomy specimen subset, with a high concordance for index (80.1%) and a moderate concordance for total (67%) lesions between the 2 imaging modalities. The additional detection yield favoured 68Ga-PSMA PET/CT over mpMRI for index (13.5% vs 4.3%) and total (18.2% vs 5.4%) lesions; both modalities missed 2.1% and 12.3% of index and total lesions, respectively. 68Ga-PSMA PET/CT identified 9 of 11 patients with PIRADS 2 mpMRI but subsequently diagnosed with Gleason ≥ 3 + 4 disease.

**Conclusions** Despite high concordance rates, 68Ga-PSMA PET/CT incrementally improved tumour localisation compared with mpMRI. These results suggest that 68Ga-PSMA PET/CT may have an incremental value to that of mpMRI in the diagnostic process for prostate.

**Keywords** Prostatic neoplasms · Positron-emission tomography · Magnetic resonance imaging · Glutamate carboxypeptidase II · Human · Prostatectomy · Prostate specific membrane antigen

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## Introduction

Multiparametric magnetic resonance imaging (mpMRI) has changed the paradigm in the diagnosis of prostate cancer (PCa) [1–3]. Several studies have shown that a mpMRI-triage pathway improves diagnostic accuracy of clinically significant PCa (csPCa) (93% vs. 48%) and improved csPCa detection (38% vs 26%) while preventing unnecessary biopsies (27–28%) and decreasing insignificant PCa diagnoses by 5–13% in comparison with systematic transrectal ultrasound (TRUS) [1, 2]. These benefits have been confirmed in a day-to-day clinical practice, equating to a 47% biopsy avoidance and a 60.5% csPCa diagnosis rate in our centre [3].

Although mpMRI has demonstrated an accuracy of > 90% in identification of index lesions, its accuracy in identification of secondary foci and smaller csPCa is less well-established [4–7]. On per lesion analysis, mpMRI misses between 16 and 25.4% of csPCa tumour foci [5, 8]. Also, there is increased difficulty with transition zone tumour identification [9], and mpMRI has been shown to under estimate tumour size by as much as 3 times the actual tumour volume in comparison with whole gland histology [10]. Despite the clinical benefit of mpMRI in biopsy triage, lesion targeting and surgical planning, the limitations of mpMRI restrict its application to replace biopsy.

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that has increased expression in malignant prostate cells, being expressed in > 90% of primary and secondary cases [11]. Accumulating evidence supports the utilization of PSMA positron-emission tomography (PSMA-PET) in prostate cancer staging, with most studies focusing on men who demonstrate biochemical recurrence after treatment for localised disease [11–16]. The limited evidence available suggests superior performance of PSMA-PET in comparison with mpMRI for lesion characterisation and intra-prostatic staging [17–20]. However, due to the small sample size and correlation with radical prostatectomy histopathology in these studies, it is unclear how translatable these findings are to a wider spectrum of PCa patients, including those who will undergo alternative forms of management.

The aim of this study was to evaluate PCa lesion concordance and differences according to 68Ga-PSMA PET/CT avidity and mpMRI as determined by radical prostatectomy and prostate biopsy-based PCa detection.

## Methods

### Study population

In this retrospective analysis of a single-centre's experience, consecutive patients from June 2014 to July 2017 with suspected PCa based on elevated serum prostate-specific antigen (PSA) levels and/or an abnormal digital rectal examination (DRE) underwent a triage mpMRI. Patients with suspicious findings or mpMRI, as well as those with ongoing clinical concern despite a normal MRI underwent a transrectal ultrasound-guided transperineal prostate biopsies (TPB). Once a cancer diagnosis was made, they were then staged using $^{68}$Ga-PSMA PET/CT imaging according to the local departmental protocol [20]. Patients were excluded from the study if they had previously received treatment with radiotherapy.

The study was approved by the Ethics Committee of the Royal Brisbane and Women's Hospital (RBWH) Human Research Ethics Committee (approval number HREC/17/QRBW/644). The initial analysis of this dataset ($n = 58$), being a comparison of mpMRI, $^{68}$Ga-PSMA PET/CT with radical prostatectomy histology, has been published previously [20]. Here, we present an expanded dataset, including patients referred for radiotherapy so more applicable to the general population encountered in a urology clinic, with comparison with biopsy accuracy and a sub-analysis for patients with PCa not visible on mpMRI.

### Magnetic resonance imaging protocol

Our institution utilises a mpMRI-based triage system to select patients for prostate biopsy based on favourable results from cohort and randomised studies [1, 2, 3, 21]. All mpMRI prostate scans were conducted at 3 tesla (Magnetom Skyra, Siemens) without endorectal coil using intravenous contrast (Gadovist 5–15 mL IV dynamic). The mpMRI images were interpreted by both radiologist and treating urologist with experience in prostate mpMRI interpretation of average 15 cases per month and 50 cases per month, respectively. All mpMRI scans were evaluated using the Prostate Imaging Reporting and Data System (PIRADS), transitioning from version 1 to version 2 in 2016 and considering variables such as apparent diffusion coefficient (**ADC**); images were subsequently reported as low-risk (PIRADS 2), equivocal (PIRADS 3) or intermediate/high-risk (PIRADS 4/5) depending on the presence and characteristics of the lesion.

### Prostate biopsy protocol

The decision to biopsy was at the discretion of one of eight treating urologists, based on assessment of mpMRI result, PSA, PSA density (PSAD), PSA kinetics, age, clinical history and examination. In patients with PIRADS 3–5, cognitive directed ultrasound-guided transperineal targeted biopsies were performed through the lesion with systematic biopsies also performed in 91.7% of cases. Patients without a suspicious lesion on mpMRI (PIRADS 2) underwent systematic TPB only. Biopsies were performed under general or spinal anaesthesia, by one of eight consultant urologists or by a

registrar/trainee under consultant supervision. Surgeons reviewed patient's clinical details including PSA and imaging prior to each procedure and made final decision on proceeding to biopsy.

### $^{68}$Ga PSMA PET/CT protocol

The use of $^{68}$Ga PSMA PET/CT was at the discretion of the treating urologist and most commonly requested following PCa diagnosis. PET images were obtained using $^{68}$Ga-PSMA-11 (ABX AG, Germany) manufactured at the Specialised PET Services Queensland Radiopharmaceutical Laboratory. A total of 150 MBq ± 5% of tracer was injected intravenously, 60 min prior to image acquisition. Emission tomographic images were obtained from the skull vertex to thighs, and a low dose CT scan was performed during tidal respiration for attenuation correction and lesion localization. All $^{68}$Ga PSMA PET/CT images were acquired from a Biograph mCT scanner (Siemens Medical Solutions), then evaluated by two experienced nuclear medicine specialists with appropriate viewing software (Syngo.via; Siemens Medical Solutions). Each of our nuclear medicine specialists with urological imaging specialty reads approximately 200 $^{68}$Ga PSMA PET/CT per year. Lesions detected with PET/CT were considered positive for PCa if they demonstrated focal $^{68}$Ga-PSMA uptake significantly higher than background prostatic uptake according to nuclear medicine specialist's interpretation, and equivocal if uptake was only marginally higher than background according to the nuclear medicine specialist's interpretation. The image reports were converted to a 3-point Likert scale (*likely*, *equivocal*, *unlikely*), as previously reported [17]. Furthermore, semi-quantitative analysis using an automated standardized maximum uptake value (SUV max) was considered for each lesion, although these values were not used to report primary lesions, in keeping with local reporting guidelines.

### Histological examination and lesion concordance

Histopathological analysis and reporting was performed according to the International Society of Urological Pathology (ISUP) standard protocols by four experienced uropathologists, and structured according to the 2014 ISUP Gleason Grading Guidelines [22]. Clinically significant disease (csPCa) was defined as PCa with Gleason score 3 + 4 = 7 or greater [23]. Index tumours were defined as the tumour focus with highest Gleason score; if there were two foci with identical tumour grade, the larger focus would be designated as index [24].

For concordance analysis, both whole-gland radical prostatectomy (RP) histology and prostate biopsy histology were analysed. For whole-gland prostate analysis, tumour foci locations were determined according to the sextant-based descriptions included in structured pathology reports [20]. To compare lesions with biopsy histology, biopsy location was described by the operating surgeon and was correlated with both operation and pathology reports. Tumour foci locations, from both the biopsy and RP histopathology, were then compared with lesion locations on each imaging modality. To assess for bias, subgroup analysis was carried out on the biopsy results of patients whom underwent RP.

Tumour foci were allocated to one of four concordance groups, both imaging modalities were concordant with histopathology (concordant; group C), only $^{68}$Ga-PSMA PET/CT was concordant (group P), only mpMRI was concordant (group M), and neither imaging modality was concordant (invisible; group I). All lesions described within the imaging reports for $^{68}$Ga-PSMA PET/CT and mpMRI were considered, as previously described [20].

### Statistical analysis

Relevant patient clinical, imaging and histopathological data was extracted from the hospital database and stored confidentially in Excel. All statistical analysis was performed using the SPSS Statistics v25 (IBM; Armonk, NY, USA). Patient demographics and baseline clinical characteristics were summarized using descriptive statistics. Frequency distribution with percentages were used when summarizing categorical variables, and medians with interquartile range was used to summarize continuous variables. Data was curated into dichotomous or categorical variables for most comparative analyses, except for continuous variables, including prostate volume (PV), PSA, PSAD, SUVmax, ADC and age. Categorical values 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.

## Results

### Demographics

From 653 patients undergoing mpMRI, 344 proceeded to biopsy, of which 144 had a $^{68}$Ga-PSMA PET/CT and were included in the study population (Table 1). $^{68}$Ga-PSMA PET/CT was predominantly used in higher risk men, based on serum PSA (8.60, IQR 6.00–12.75 ng/mL vs 6.40, IQR 4.60–9.45 ng/ml; $p < 0.001$), PSAD (0.242, IQR 0.153–0.322 ng/mL$^2$ vs 0.120, IQR 0.090–0.190; $p < 0.001$) and proportion of patients with Gleason score ≥ 4 + 3 csPCa (47.2% vs 21.20%; $p < 0.001$) when compared with those who did not undergo $^{68}$Ga-PSMA PET/CT. Most mpMRI lesions were PIRADS 4/5 (125; 86.7%). RP was the most common treatment method (49%; Table 1), followed by

**Table 1** Demographic details of the patients including prostatectomy and radiation therapy cohorts; Mann-Whitney test was performed to determine significant differences in prostatectomy cohort to radiation therapy cohort

| Demographics | Total *n* (%) | Prostatectomy *n* (%) | Radiation Therapy *n* (%) | *p* value |
|---|---|---|---|---|
| No. patients | 144 | 71 | 36 | |
| Age | 66.5 (61.75–71.25) | 64 (58.5–67) | 69 (65.8–72.5;) | $p < 0.001$ |
| PSA | 8.6 (6–12.25) | 7.4 (5.5–11) | 10 (7.5–13) | $p = 0.026$ |
| PV | 36.75 (30–51.25) | 35 (28.1–50) | 39 (30.8–51.3) | $p = 0.456$ |
| PSAD | 0.242 (0.153–0.322) | 0.204 (0.148–0.283) | 0.253(0.179–0.339) | $p = 0.138$ |
| mpMRI | | | | |
| PIRADS 2 | 15 (10.4) | 9 (12.7) | 1 (2.8) | |
| PIRADS 3 | 4 (2.8) | 3 (4.2) | 0 | |
| PIRADS 4 | 54 (37.5) | 33 (46.5) | 12 (33) | |
| PIRADS 5 | 71 (49.3) | 26 (36.6) | 23 (63.9) | |
| PSMA | | | | |
| Negative | 5 (3.5) | 3 (4.2) | 0 | |
| Equivocal | 8 (5.6) | 5 (8.5) | 0 | |
| Likely | 131 (91.0) | 62 (87.3) | 36 (100) | |
| Biopsy Histology | | | | |
| Nil cancer | 3 (2.1) | 0 | 0 | |
| 3 + 3 | 5 (3.5) | 1 (1.4) | 0 | |
| 3 + 4 | 68 (47.2) | 38 (53.5) | 15 (41.7) | |
| 4 + 3 | 32 (22.2) | 18 (25.4) | 8 (22.2) | |
| 4 + 4 | 10 (6.9) | 5 (7.0) | 2 (5.6) | |
| ≥4 + 5 | 26 (18.1) | 9 (12.7) | 11 (30.6) | |

radiation therapy (36 patients; 25.9%), androgen deprivation therapy (8.6%), active surveillance (6.5%) and watchful waiting (2.9%), while 9 (6.5%) had incomplete medical documentation at time of publication. The radiation therapy cohort was older, with higher PSA, PSAD and Gleason scores than men who underwent prostatectomy (Table 1). The 3 patients without PCa on biopsy underwent routine PSA surveillance. Index lesion Gleason grade according to RP histopathology were mostly Gleason 3 + 4 = 7 ($n = 41$; 58%), 4 + 3 = 7 ($n = 18$; 25%), and ≥ 4 + 4 = 9 ($n = 12$; 17%).

## Imaging diagnostic performance according to RP histopathology

The RP subset was initially considered as the "gold standard" for histopathological accuracy of index lesions (Table 2). All 71 patients who underwent RP had whole-gland histopathology demonstrating csPCa. For detection of the index lesion, the sensitivities of mpMRI and $^{68}$Ga-PSMA PET/CT were 83.1% vs 90.1% ($p = 0.267$) when *equivocal or likely* lesions were considered, and 80.3% vs 87.3% ($p = 0.267$) when only *likely* lesions were considered. Furthermore, the median size of index tumour foci missed by mpMRI was larger than those missed by $^{68}$Ga-PSMA PET/CT (1.66 cm$^3$; IQR 0.79–2.53 cm$^3$ vs 0.72 cm$^3$; IQR 0.36–1.0 cm$^3$; $p = 0.034$) despite similar serum PSA, prostate volume and PSAD ($p > 0.05$).

$^{68}$Ga-PSMA PET/CT demonstrated 90 lesions (*equivocal or likely*), of which 85 were concordant with csPCa per whole-gland histopathology (specificity 94.4%; Fig. 1a; Table 3). Although mpMRI detected similar total ($n = 74$) and concordant ($n = 68$) lesions compared with $^{68}$Ga-PSMA PET/CT, with specificity not reaching statistical significance (90.7%; $p = 0.55$). In the more likely lesions there was also no statistically significant difference in specificity (Table 3; 97.4% vs 93.8%; $p > 0.05$) between $^{68}$Ga-PSMA PET/CT and MRI.

## Imaging performance according to biopsy histopathology in patients who underwent RP

When biopsy histopathology of the subset of patients who underwent RP was considered (Fig. 1b), the specificity of MRI in detecting csPCa was unchanged, despite identifying fewer lesions (both *likely* and *equivocal or likely*). The specificity of $^{68}$Ga-PSMA PET/CT was slightly reduced to 88.9% in *equivocal or likely* and 94.8% for *likely* only lesions. The specificities of $^{68}$Ga-PSMA PET/CT ($p = 0.570$) or mpMRI ($p = 0.807$) were similar in lesion detection according to RP and biopsy (among those who underwent RP) histopathology.

## Imaging diagnostic performance according to biopsy histopathology in entire cohort

When the entire cohort was considered, there were 141 patients (97.9%) with biopsies positive for PCa, with 136 (94.4%) demonstrating csPCa (Table 2). Considering lesions that were *equivocal or likely* with corresponding biopsy

**Table 2** "Per patient"/index lesion analysis. Histopathology descriptions for imaging lesions which were concordant with whole-gland histopathology (A) and biopsy histopathology (B); *PCa*, prostate cancer; *csPCa*, clinically significant prostate cancer, as defined above (≥ Gleason 3 + 4)

| | | mpMRI | | | | $^{68}$Ga-PSMA PET/CT | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | ≥ PIRADS 3 | % | ≥PIRADS 4 | % | ≥ Equivocal | % | Likely | % |
| A) | | | | | | | | | |
| GS 3 + 3 | 0 | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| GS 3 + 4 | 41 | 33 | 80.49% | 32 | 78.05% | 35 | 85.37% | 33 | 80.49% |
| GS 4 + 3 | 18 | 15 | 83.33% | 14 | 77.78% | 17 | 94.44% | 17 | 94.44% |
| GS 4 + 4 | 1 | 1 | 100.00% | 1 | 100.00% | 1 | 100.00% | 1 | 100.00% |
| GS ≥ 4 + 4 | 11 | 10 | 90.91% | 10 | 90.91% | 11 | 100.00% | 11 | 100.00% |
| PCa | 71 | 59 | 83.10% | 57 | 80.28% | 64 | 90.14% | 62 | 87.32% |
| csPCa | 71 | 59 | 83.10% | 57 | 80.28% | 64 | 90.14% | 62 | 87.32% |
| B) | | | | | | | | | |
| 3 + 3 | 5 | 2 | 40.00% | 2 | 40.00% | 3 | 60.00% | 2 | 40.00% |
| 3 + 4 | 68 | 58 | 85.29% | 56 | 82.35% | 62 | 91.18% | 57 | 83.82% |
| 4 + 3 | 32 | 26 | 81.25% | 26 | 81.25% | 31 | 96.88% | 31 | 96.88% |
| + 4 | 10 | 8 | 80.00% | 8 | 80.00% | 10 | 100.00% | 10 | 100.00% |
| ≥ 4 + 4 | 26 | 25 | 96.15% | 25 | 96.15% | 26 | 100.00% | 26 | 100.00% |
| PCa | 141 | 119 | 84.40% | 117 | 82.98% | 132 | 93.62% | 126 | 89.36% |
| csPCa | 136 | 117 | 86.03% | 115 | 84.56% | 129 | 94.85% | 124 | 91.18% |

histopathology, mpMRI detected significantly fewer cases of csPCa than $^{68}$Ga-PSMA PET/CT (117 vs 129 patients; sensitivity 86.0% vs 94.9%; $p = 0.017$). When looking specifically at the *likely* lesions, the difference in csPCa detection between mpMRI and $^{68}$Ga-PSMA PET/CT was not statistically significant (115 vs 124 patients; sensitivity 84.6% vs 91.2%, $p = 0.064$). Both mpMRI and $^{68}$Ga-PSMA PET/CT had high specificity for csPCa, with *equivocal or likely* lesions detected with specificity of 93.8% and 92.8% and *likely* only with specificity of 95.2% and 95.4%, respectively.

When all lesions on mpMRI and $^{68}$Ga-PSMA PET/CT were considered (Table 3), mpMRI detected less lesions than $^{68}$Ga-PSMA PET/CT. For *likely* only lesions, mpMRI detected 142 lesions, of which 6 (4.2%) were benign and 3 (2.1%) were Gleason 3 + 3, while $^{68}$Ga-PSMA PET/CT detected 164 lesions, of which 11 (6.7%) were benign and 3 (1.8%) were Gleason 3 + 3. For *equivocal* lesions, Gleason 3 + 4 ($n = 7$) and Gleason 3 + 3 ($n = 1$) were detected with both mpMRI and $^{68}$Ga-PSMA PET/CT, while mpMRI harboured a case of Gleason 4 + 3 ($n = 1$) and the remainder were benign (mpMRI $n = 1$, $^{68}$Ga-PSMA PET/CT $n = 11$).

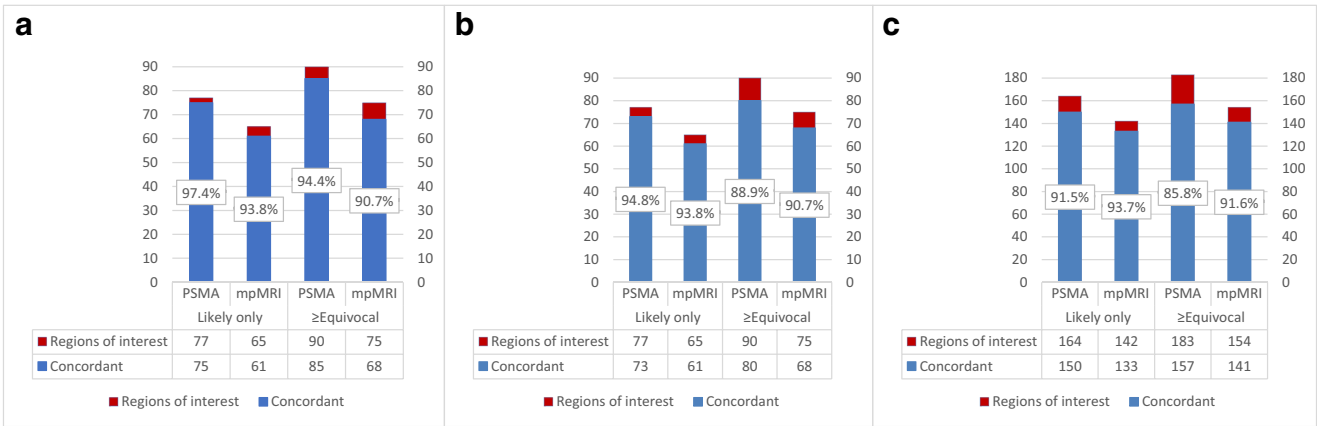


**Fig. 1** Imaging lesion concordance analysis comparing PSMA and mpMRI according to whether the lesions were *equivocal* or *likely* (>= Equivocal) or *likely* only. Percentage of lesions concordant with respective histopathology tumour foci is described. **a** Comparison of PSMA and mpMRI lesions to radical prostatectomy (RP) histopathology. **b** Comparison to biopsy histopathology within radical prostatectomy (RP) cohort. **c** Comparison to biopsy histopathology in entire cohort

## Concordance group analysis

Considering index lesions (Fig. 2a), group "C" was most common, with both imaging modalities detecting 80.1% of the cancerous biopsy regions and 77.5% of RP tumour foci. mpMRI detected an additional 4.3% and 5.6% foci compared with $^{68}$Ga-PSMA PET/CT (group "M"), however $^{68}$Ga-PSMA PET/CT detected an additional 13.5% ($p = 0.005$) and 12.7% ($p = 0.121$) index foci/lesions than mpMRI (group "P" patients) according to biopsy and RP histopathology, respectively. Both imaging modalities missed 2.1% and 4.2% of index foci, which remained "invisible" (group "I"). Considering the RP cohort, SUVmax of group "I" patients were 5.2, 2.9 and 4.22 with histopathology demonstrating Gleason's 4 + 4, 4 + 4 and 4 + 3, with tumour volumes of 1.0 cc, 3.8 cc and 0.2 cc, respectively.

Considering total lesions, or all cancer foci (Fig. 2b), group "C" was most common across each of the cohorts, identifying 64.0% of the cancerous biopsy regions in the entire cohort and 67% of RP tumour foci. mpMRI detected an additional 5.4% and 5.2% foci compared with $^{68}$Ga-PSMA PET/CT (group "M"), however $^{68}$Ga-PSMA PET/CT detected an additional 18.2% ($p < 0.001$) and 19.6% ($p = 0.004$) total foci than mpMRI (group "P" patients) according to biopsy and RP histopathology, respectively. Both imaging modalities missed 12.3% and 8.2% of total foci, which remained "invisible" (group "I"). There were no significant differences between cohorts for any of the concordance groups ("C" $p = 0.388$, "P" $p = 0.528$, "M" = 0.445 and "I" $p = 0.321$). Overall, $^{68}$Ga-PSMA PET/CT detected significantly more lesions than mpMRI for the entire cohort according to both biopsy ($p = 0.004$) and RP histopathology ($p = 0.02$) ($p = 0.004$ and $p = 0.020$, respectively).

**Table 3** Lesions on imaging modality and corresponding Gleason score (GS) for prostatectomy (A; $n = 71$) and biopsy (B; $n = 144$) histopathology

| | mpMRI | | 68Ga-PSMA PET/CT | |
|---|---|---|---|---|
| | PIRADS 3 | ≥PIRADS 4 | Equivocal | Likely |
| A) Prostatectomy | | | | |
| Benign | 3 | 4 | 4 | 1 |
| GS 3 + 3 | 0 | 0 | 0 | 1 |
| GS 3 + 4 | 6 | 34 | 8 | 43 |
| GS 4 + 3 | 1 | 16 | 0 | 20 |
| GS 4 + 4 | 0 | 1 | 1 | 1 |
| GS >4 + 4 | 0 | 10 | 0 | 11 |
| Total | 10 | 65 | 13 | 77 |
| B) Biopsy | | | | |
| Benign | 1 | 6 | 11 | 11 |
| GS 3 + 3 | 1 | 3 | 1 | 3 |
| GS 3 + 4 | 7 | 65 | 7 | 71 |
| GS 4 + 3 | 1 | 34 | 0 | 40 |
| GS 4 + 4 | 0 | 8 | 0 | 11 |
| GS >4 + 4 | 0 | 26 | 0 | 28 |
| Total | 10 | 142 | 19 | 164 |

## PIRADS 2 subgroup analysis

Of 15 patients who had PIRADS 2 mpMRI reports but proceeded to biopsy due to ongoing suspicion of PCa, which was subsequently followed by $^{68}$Ga-PSMA PET/CT in most cases (93.3%), 13 had a positive biopsy, and 11 (73%) had csPCa (Supplementary Table 1). $^{68}$Ga-PSMA PET/CT detected 10 of 13 (76.92%) cases of PCa and 9 of 11 (81.82%) cases of csPCa in patients with PIRADS 2 MRI. Those with PIRADS 2 mpMRI and csPCa had a PSAD of 0.262 (interquartile range; IQR 0.131–0.289) versus PSAD 0.105 (interquartile range; IQR 0.094–0.126) in those without csPCa ($p = 0.138$). Nine of these 11 patients underwent RP, and 5 were found to have Gleason 3 + 4, 3 had Gleason 4 + 3 and 1 had Gleason 4 + 5; median tumour volume was 1.88 cc (IQR 1.01–3.23 cc).

## Discussion

Our data suggests that while both $^{68}$Ga-PSMA PET/CT and mpMRI modalities have excellent rates of prostate cancer index lesion detection, $^{68}$Ga-PSMA PET/CT is superior, especially in detecting secondary cancer foci and smaller lesions, providing additional detection. This superiority was consistent across the entire biopsy cohort and RP subset. These data have significant implications for PCa detection with the increasing use of imaging prior to biopsy and may provide insight into the future of the "PSMA-era".

While previous studies provide conflicting reports as to the superiority of $^{68}$Ga-PSMA PET/CT based on RP specimen when compared with mpMRI [17, 20, 25–27], the current study confirms higher sensitivity for csPCa detection than mpMRI (94.85% vs 86.03%; $p = 0.022$) and incremental benefit of $^{68}$Ga-PSMA PET/CT within a wider population with both RP and biopsy histopathology. Overall, in the biopsy cohort $^{68}$Ga-PSMA PET/CT led to an additional yield of 13.5% on a *per patient* basis and 18.2% in a *per lesion* basis. Thus, $^{68}$Ga-PSMA PET/CT was significantly more sensitive than mpMRI while maintaining high specificity.

Within this cohort, in which a mpMRI-based triage approach was used, an 80% index lesion detection rate was observed for the RP and biopsy cohorts, consistent with substantial local and international evidence supporting the use of mpMRI in improving efficiency of PCa detection [1, 3, 21, 28, 29]. However, concern persists over limitations in mpMRI failure to detect csPCa in 5–15% of patients [1, 21, 30], while up to a third of men will have a secondary focus of csPCa

missed [31]. Indeed, a high detection rate of index lesions is favourable given the evidence that the index lesion is often rich in genomic alterations and potentially the basis for aggressive disease and metastatic spread [32].

Here, the improved sensitivity of $^{68}$Ga-PSMA PET/CT resulted in additional detection yield of 13.5% on a *per patient* basis and 18.2% in a *per lesion* basis, while 2–4% of index lesions were missed with both imaging modalities. When all lesions were considered, approximately 60% concordance was observed, while $^{68}$Ga-PSMA PET/CT and mpMRI contributed an additional approximately 20% and 5% of lesions, respectively. This is consistent with reports on simultaneous $^{68}$Ga-PSMA HBED-CC PET/MRI, where AUC values of 0.83, 0.73 and 0.88 were reported, respectively [33]. Furthermore, $^{68}$Ga-PSMA PET/CT has high sensitivity for detection of Gleason 3 + 4 and 4 + 3 disease, as seen here, as well as by the others [34].

A contributor to the improved sensitivity was detection of index lesions by $^{68}$Ga-PSMA PET/CT in 81.26% of patients with no suspicious lesion on mpMRI (PIRADS 2) but later found to have csPCa on biopsy. While this population is selected toward a diagnosis of PCa, as $^{68}$Ga-PSMA PET/CT was performed after a confirmed diagnosis in most cases, most patients (73%) demonstrated intraprostatic lesions on $^{68}$Ga-PSMA PET/CT. This group also demonstrated other concerning features that would prompt biopsy despite a negative MRI, such as PSA density. A negative $^{68}$Ga-PSMA PET/CT in men with equivocal or negative mpMRI with other concerning features prompting biopsy (e.g. elevated PSA density), $^{68}$Ga-PSMA PET/CT prior to biopsy may facilitate targeted biopsy to improve diagnostic accuracy similar to mpMRI; $^{68}$Ga-PSMA PET/CT used in this context may reduce unnecessary biopsies and their complications [35], as well as decrease the diagnosis of low grade, indolent disease. Emerging evidence suggests PSMA may be a prognostic tool, with PSMA expression on biopsy and RP immunohistochemistry reported to be predictive of disease recurrence [36], as well as lymph node avidity and PSA persistence [37] following surgery. However, prospective studies in the primary diagnostic setting of prostate cancer are required to validate the role of $^{68}$Ga-PSMA PET/CT, above the results already obtained with a MRI-triage approach.

This study has several limitations. Firstly, the order of testing may have affected our result. mpMRI was used as a triage test and for cognitive targeting of biopsies, which may have overestimated its accuracy. Patients underwent $^{68}$Ga-PSMA PET/CT after a diagnosis of prostate cancer and had the mpMRI available for review at the time. While the complete biopsy histology results were not routinely provided on the PSMA PET/CT request form, general comments about histology results on the request form may also have assisted nuclear medicine specialists in identifying lesions, overestimating its sensitivity. Conversely, the true specificity of $^{68}$Ga-PSMA PET/CT may be even higher than reported in the overall cohort because (1) the biopsies were performed with cognitive MRI targeting but not with $^{68}$Ga-PSMA PET/CT; (2) it is well established that systematic biopsies have suboptimal sensitivity in detecting all foci of csPCa and it follows that some foci

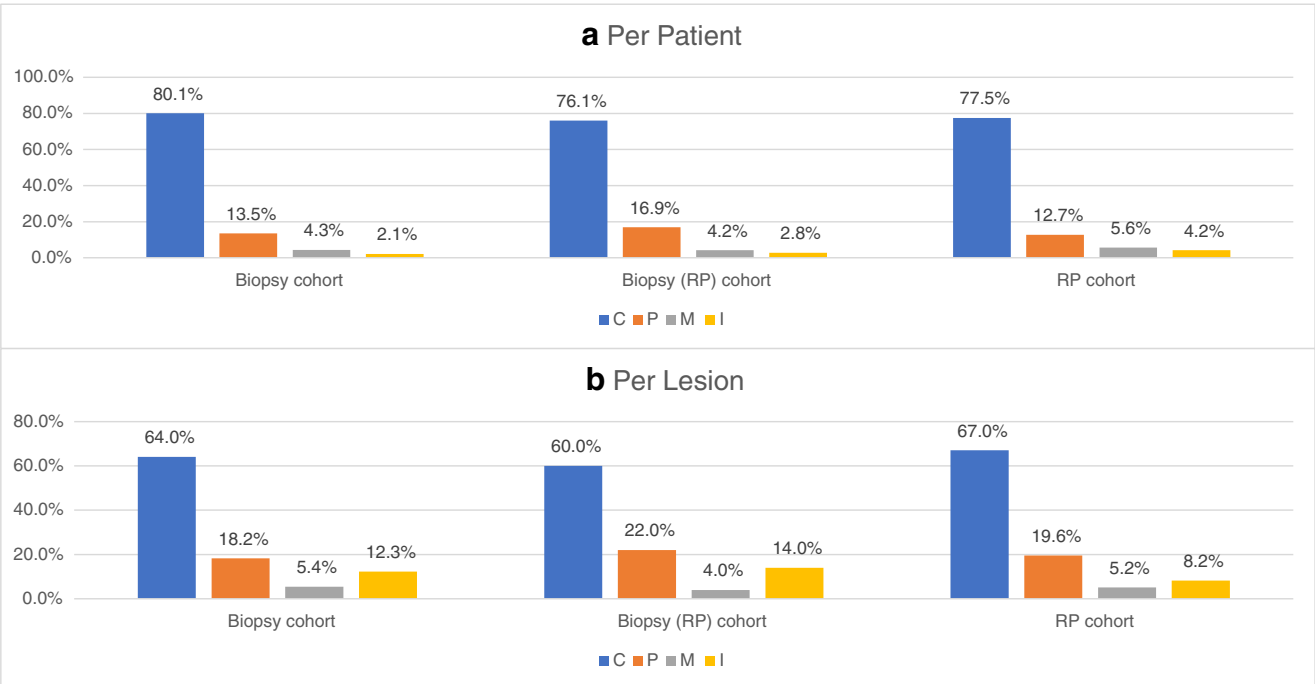


**Fig. 2** Concordance analysis according to index (**a**) and total (**b**) lesions among groups. C concordant; P PSMA positive, MRI negative; M MRI positive, PSMA negative; I "Invisible" i.e. PSMA and MRI negative

detected on imaging will only be detected in the radical prostatectomy specimen. However, the differences across the entire cohort and radical prostatectomy subset were small, supporting the validity of the findings.

In conclusion, our data suggest that while both modalities have excellent rates of prostate cancer index lesion detection, 68Ga-PSMA PET/CT demonstrates superior detection of both index and secondary cancer foci compared with mpMRI, a finding that is consistent across biopsy and RP histopathology. There is increasing evidence supporting the use of $^{68}$Ga-PSMA PET/CT in primary staging following diagnosis [16] as well as re-staging in men who demonstrate biochemical recurrence. The superior diagnostic ability and multifocal tumour identification of $^{68}$Ga-PSMA PET/CT suggests a potential role in the diagnostic pathway, especially in patients with ongoing clinical concern of prostate cancer despite negative mpMRI. The promising results presented here support a PSMA-guided biopsy approach, and the results of prospective trials (ACTRN12618001640291, ClinicalTrials.gov Identifier: NCT03471650) are eagerly awaited.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The study was approved by the Ethics Committee of the Royal Brisbane and Women's Hospital (RBWH) Human Research Ethics Committee (approval number HREC/17/QRBW/644).

**Informed consent** Informed consent was not deemed necessary by the Ethics Committee of the Royal Brisbane and Women's Hospital (RBWH) Human Research Ethics Committee.

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