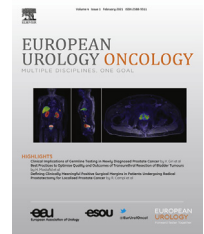


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Combined Utility of ^{68}Ga -Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography and Multiparametric Magnetic Resonance Imaging in Predicting Prostate Biopsy Pathology

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Abstract

Background: ^{68}Ga -Gallium-labelled prostate-specific membrane antigen positron emission tomography (^{68}Ga -PSMA-11 PET) is a valuable staging tool, but its utility in characterising primary prostate cancer remains unclear. The maximum standardised uptake value (SUVmax) is a quantification measure of highest radiotracer uptake within PET-avid lesions.

Objective: To assess the utility of SUVmax in detecting clinically significant prostate cancer (csPCa) on biopsy alone and in combination with multiparametric magnetic resonance imaging (mpMRI).

Design, setting, and participants: This was a retrospective analysis of 200 men who underwent ^{68}Ga -PSMA-11 PET/CT, mpMRI, and transperineal template prostate biopsy between 2016 and 2018.

Outcome measurements and statistical analysis: The primary and secondary outcomes were detection of grade group (GG) 3–5 and GG 2–5 prostate cancer, respectively. We used the Mann-Whitney *U* test to compare SUVmax by GG, and calculated sensitivity and specificity for csPCa detection via ^{68}Ga -PSMA-11 PET/CT, mpMRI, and both. Multivariable logistic regression analyses were used to identify predictors of csPCa on biopsy.

Results and limitations: The median SUVmax was greater for GG 3–5 tumours (6.40, interquartile range [IQR] 4.47–11.0) than for benign and GG 1–2 tumours (3.14, IQR 2.55–3.91; $p < 0.001$). The median SUVmax was greater for GG 3 (5.70, IQR 3.68–8.67) than for GG 2 (3.47, IQR 2.70–4.74; $p < 0.001$). For GG 3–5 disease, sensitivity was 86.5%, 95.9%, and 98.6%, and the negative predictive value (NPV) was 88.4%, 88.5%, and 93.3% using SUVmax ≥ 4 , a Prostate Imaging-Reporting and Data System (PI-RADS) score of 3–5, and both, respectively. This combined model detected more GG 3–5 disease than mpMRI alone (98.6% vs 95.9%; $p = 0.04$).

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SUVmax was an independent predictor of csPCa for GG 3–5 disease only (odds ratio 1.27 per unit, 95% confidence interval 1.13–1.45). Our results are limited by the retrospective study design.

Conclusions: Greater SUVmax on ^{68}Ga -PSMA-11 PET/CT is associated with detection of GG 3–5 cancer on biopsy. The combination of PI-RADS score and SUVmax provides higher sensitivity and NPV than either alone. ^{68}Ga -PSMA-11 PET/CT may be useful alongside mpMRI in improving risk stratification for localised disease.

Patient summary: The amount of a radioactive tracer taken up in the prostate during a type of scan called PET (positron emission tomography) can predict whether aggressive prostate cancer is likely to be found on biopsy. This may complement the more usual type of scan, MRI (magnetic resonance imaging), used to detect prostate cancer.

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1. Introduction

Prostate cancer remains among the most commonly diagnosed cancers worldwide [1]. The clinical utility of multiparametric magnetic resonance imaging (mpMRI) has now shifted towards prebiopsy mpMRI [2]. In deciding between radical treatment and active surveillance, assurance is required that negative imaging truly indicates the absence of clinically significant disease. Despite evidence that mpMRI can reduce overdiagnosis of insignificant prostate cancer [3], there remains a need to further minimise the rates of clinically significant disease missed and undertreatment.

^{68}Ga -labelled prostate-specific membrane antigen positron emission tomography (^{68}Ga -PSMA-11 PET) is used primarily as a staging tool. PSMA is a transmembrane protein found on prostatic cells and overexpressed in prostate cancer [4]. Targeting of PSMA has shown promise in detecting nodal metastases and recurrent disease [5]. The role of ^{68}Ga -PSMA-11 PET/CT in characterising intraprostatic lesions is currently being explored, with promising early results [6,7].

The maximum standardised uptake value (SUVmax) is a measure quantifying the highest radiotracer uptake within a tumour visualised on PET relative to the radiation dose administered, body weight, and time from dose [8]. SUVmax correlates with greater cellular PSMA expression [9], which in turn is associated with higher tumour grade [10]. However, the accuracy of SUVmax in predicting primary tumour grade remains unclear, particularly in low- to intermediate-risk disease [11]. We sought to evaluate the relationship between SUVmax on ^{68}Ga -PSMA-11 PET/CT and tumour grade on prostate biopsy, and any added utility in detecting clinically significant prostate cancer when combined with the Prostate Imaging-Reporting and Data System (PI-RADS) score on mpMRI.

2. Patients and methods

We performed a review of consecutive men who underwent ^{68}Ga -PSMA-11 PET/CT, mpMRI, and transperineal template prostate biopsy across two Australian centres between February 2015 and December 2018 whose data were entered into a prospectively collected ethics committee-approved database (ID 13858, Monash University, Australia).

Indications for imaging and biopsy included elevated prostate-specific antigen (PSA) before diagnosis or repeat biopsy on active surveillance. Men with PI-RADS 1–2 lesions on mpMRI underwent systematic biopsies only, while additional targeted cores were sampled for those with PI-RADS 3–5 lesions on mpMRI. ^{68}Ga -PSMA-11 PET/CT was offered to all patients diagnosed with prostate cancer. Patients undergoing rebiopsy after any treatment, including focal therapy, or restaging for recurrent disease were excluded. Clinical characteristics collected included age, prebiopsy PSA, number of previous biopsies, and active surveillance status.

2.1. Ga -PSMA-11 PET/CT

All patients underwent ^{68}Ga -PSMA-11 PET/CT at one of two institutions. Images were obtained with the ^{68}Ga -labelled HBED-CC ligand for PSMA. The ligand was labelled with $^{68}\text{Ga}^{3+}$ (half-life 67.6 min) from $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generators (iThemba Labs, Cape Town, South Africa; Eckert & Ziegler, Berlin, Germany) by a qualified radiopharmacist. The final product was prepared for administration by dissolution in saline, followed by sterile filtration. PET images were acquired 45–60 min after administration of $2\text{ MBq/kg} \pm 5\%$ of ^{68}Ga -labelled HBED-CC. All ^{68}Ga -PSMA PET/CT imaging was performed using Siemens Biograph mCT or Siemens Biograph Truepoint PET/CT scanners. Emission tomographic images were obtained from the thighs to the vertex. A low-dose CT scan was performed during tidal respiration for attenuation correction and anatomical correlation. Detailed descriptions of the ^{68}Ga -PSMA-11 PET/CT acquisition protocols used are presented in the Supplementary material.

^{68}Ga -PSMA-11 PET/CT images were reviewed by one of two experienced nuclear medicine physicians (Z.E.B., SR) and the presence of focal lesions was reported. SUVmax was calculated by selecting a region of interest within the prostate. The index lesion on ^{68}Ga -PSMA-11 PET/CT was defined as the focal lesion with highest avidity, denoted by SUVmax. Secondary lesions with lower SUVmax were designated as non-index lesions. The index-lesion SUVmax was recorded, along with the highest SUVmax “per segment” in each of the left and right prostatic lobes. There was no defined order for performing mpMRI or ^{68}Ga -PSMA-11 PET/CT; however, patients only underwent PET/CT following diagnosis of prostate cancer.

2.2. mpMRI

All patients underwent mpMRI using a 3-T MRI scanner and all images were reviewed by an experienced MRI radiologist (R.O.S.). Focal lesions on mpMRI were scored according to PI-RADS v2 [12]. The index tumour on mpMRI was defined as the lesion with the highest PI-RADS score. We defined “positive” mpMRI as the presence of a PI-RADS 3–5 lesion. Prostate volume was calculated on mpMRI.

2.3. Prostate biopsy

All patients underwent transperineal template biopsy. All biopsy specimens were analysed by a specialised uropathologist (A.R.) and tumour grade was reported according to the International Society of Pathologists (ISUP) grade group (GG) system (GG 1–5). The biopsy index tumour was defined as the focus of tumour with the highest grade. The index-tumour GG was reported, along with the highest GG “per segment” in each of the left and right prostatic lobes. Our primary outcome was detection of clinically significant disease, defined as GG 3–5 (Gleason score [GS] $\geq 4 + 3 = 7$). The secondary outcome was detection of GG 2–5 disease (GS $\geq 3 + 4 = 7$).

2.4. Statistical analysis

Descriptive statistics were used to summarise clinical, imaging, and biopsy findings. PSA density (PSAD) was calculated using the mpMRI prostate volume. Continuous variables, including SUVmax, were summarised using the median for skewed distributions. Categorical variables were summarised as frequencies. Considering biopsy and PSMA PET/CT findings per segment, SUVmax was compared between ISUP GG scores using the Mann-Whitney *U* test. Segment-based analysis was performed to ensure that SUVmax was compared across all tumour grades, including GG 1 and benign tissue, rather than index tumours only. Considering index lesions on biopsy and imaging of the whole prostate, receiver operating characteristic (ROC) curve analysis was performed for the presence of GG 3–5 and GG 2–5 disease. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for discrete SUVmax thresholds. We also evaluated these performance metrics for PI-RADS 3–5 on mpMRI, and a combination of either SUVmax or PI-RADS 3–5. This composite measure was chosen to maximise both sensitivity in detecting and negative predictive value in excluding significant disease.

We then performed a multivariable logistic regression to predict clinically significant disease of the overall index tumour on biopsy, adjusting for clinical and imaging factors considered in the decision to perform biopsy, including the PI-RADS score for the index lesion on mpMRI and SUVmax for the index lesion on ^{68}Ga -PSMA-11 PET/CT. Statistical significance was set at 0.05 and all *p* values are two-sided. Statistical analysis was performed using R v3.4 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 200 patients were included in our analysis. Demographic data and clinical and imaging characteristics of the index lesions are presented in Table 1. Some 178 men (89%) were undergoing diagnostic biopsy. The median time between mpMRI and prostate biopsy was 27 d (interquartile range [IQR] 13–44). The median time between biopsy and ^{68}Ga -PSMA-11 PET/CT was 14 d (IQR 8–21).

Of the 200 men, 74 (37%) had GG 3–5 and 162 (81%) had GG 2–5 disease on biopsy. Four men (2%) had a negative prostate biopsy. The pathology of the index tumour on biopsy by GG is shown in Table 1.

3.1. Correlation between SUVmax and tumour GG on biopsy

Analysis of SUVmax and tumour GG per prostatic lobe yielded 400 segments from 200 men. The median SUVmax for any prostate cancer was 3.58 (IQR 2.74–5.60), which is

Table 1 – Demographic, PET/CT, mpMRI, and biopsy characteristics

Demographics	
Median age, yr (IQR)	67.5 (61.7–73.1)
Median prostate-specific antigen, ng/mL (IQR)	6.95 (4.70–9.13)
Median prostate-specific antigen density, ng/mL/cm ³ , (IQR)	0.188 (0.131–0.261)
Number of previous biopsies, <i>n</i> (%)	
0	167 (83.5)
1	19 (9.5)
2	10 (5)
3	3 (1.5)
4	1 (0.5)
Prior active surveillance, <i>n</i> (%)	22 (11)
^{68}Ga -PSMA PET/CT	
Median SUVmax for the index lesion (IQR)	4.4 (3.3–6.8)
Median radioactive dose, MBq (IQR)	151 (127–172)
Median time from dose to scan, min (IQR)	64 (60–69)
mpMRI	
Median prostate volume, cm ³ (IQR)	35 (25–41)
Index lesion score, <i>n</i> (%)	
PI-RADS 2	26 (13)
PI-RADS 3	26 (13)
PI-RADS 4	90 (45)
PI-RADS 5	58 (29)
Systematic biopsy	
Median number of cores sampled, <i>n</i> (IQR)	24 (24–24)
ISUP grade group for the index lesion, <i>n</i> (%)	
Benign	4 (2)
Grade group 1	34 (17)
Grade group 2	88 (44)
Grade group 3	50 (25)
Grade group 4	8 (4)
Grade group 5	16 (8)

IQR = interquartile range; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; PSMA PET/CT = prostate-specific membrane antigen positron emission tomography/computed tomography.

greater than the median SUVmax for benign tissue 2.76 (IQR 2.32–3.56; *p* < 0.001).

SUVmax stratified by tumour GG is shown in Table 2. The median SUVmax was significantly greater for GG 3–5 tumours than for benign tissue and GG 1–2 tumours (*p* < 0.001). The median SUVmax was also greater for GG 2–5 tumours than for benign tissue or GG 1 tumours (*p* < 0.001). The proportion of GG 3–5 disease above specific SUVmax thresholds also increased with SUVmax (Fig. 1).

The median SUVmax was greater for GG 3 tumours than for GG 2 tumours (*p* < 0.001) and, in turn, was greater for GG 2 tumours than for GG 1 tumours (*p* < 0.001). However, there was no difference in median SUVmax between benign prostate tissue and GG 1 tumour (*p* = 0.286). Similarly, there was no difference in median SUVmax between GG 3 and GG 4 (*p* = 0.668) or between GG 4 and GG 5 tumours (*p* = 0.117; Fig. 2).

3.2. Detection of clinically significant index tumours

ROC analysis was performed to quantify performance in discriminating clinically significant disease in index tumours among all 200 men. The area under the ROC curve (AUC) using SUVmax was 0.81 for GG 3–5 and 0.71 for

Table 2 – ^{68}Ga -PSMA PET/CT and biopsy characteristics on a per-segment basis (200 patients with 400 segments)^a

^{68}Ga -PSMA PET/CT	
Median SUVmax by individual and pooled ISUP grade groups (IQR)	
Benign tissue	2.76 (2.32–3.54)
Grade group 1	2.96 (2.57–3.54)
Grade group 2	3.47 (2.70–4.74)
Grade group 3	5.70 (3.68–8.67)
Grade group 4	6.84 (4.39–10.8)
Grade group 5	15.2 (5.93–18.5)
Benign tissue and grade group 1	2.89 (2.39–3.54)
Benign tissue and grade groups 1–2	3.14 (2.55–3.91)
Grade groups 1–5	3.58 (2.74–5.60)
Grade groups 2–5	4.39 (2.96–6.87)
Grade groups 3–5	6.40 (4.47–11.0)
Biopsy	
ISUP grade group, n (%)	
Benign tissue	69 (17.2)
Grade group 1	97 (24.2)
Grade group 2	135 (33.8)
Grade group 3	66 (16.5)
Grade group 4	11 (2.8)
Grade group 5	22 (5.5)
IQR = interquartile range; ISUP = International Society of Urological Pathology; PSMA PET/CT = prostate-specific membrane antigen positron emission tomography/computed tomography; SUVmax = maximum standardised uptake value.	
^a Note: PI-RADS scores on mpMRI were unavailable by segment.	

GG 2–5. The AUC using PI-RADS 3–5 was 0.69 for GG 3–5 and 0.74 for GG 2–5 disease.

The sensitivity, specificity, PPV, and NPV were identified at SUVmax thresholds (Table 3). Using ^{68}Ga -PSMA-11 PET/CT alone, an SUVmax threshold of 4.0 yielded high sensitivity of 86.5% and NPV of 88.4% for detection of GG 3–5 disease, and 63% and 30.2%, respectively, for GG 2–5.

All 200 patients underwent mpMRI, of whom 174 (87%) had an index lesion on mpMRI scored as PI-RADS 3–5

(Table 1). PI-RADS 3–5 scores on mpMRI demonstrated high sensitivity of 95.9% and NPV of 88.5% for detection of GG 3–5 disease (Table 3) and 92.6% and 53.8%, respectively for GG 2–5.

A combined model using either SUVmax greater than a set threshold or PI-RADS 3–5 scores resulted in greater sensitivity and NPV compared to either modality alone (Table 3). A combination of either SUVmax >4.0 or PI-RADS 3–5 yielded sensitivity of 98.6% and NPV of 93.3% for detection of GG 3–5 disease, and 96.9% and 66.7%, respectively, for GG 2–5 (Supplementary Fig. 1). Among the 74 men with GG 3–5 disease, 73 (98.6%) were identified using this combined model, compared to 71 (95.9%) with mpMRI alone ($p = 0.04$) and 64 (86.5%) with ^{68}Ga -PSMA-11 PET/CT alone ($p = 0.14$).

3.3. Using ^{68}Ga -PSMA PET/CT to differentiate equivocal lesions on mpMRI

^{68}Ga -PSMA-11 PET/CT also showed utility in both confirming and excluding high-grade disease in men with equivocal lesions on mpMRI. Some 26 of 200 men (13%) had a PI-RADS 3 index lesion on mpMRI, of whom five (19.2%) had GG 3–5 disease. Four of these five patients had SUVmax >4. Conversely, 21 of 26 men (80.8%) with a PI-RADS 3 index lesion had a benign biopsy or GG 1–2 tumour. Fourteen (66.7%) of these had SUVmax >4. Fifteen men had a PI-RADS 3 index lesion and SUVmax <4, of whom one man (6.7%) had GG 3–5 disease. Similarly, 15 men had a PI-RADS 1–2 tumour and SUVmax <4, of whom one (6.7%) had GG 3–5 disease.

3.4. Multivariable regression

Results for the multivariable logistic regression are shown in Table 4. SUVmax was an independent predictor of clinically significant disease, defined as GG 3–5 (odds ratio

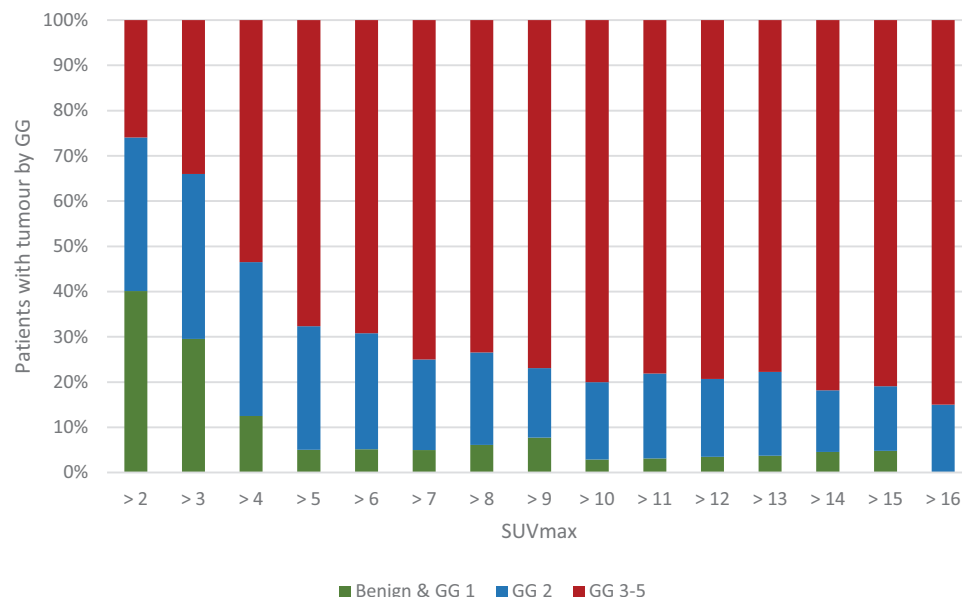


Fig. 1 – Cumulative distribution of tumour grade group (GG) above maximum standardised uptake value (SUVmax) cutoff thresholds.

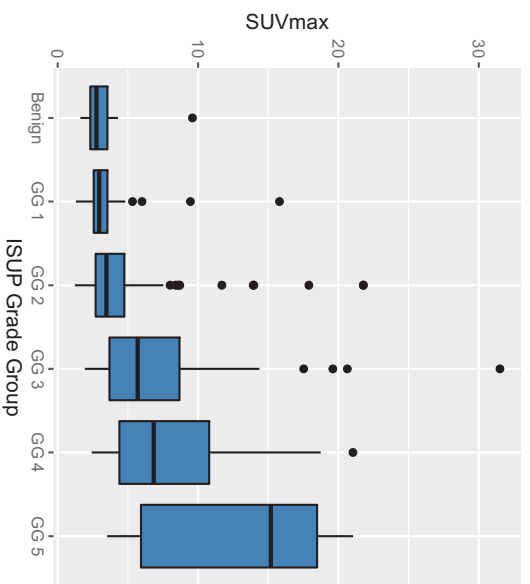


Fig. 2 – Maximum standardised uptake value (SUVmax) stratified by International Society of Urological Pathology grade group (GG) on biopsy.

1.27 per unit increase, 95% confidence interval 1.13–1.45), but not GG 2–5 cancer.

4. Discussion

Accurate risk stratification lies at the crux of contemporary management of localised prostate cancer. The decision to biopsy and subsequently treat is complex, and has traditionally relied on PSA and tumour grade. ^{68}Ga -PSMA-11 PET/CT has emerged as an adjunct to MRI in the diagnostic algorithm. We confirmed a positive relationship between SUVmax on ^{68}Ga -PSMA-11 PET/CT and clinically significant prostate cancer on transperineal template biopsy. To the best of our knowledge, this is the largest published series comparing ^{68}Ga -PSMA-11 PET/CT and mpMRI in quantifying biopsy pathology in men with localised prostate cancer.

We found that ^{68}Ga -PSMA-11 PET/CT has high sensitivity for clinically significant prostate cancer, and that GG 3–5 tumours are associated with higher SUVmax than GG 1–2 and benign lesions. These findings are consistent with studies in cohorts of men with intermediate- to high-risk and metastatic disease that reported high sensitivity for intraprostatic tumours [11,13] and significant differences in SUVmax between benign and malignant tissue [14]. Reports also support the utility of SUVmax in differentiating GS 6 from GS 7 [15], and GS 6–7 from GS ≥ 8 tumours [16].

In addition, SUVmax predicts GG 3–5 disease, independent of clinical and mpMRI findings. An Australian study of 20 men undergoing ^{68}Ga -PSMA-11 PET/CT reported a similar relationship between SUVmax and GS $\geq 3+4=7$ tumours, despite only moderate correlation with PSA or tumour volume [15]. In combination with our findings, this suggests that SUVmax holds diagnostic utility alongside existing clinical variables.

Table 3 – Detection of clinically significant disease (GG 2–5 or GG 3–5) using SUVmax, PI-RADS score, and their combination on a per-patient basis^a

	Outcome: GG 2–5 disease				Outcome: GG 3–5 disease			
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
^{68}Ga -PSMA PET/CT alone								
SUVmax threshold 3.0	84.6 (78.1–89.8)	21.1 (9.6–37.3)	82.0 (75.4–87.5)	24.2 (11.1–42.3)	91.9 (83.2–97.0)	21.4 (14.6–29.6)	40.7 (33.2–48.6)	81.8 (64.5–93.0)
SUVmax threshold 3.5	75.9 (68.6–82.3)	50.0 (33.4–66.6)	86.6 (79.9–91.7)	32.8 (21.0–46.3)	90.5 (81.5–96.1)	40.5 (31.8–49.6)	47.2 (38.8–55.7)	87.9 (76.7–95.0)
SUVmax threshold 4.0	63.0 (55.0–70.4)	68.4 (51.3–82.5)	89.5 (82.3–94.4)	30.2 (20.8–41.1)	86.5 (76.5–93.3)	60.3 (51.2–68.9)	56.1 (46.5–65.4)	88.4 (79.7–94.3)
SUVmax threshold 4.5	57.4 (49.4–65.1)	84.2 (68.7–94.0)	93.9 (87.3–97.7)	31.7 (22.8–41.7)	82.4 (71.8–90.3)	69.8 (61.0–77.7)	61.6 (51.3–71.2)	87.1 (79.0–93.0)
SUVmax threshold 5.0	50.0 (42.1–57.9)	92.1 (78.6–98.3)	96.4 (89.9–99.3)	30.2 (22.0–39.4)	78.4 (67.3–87.1)	79.4 (71.2–86.1)	69.0 (58.0–78.7)	86.2 (78.6–91.9)
mpMRI alone								
PI-RADS 3–5	92.6 (87.4–96.1)	36.8 (21.8–54.0)	86.2 (80.2–91.0)	53.8 (33.4–73.4)	95.9 (88.6–99.2)	18.3 (11.9–26.1)	40.8 (33.4–48.5)	88.5 (69.8–97.6)
PI-RADS 4–5	82.7 (76.0–88.2)	63.2 (46.0–78.2)	90.5 (84.6–94.7)	46.2 (32.2–60.5)	89.2 (79.8–95.2)	34.9 (26.6–43.9)	44.6 (36.4–53.0)	84.6 (71.9–93.1)
Combined ^{68}Ga -PSMA PET/CT and mpMRI								
SUVmax 3.5 or PI-RADS 3–5	98.1 (94.7–99.6)	15.8 (6.0–31.3)	83.2 (77.2–88.2)	66.7 (29.9–92.5)	98.6 (92.7–100)	6.3 (2.8–12.1)	38.2 (31.3–45.5)	88.9 (51.8–99.7)
SUVmax 4.0 or PI-RADS 3–5	96.9 (92.9–99.0)	26.3 (13.4–43.1)	84.9 (78.9–89.7)	66.7 (38.4–88.2)	98.6 (92.7–100)	11.1 (6.2–17.9)	39.5 (32.4–46.9)	93.3 (68.1–99.8)
SUVmax 4.5 or PI-RADS 3–5	96.3 (92.1–98.6)	34.2 (19.6–51.4)	86.2 (80.3–90.9)	68.4 (43.4–87.4)	98.6 (92.7–100)	14.3 (8.7–21.6)	40.3 (33.1–47.9)	94.7 (74.0–99.9)
SUVmax 5.0 or PI-RADS 3–5	95.7 (91.3–98.2)	36.8 (21.8–54.0)	86.6 (80.7–91.2)	66.7 (43.0–85.4)	98.6 (92.7–100)	15.9 (10.0–23.4)	40.8 (33.5–48.4)	95.2 (76.2–99.9)

GG = grade group; mpMRI = multiparametric magnetic resonance imaging; NPV = negative predictive value; PI-RADS = Prostate Imaging-Reporting and Data System; PPV = positive predictive value; PSMA PET/CT = prostate-specific membrane antigen positron emission tomography/computed tomography; SUVmax = maximum standardised uptake value.

^a Results presented with the 95% confidence interval in parentheses.

Table 4 – Multivariable logistic regression model for detection of clinically significant disease (GG 2–5 or GG 3–5) on transperineal template biopsy

Variable	Outcome: GG 2–5 disease		Outcome: GG 3–5 disease	
	AOR (95% CI)	p value	AOR (95% CI)	p value
Age	1.16 (1.10–1.25)	<0.001*	1.06 (1.01–1.11)	0.011*
PSAD (per ng/mL/cm ³ increase)	1.34 (0.90–2.25)	0.22	0.85 (0.19–6.80)	0.86
AS status				
Not on AS	1 (reference)		1 (reference)	
Prior AS	1.16 (0.34–4.32)	0.82	0.88 (0.22–2.94)	0.84
SUVmax for the index lesion (per unit increase)	1.20 (0.99–1.60)	0.13	1.27 (1.13–1.45)	<0.001*
PI-RADS score for the index lesion				
PI-RADS 2	1 (reference)		1 (reference)	
PI-RADS 3	3.58 (0.97–14.3)	0.061	2.27 (0.46–13.01)	0.32
PI-RADS 4	18.5 (5.25–75.5)	<0.001*	3.31 (0.94–15.78)	0.09
PI-RADS 5	8.14 (2.04–37.1)	0.004*	4.31 (1.14–21.5)	0.045*

AOR=adjusted odds ratio; AS=active surveillance; CI=confidence interval; GG=grade group; PI-RADS=Prostate Imaging-Reporting and Data System; PSAD=prostate-specific antigen density; SUVmax=maximum standardised uptake value.

* Significant p value.

⁶⁸Ga-PSMA-11 PET/CT may be useful in clinical situations in which mpMRI is unavailable or impractical. An Italian group assessed 45 men with negative mpMRI, or no mpMRI because of contraindications, undergoing ⁶⁸Ga-PSMA-11 PET/CT-guided biopsy and found higher SUVmax (>5.4) for GS ≥ 7 disease than for benign tissue/GS 6 [17]. In our cohort, use of SUVmax >4 alone yielded slightly lower sensitivity than PI-RADS 3–5 for the detection of GG 3–5 disease, but improved the specificity and PPV.

PI-RADS 3 lesions on mpMRI pose a diagnostic dilemma, as the likelihood of clinically significant cancer is equivocal [12,18,19]. Men with PI-RADS 3 lesions often proceed to biopsy because of an inability to confidently exclude aggressive disease. SUVmax may provide additional risk stratification information, as low SUVmax values were observed for two-thirds of men with PI-RADS 3 lesions and low-risk biopsy pathology.

The combination of PI-RADS with SUVmax yielded higher sensitivity and NPV than either modality alone in our cohort. This has important implications for both diagnosis and treatment. High SUVmax on ⁶⁸Ga-PSMA-11 PET/CT may provide a reason to pursue treatment or early rebiopsy in men with favourable intermediate-risk disease being considered for active surveillance, or men with high clinical suspicion for high-grade disease despite benign/low-grade findings on MRI-targeted biopsy. However, combining SUVmax 4.0 and PI-RADS 3–5 resulted in a higher NPV for GG 3–5 (93.3%) than for GG 2–5 (66.7%), suggesting that low SUVmax excludes high-grade disease, but not GG 2 cancer reliably. The combination of modalities also resulted in a reduction in specificity and PPV, the former probably because of the high prevalence of disease in our cohort.

Our results raise the potential of a combined PET/MRI approach as the ideal imaging tool for characterising primary disease. ⁶⁸Ga-PSMA-11 PET adds high sensitivity and staging accuracy to the anatomical detail afforded by mpMRI [5], and early studies have shown promising results in localisation [20] and prediction of the primary tumour

grade [21]. A small study of combined PET/MRI imaging showed utility in the setting of a prior negative biopsy [22]. Not all lesions visible or invisible on mpMRI are detected using ⁶⁸Ga-PSMA-11 PET/CT [7] and hence men with suspicious PSA or mpMRI require a biopsy irrespective of SUVmax.

Our findings are strengthened by the use of systematic transperineal template biopsy in all patients, with additional targeting of any mpMRI-visible lesions. We used biopsy pathology to mitigate any selection bias associated with radical prostatectomy specimens, as men proceeding to surgery are of inherently higher risk and may be radiologically distinct from men who are conservatively managed. We are conducting further analyses comparing ⁶⁸Ga-PSMA-11 PET/CT results to radical prostatectomy specimens.

Our study has a number of limitations. First, owing to its retrospective and observational nature, the MRI radiologists and nuclear medicine physicians were not blinded to the results of the opposing test when reporting scans. Patients commonly underwent mpMRI before PET/CT, so there is potential for overestimating the sensitivity of PET/CT. Second, although absolute SUVmax values in our cohort correlate well with published values, variations may exist because of differences in scanner calibration [14,23]. Therefore, SUVmax thresholds may not yet be generalisable across sites, and larger multicentre studies using different types of PET/CT scanner may be required to validate the reproducibility. Nevertheless, our results support the use of SUVmax as a spectrum to facilitate the decision between conservative and definitive therapy.

5. Conclusions

GG 3–5 tumours on biopsy are associated with greater SUVmax than benign or GG 1–2 tumours on ⁶⁸Ga-PSMA-11 PET/CT, independent of MRI findings. When combined with mpMRI, ⁶⁸Ga-PSMA-11 PET/CT improves the already excellent sensitivity and NPV of PI-RADS scoring of mpMRI for GG

3–5 disease. This improvement is less prominent for GG 2–5 cancer. ^{68}Ga -PSMA-11 PET/CT may be a useful adjunct to mpMRI in better risk stratification of intermediate-risk prostate cancer.

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Acquisition of data: Frydenberg, Kalapara, Ballok, Ramdave, O'Sullivan, Ryan, Grummet.

Analysis and interpretation of data: Frydenberg, Kalapara.

Drafting of the manuscript: Frydenberg, Kalapara.

Critical revision of the manuscript for important intellectual content: Frydenberg, Ballok, Ramdave, O'Sullivan, Ryan, Konety, Grummet.

Statistical analysis: Kalapara.

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Appendix A. Supplementary data

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