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The PRIMARY Score: Using intra-prostatic PSMA PET/CT patterns to optimise prostate cancer diagnosis.

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ABSTRACT

Background

Multi-parametric magnetic resonance imaging (mpMRI) is validated for the diagnosis of clinically significant prostate cancer (csPCa). ^{68}Ga-PSMA -11 PET/CT (PSMA-PET/CT) combined with mpMRI has improved negative predictive value over mpMRI alone for csPCa. The aim of this post-hoc analysis of the PRIMARY study was to evaluate the clinical significance of patterns of intra-prostatic PSMA activity, proposing a 5- point PRIMARY score to optimise accuracy of PSMA-PET/CT for csPCa in a low prevalence population.

Methods

The PRIMARY trial is a prospective multi-centre phase II imaging trial that enrolled biopsy-naïve men with suspected PCa, no prior biopsy, recent mpMRI (6 months) and planned for prostate biopsy. 291 men underwent mpMRI, PSMA-PET/CT and systematic +/- targeted biopsy. The mpMRI was read separately using PI-RADS (V2). PSMA-PET/CT (pelvic only) was acquired a minimum 60 minutes post injection. PSMA-PET/CT was centrally read for pattern (diffuse transition zone (TZ), symmetrical central zone (CZ), focal TZ or peripheral zone (PZ), and intensity (SUVmax). In this post-hoc analysis, a 5-level PRIMARY score was assigned based on analysis of the central read: 1. No pattern, 2. Diffuse TZ or CZ (no focal), 3. Focal TZ, 4. Focal PZ or 5. SUVmax ≥ 12. Two further readers independently assigned a PRIMARY score to 118 scans for inter-rater agreement. Associations between PRIMARY score and csPCa (ISUP≥2) were evaluated.

Results

Of 291 men enrolled, 162 (56%) had csPCa. PRIMARY score-1 was present in 16% (47), score-2 in 19% (55), score-3 in 10% (29), score-4 in 40% (117) and score-5 in 15% (43). The proportion of patients with csPCa and PRIMARY score 1 to 5 was 8.5% (4/47), 27% (15/55), 38% (11/29), 76% (89/117) and 100% (43/43) respectively. Sensitivity, specificity, PPV and NPV for PRIMARY score 1,2 (low-risk patterns) vs PRIMARY score 3-5 (high-risk patterns) was 88%, 64%, 76% and 81%, compared to 83%, 53%, 69% and 72% for PI-RADS (2 vs 3-5) on mpMRI. The inter-rater agreements for PRIMARY score 1,2 vs. PRIMARY score 3-5 was 0.76 (CI: 0.64-0.88) and 0.64 (CI: 0.49-0.78).

Conclusion

A PRIMARY score incorporating intra-prostatic pattern and intensity on PSMA-PET/CT shows potential with high diagnostic accuracy for csPCa. Further validation is warranted prior to implementation.

Key Words

PSMA, prostate specific membrane antigen, PET, Multi-parametric MRI, prostate cancer, diagnosis.

INTRODUCTION

Multiparametric MRI (mpMRI) is currently standard of care for the diagnosis of prostate cancer with validated standardisation of reporting using PI-RADS v2 (*1*). However, PSMA PET/CT has recently been reported to demonstrate similar diagnostic accuracy to MRI for the diagnosis of prostate cancer, with significant improvement in NPV if the two modalities are used in combination(*2*). The specificity of PSMA PET/CT for clinically significant prostate cancer (csPCa) in the PRIMARY trial was lower than previously published, likely due to the lower prevalence of csPCa (*3,4*). In a screening setting, PSMA activity in intra-prostatic processes such as benign prostatic hypertrophy, prostate intra-epithelial neoplasia and low grade ISUP 1 malignancy can be difficult to distinguish from csPCa on PSMA intensity alone. Current interpretation of intra-prostatic PSMA PET/CT depends on the level of uptake being greater than background activity for the detection of tumour. By contrast, the MRI PI-RADS system utilises intra-prostatic anatomy, differentiating the peripheral and transition zones to better categorise likelihood of malignancy. As the majority of prostate cancers arise within the peripheral zone (PZ), incorporating anatomic differentiation helps improve diagnostic certainty. It is unknown whether the incorporation of anatomic localization, and pattern characterisation can improve the diagnostic accuracy of PSMA PET/CT in a pre-biopsy patient population. The aim of this post-hoc analysis of the PRIMARY study was to explore the value of intra-prostatic PSMA PET/CT patterns and intensity scores, developing a 5-level score to improve diagnostic accuracy for csPCa.

MATERIALS AND METHODS

Study Design

The PRIMARY trial is a prospective multi-centre, phase II imaging trial conducted across 3 academic institutions in Australia (*5*). The study protocol was approved by the St. Vincent's Hospital institutional review board (HREC/18/SVH/239), and all patients provided written consent. The study was registered with ANZCTR (ANZCTRN12618001640291) with protocol and initial results previously published(*2,5*). This was a pos-hoc analysis of the PRIMARY trial to evaluate the diagnostic performance of a 5-point scoring system to detect csPCa.

Screening

Men were considered eligible for the trial if there was clinical suspicion of prostate cancer based on abnormal PSA (<20ng/ml) or abnormal digital rectal examination after assessment by a study urologist. Men were excluded if they had a prior diagnosis of prostate cancer, prostate biopsy or prostate MRI. All men underwent multi-parametric MRI (mpMRI) within 6 months and were consented for trans-perineal systematic +/- targeted biopsy. Men with low-risk MRI (PI-RADS 1), or PI-RADs 2 with low-risk clinical features not planned for biopsy, were not enrolled.

MRI

mpMRI was performed and reported locally by the urology investigator preferred sub-specialist prostate MRI radiologist, reported as per the prostate imaging-reporting and data system version 2 (PI-RADS v2). In all cases where a lesion was identified on mpMRI, images were provided to the treating investigator for MRI targeted biopsy. PI-

RADS score and location was documented for each lesion, in addition to overall prostate volume. A PI-RADS score 3-5 was defined as positive for analysis.

PSMA PET Acquisition

A pelvic only PSMA PET/CT was undertaken at a minimum 60 minutes following administration of 1.8– 2.2 MBq/kg ^{68}Ga-PSMA-11 and acquired using a low dose non-contrast CT protocol (3 minutes per bed position). This limited protocol reduced radiation dose to less than 4 mSv, appropriate to the screening context. PET/CT cameras at all 3 participating centres were harmonised via standardised phantom calibration through the Australasian Radiopharmaceutical Trials Network (ARTnet). An initial local PSMA read was undertaken and local readers provided key images to treating urologists to allow PSMA targeting at biopsy. Pelvic lymph nodes and metastatic disease were documented and if identified, sites undertook whole body PSMA PET outside of protocol (6.2% of patients had additional whole body PSMA PET.

PSMA PET Interpretation

All PSMA PET were centrally read by two experienced nuclear medicine specialists (LE, JB) blinded to the previous MRI imaging and clinical outcomes. Differentiation between the peripheral zone (PZ), central zone (CZ) or transition zone (TZ) was undertaken using the fused PET/CT images and known anatomic definitions of zonal boundaries (Figure 1). Readers interrogated the PSMA PET/CT for specific patterns: diffuse TZ activity (Pattern A), symmetrical CZ activity (Pattern B), and focal PZ (Pattern C) or focal TZ activity (Pattern D) (Figure 1). All patterns were documented, as was uptake (SUVmax) of each prostate quadrant with the single highest value used for analysis.

A region was defined as TZ if centrally placed within the prostate, with no PSMA activity extending to the edge of the prostate margin on the CT using the fused PET/CT images (Figure 1, pattern A). Symmetrical CZ activity was localised to the CZ with no PSMA activity extending to the prostate margin on the fused PET/ CT (Figure 1, pattern B). If symmetrical CZ activity extended to the posterior margin of the prostate on fused PET/CT, this was classified as PZ as well as CZ activity. Focal activity within the TZ was defined visually as more than twice background TZ activity (Figure 1, pattern C). All findings within the prostatic apex were defined as PZ, as were all findings that included the peripheral margin of the prostate on the fused PET/CT images (Figure 1, pattern D). Any focal activity in the PZ was considered abnormal. No SUV minimal threshold was utilized excepting those lesions that had very high intensity (SUV max > 12).

A PRIMARY score utilising the combination of pattern information and SUVmax was assigned to each patient. Score 1: No pattern, low grade activity. Score 2: Diffuse TZ or symmetrical CZ activity without focal uptake (This included diffuse TZ activity with irregular focal uptake that is not well above background TZ activity). Score 3: Focal TZ activity (Focal TZ activity must be visually above twice background TZ activity). Score 4: Focal PZ activity, and Score 5: Any pattern with SUVmax ≥ 12 (Table 1).
In some cases, multiple patterns were identified, and the PRIMARY score represented the most clinically significant pattern (Focal pattern above diffuse or symmetrical, peripheral above transition, and SUVmax > 12 above any reported pattern).
Differentiating CZ activity from PZ activity in the posterior basal prostate (where the PZ may be thin) can be difficult, and if there was any doubt the readers were asked to classify this as a PRIMARY score 4 rather than a PRIMARY score 2.

A further two blinded independent reads (VL, BH) was undertaken for a random sample of 120 PSMA PET/CT scans by 2 experienced nuclear medicine specialists following a training set explanation of the PRIMARY 5-point score definitions and criteria. These additional reads were used to determine inter-rater variability of the PRIMARY score. No a-priori hypothesis for a minimum acceptable concordance measure was considered. Two patient's imaging was not immediately available for remote interrogation leaving 118 pairs of evaluable concordance reads.

Prostate Biopsy and Histopathology

Systematic trans-perineal prostate biopsies with a recommended minimum 18 cores (dependent on prostate volume) were mandated. Additional targeted biopsies were obtained, when possible, with all urology investigators provided with key images to demonstrate sites of both MRI and/ or PSMA PET abnormalities prior to biopsy. All biopsies were processed and reported according to Grade group protocols by sub-specialist uro-pathologists at each study centre. For analysis, any overall ISUP grade group ≥ 2 on biopsy (systematic or targeted) was considered csPCa.

Statistical Analysis

In addition to basic descriptive statistics, the AUC for the five-level PRIMARY score and Pi-RADS were compared using the DeLong test, though note there was no *a priori* hypothesis. Inter-rater agreement was evaluated with Cohen's kappa and associated confidence intervals were provided by the *kappaetc* command. The interaction between SUVmax and PSMA pattern type (none, non-focal, focal) was explored in a logistic regression model where both variables and an interaction term were simultaneously

entered. The estimated marginal probabilities of csPCa versus SUVmax plotted per pattern type. Stata v16.0MP (College Station, TX) was used for analysis.

RESULTS

In total, 291 men with a median age of 64 years (IQR: 59-70) underwent MRI, PSMA PET/CT and biopsy. 162 (56%) men had clinically significant malignancy (ISUP ≥ 2) on biopsy and 196 (67%) had a positive MRI (PI-RADS 3-5). 47 patients (16%) had no pattern identified on PSMA PET/CT, 97 (33%) exhibited either diffuse TZ or symmetrical CZ activity, 53 (18%) had focal TZ activity and 155 (53%) had focal activity in the PZ (Table 1).

PRIMARY Score

The PRIMARY score distribution was score 1: 16% (n=47), score 2: 19% (n=55), score 3: 10% (n=29), score 4: 40% (n=117), and score 5: 15% (n=43) (Table 2, Figure 2). The proportion of men with csPCa and a PRIMARY score of 1 to 5 was 8.5% (4/47), 27% (15/55), 38% (11/29), 76% (89/117) and 100% (43/43) respectively. The estimated AUC of the five-level PRIMARY score was 0.85 (95%CI: 0.81 – 0.89) and exceeded that of PI-RADS 0.76 (95%CI: 0.71 – 0.81), p-value=0.003 (Figure 3). Sensitivity, specificity, PPV and NPV for PRIMARY score 3 to 5 (high risk patterns) vs. PRIMARY score 1,2 (low risk patterns) was 88%, 64%, 76% and 81%, compared to 83%, 53%, 69% and 72% for PI-RADS 3-5 vs 2 (Table 3 and supplemental table 1).

Inter-rater Agreement

Two further readers assessed PSMA PET in 118 patients (51% had csPCa). Cohen's kappa for PRIMARY score 1,2 vs PRIMARY score 3-5 for reader 1 was 0.76 (95%CI: 0.64-0.88) and 0.64(95%CI: 0.49-0.78) for reader 2. Cohen's Kappa for the five-point PRIMARY score was 0.73 (95%CI: 0.63 – 0.83) for reader 1 and 0.56 (95%CI: 0.45 – 0.68) for reader 2. Diagnostic performance of the PRIMARY score as used by the readers was broadly similar to the central read (Table 3).

PRIMARY Score and Overall Grade Group

Overall grade group (GG) on histopathology was associated with PRIMARY score (Figure 4). All four patients with PRIMARY score 1 and csPCa had GG 2 cancer. For PRIMARY score 2, 2/55 (4%) had GG ≥ 3 cancer. Conversely for PRIMARY score 5, 27/43 (63%) were GG ≥ 3 cancer. For PI-RADS 2 patients, 10/95 (11%) had GG ≥ 3 cancer, while 5/53 (9.4%) of PI-RADS 5 patients had no csPCa.

Pattern and Intensity

Exploring the effect of SUVmax on prediction of csPCa for different pattern types (none, non-focal, focal), an increasing SUVmax was associated with a higher likelihood of malignancy only with focal patterns. Increasing SUVmax did not raise the predicted probability of csPCa in patients without a pattern or those with non-focal patterns (diffuse TZ or symmetrical CZ) (Figure 5).

DISCUSSION

Multiparametric MRI is accepted standard of care for the diagnosis of prostate cancer, with the PRECISION trial demonstrating improved detection of significant malignancy and safe reduction in the number of biopsies required relative to prostate biopsy alone(*6*). PSMA PET/CT has high level evidence for its use in the staging of prostate cancer (*7*) and in biochemical recurrence following definitive primary therapy(*8-10*). However, there is little evidence for its value in the diagnosis of primary tumours(*11-13*). The PRIMARY trial recently showed that a limited field of view pelvic PSMA PET/CT combined with mpMRI significantly improved both sensitivity and negative predictive value compared to mpMRI alone in the diagnosis of prostate cancer(*2*). This PRIMARY sub-study has identified key patterns of intra-prostatic PSMA activity, determining those more likely to be benign, and those most likely to demonstrate malignancy. The initial PRIMARY study analysis utilised a minimum PSMA SUVmax cut-off [4.0] with expert reader analysis, finding a sensitivity of 90% with a specificity of 50% for csPCa. However, this method is not valid across unharmonized PET cameras and with variable PSMA ligands. Utilising key patterns within the PRIMARY score in this sub-study improved specificity without compromising sensitivity for the diagnosis of csPCa. Further, use of pattern and intensity within a 5-level score (PRIMARY) was reproducible between readers with a higher/ equivalent diagnostic accuracy for the detection of csPCa compared to mpMRI.

The prostate imaging – reporting and data system (PI-RADS) is a 5 point scale recommended for reporting of prostate MRI by a European consensus meeting in 2011 (*14*) The PI-RADS system reports by prostatic zone, separating the peripheral zone

from the transition and central zones while incorporating semiquantitative measures such as apparent diffusion coefficient maps and diffusion weighted imaging. The incidence of prostate malignancy varies by zonal location within the prostate, a fact that is utilised by PI-RADS to improve accuracy. Histopathological analysis from prostatectomy specimens have found that malignancy arises from the peripheral zone in 68%, the transition zone in 24%, and the central zone in 8% of cases (*15*). Anatomy of the prostate is well described and clearly delineated on reporting aids. The peripheral zone extends postero-laterally around the gland, involving most of the apex. The transition zone is centrally placed and enlarges with benign prostatic hypertrophy. The central zone surrounds the ejaculatory duct apparatus and makes up most of the central prostatic base. Zonal anatomy is clearly visible on prostate MRI compared to CT. However, use of the fused PSMA/CT images allows basic differentiation between transition and peripheral zone activity. Transition zone activity does not extend to the margin of the prostate on CT (leaving a photopenic rim) while peripheral zone activity extends fully to the prostate edge. While prostatic zones are less well demarcated on PSMA PET/CT than on mpMRI, this study has shown that this broad definition of patterns within zones is reproducible and improves diagnostic accuracy for csPCa.

PSMA is a transmembrane glycoprotein highly expressed on the cell surface of prostate cancer cells. However, the receptor is also expressed in benign pathology such as benign prostatic hypertrophy and prostate intra- epithelial neoplasia (*16*). Further, expression of PSMA in prostate cancer is a spectrum with higher grade pathology expressing higher levels of the receptor than low grade ISUP 1 malignancy (*4*). Benign intra-prostatic processes can have relatively high PSMA expression, with

significant overlap between the PSMA intensity expressed in low volume malignancy and benign disease. However, the pattern of PSMA activity in addition to PSMA intensity appears effective at differentiating benign causes from significant prostate malignancies in this study. The two key low risk patterns reported included diffuse transition zone activity, and symmetrical central zone activity, both occurring centrally in the prostate. Increased central zone PSMA activity has previously been reported as a potential cause of false positives (*17,18*). The incidence of malignancy associated with symmetrical central zone activity, although low, is higher than if only low-grade PSMA activity is present. This is likely because the increased PSMA activity, although benign, may mask focal uptake within small cancers directly adjacent. For this reason, if the central zone activity extended to the posterior margin of the fused PET /CT, the study was classified as a PRIMARY score 4 (peripheral zone). While this may have reduced the specificity of the PRIMARY score, it ensures sensitivity for csPCa is maintained.

The proposed PRIMARY score uses a combination of pattern (focal vs diffuse), zonal location and high SUVmax to optimise reporting accuracy. The score relies more on pattern than intensity, only using a high SUVmax (≥12) as the top score (PRIMARY score 5) due to its 100% specificity for the presence of significant malignancy. This reduced reliance on PSMA SUVmax makes the PRIMARY score more applicable across a range of PET cameras and PSMA ligands, with pattern unlikely to change significantly for these reasons. As no minimum intensity level is required in the peripheral zone for PRMARY score 4, and a PRIMARY score 3 is dependent on background transition zone counts, a fixed SUV max scale should not be used by reporters for the PRIMARY score. Further, PRIMARY score 5 (SUVmax ≥ 12) will need

to be validated across different PSMA PET ligands but was felt to be an important part of the score. The association between very high PSMA SUVmax and csPCa is strong and may be valuable as both diagnostic and prognostic tool (*19*).

Inter-rater reproducibility for differentiating PRIMARY score low risk from high risk patterns was substantial between independent readers, and equivalent to those previously reported in prospective trials for PSMA PET findings in biochemical recurrence and in evaluation of lymph node involvement in the staging setting (*9,20,21*). Inter-rater concordance was higher than that previously reported with PI-RADS V2 for mpMRI (*22*). Further, diagnostic performance remained high across all readers utilising the PRIMARY score.

This study has a number of limitations. The PRIMARY score has been developed and evaluated within the same prospective trial. While the PRIMARY score results were shown to have high inter-rater reproducibility and accuracy in this population, the score must be validated in other pre-biopsy datasets, with further evaluation of both intra and inter-reader reproducibility prior to clinical implementation. Further, while the PRIMARY score relies predominately on intra-prostatic pattern, a high SUVmax is included due to its high specificity. Further work is required to validate an optimal high SUVmax cut off across camera systems and different PSMA ligands. The option of using liver or parotid activity is not possible due to the use of a pelvic only PSMA PET/CT protocol to reduce radiation dose as appropriate for a screening setting.

The study was undertaken in a population of men who had undergone mpMRI and were planned for trans-perineal prostate biopsy. This means that men with PI-RADS 1 or low clinical risk PI-RADS 2 results were not included in the population. This

MRI triaging has reduced the negative predictive value for PI-RADS from that previously reported in low prevalence populations (*23*). However, adding PSMA PET to a low risk mpMRI population would not be clinically appropriate, and the finding that PSMA PET/CT is independently accurate for prostate cancer diagnosis in an mpMRI triaged population is an important finding.

Any ISUP 2 malignancy in the prostate was considered significant. A more detailed analysis of whole mount histopathology with overlaid PSMA may yield more accurate results. However, this study does not have whole mount histopathology as many men did not proceed to treatment.

CONCLUSION

A 5-level PRIMARY score incorporating intra-prostatic pattern and intensity on PSMA PET/CT shows potential for diagnosing clinically significant prostate cancer with high accuracy. Further validation of this scoring system in a screening population is warranted prior to clinical implementation.

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KEY POINTS

Question

Can a 5-point PRIMARY score based on patterns of intra-prostatic PSMA activity optimise accuracy of PSMA PET/CT for diagnosis of csPCa?

Pertinent Findings

The PRIMARY trial is a prospective multi-centre phase II imaging trial that enrolled biopsy-naïve men with suspected PCa, no prior biopsy, recent mpMRI (6 months) and planned for trans-perineal prostate biopsy. MRI was read separately using PI-RADS (V2), and PSMA-PET/CT was centrally read for pattern, incorporating intensity; a PRIMARY score was then assigned (1-5). The PRIMARY score had an equivalent diagnostic accuracy for the detection of csPCa than mpMRI alone: sensitivity, specificity, PPV and NPV for PRIMARY low risk (score 3-5) vs high risk (score 1,2) patterns was 88%, 64%, 76% and 81%, compared to 83%, 53%, 69% and 72% for PI-RADS (3-5 vs 2) on mpMRI.

Implications for Patient Care

A 5-Level PRIMARY score incorporating intra-prostatic patterns and intensity on PSMA-PET/CT shows potential as an accurate method for diagnosing csPCa in screening populations and warrants further validation.

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Figure 1. Anatomic representation of central, transition and peripheral prostate zones and patterns of intra-prostatic PSMA activity : Pattern A - Diffuse Transition zone, Pattern B- Symmetrical central zone, Pattern C- Focal transition zone and Pattern D- Focal peripheral zone. A simplification of prostate zones was utilised for the study with the peripheral zone encompassing the prostate peripheral margin as defined on fused PSMA PET /CT, and the entire apex.

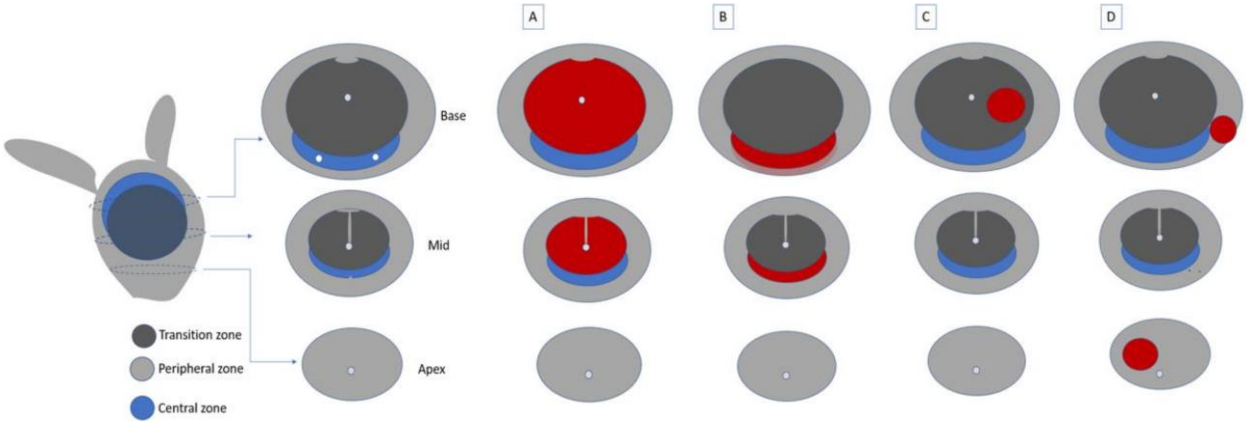


Figure 2. PRIMARY score image examples on PSMA PET/CT.

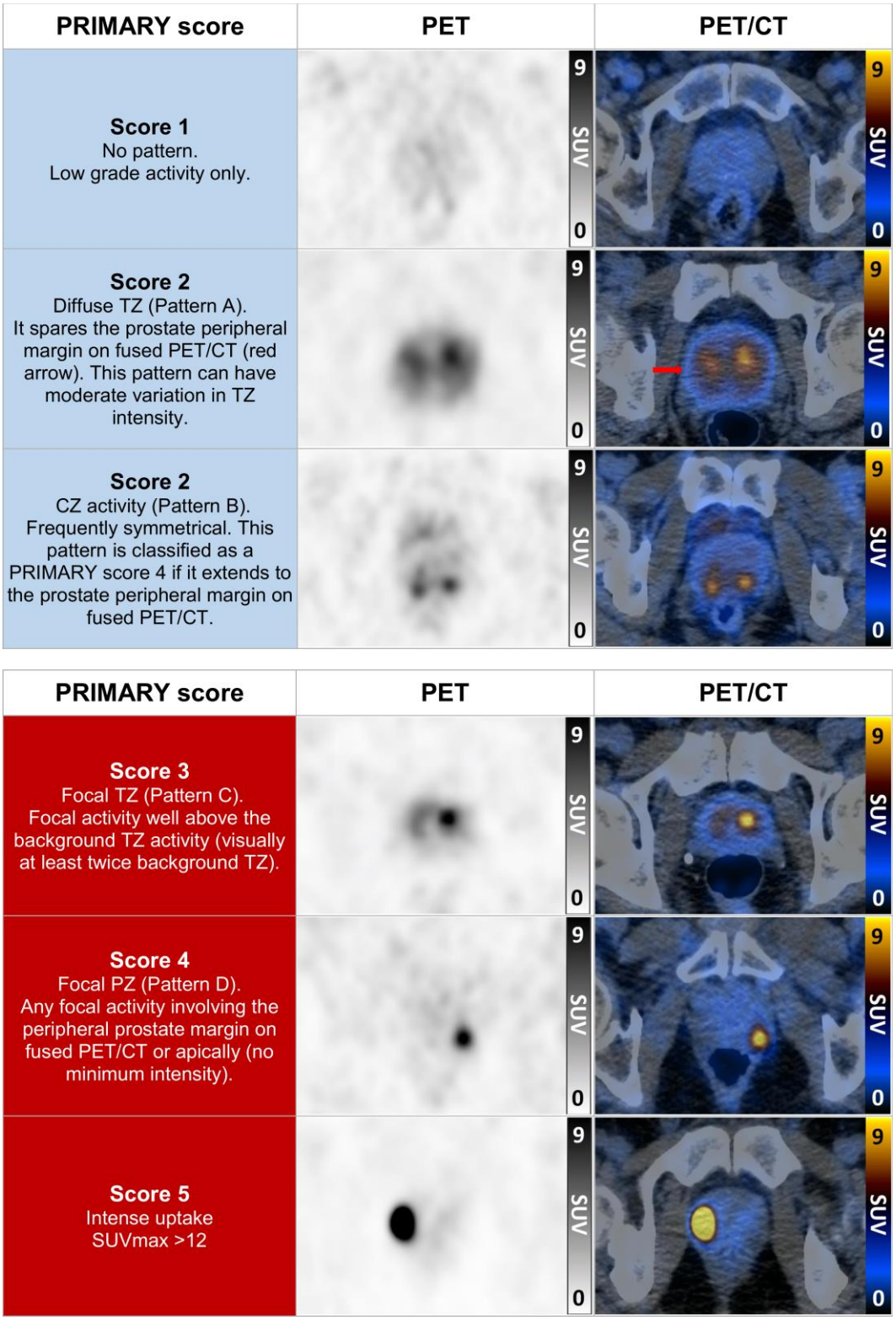


Figure 3. Receiver operating characteristic curves for the five-level PRIMARY score and PI-RADS.

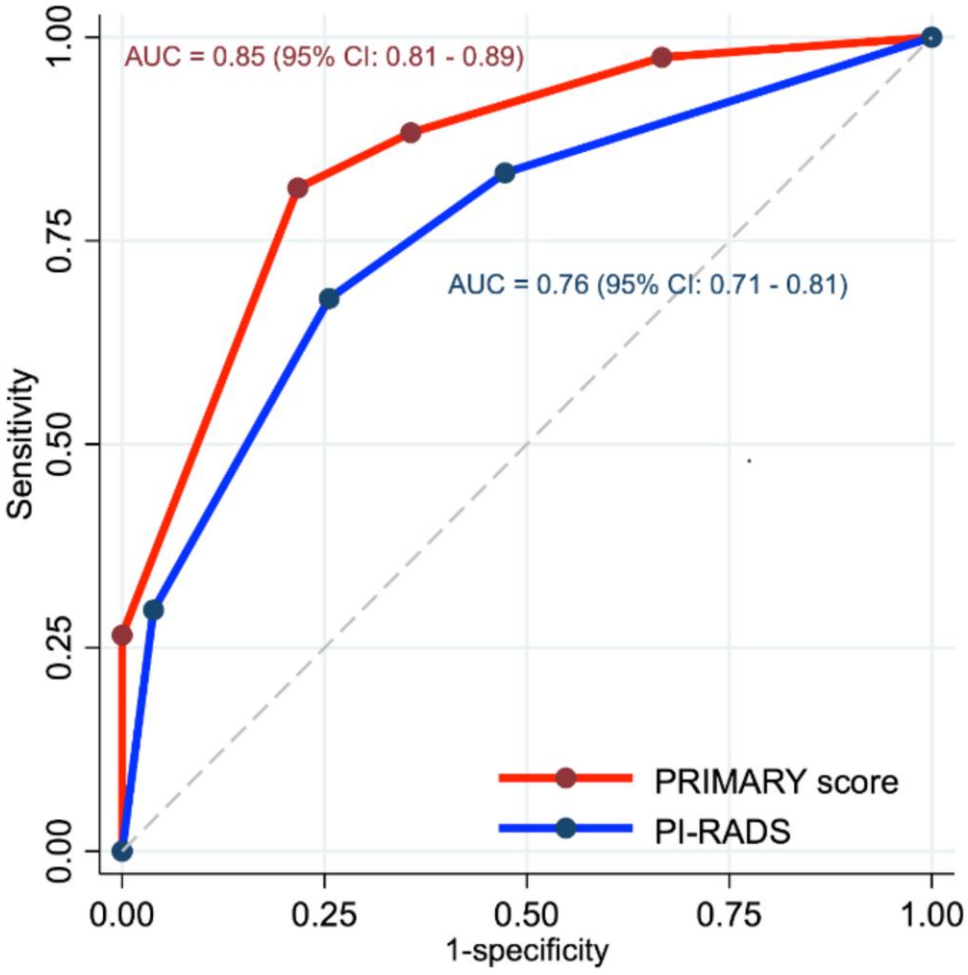


Figure 4. Distribution of overall ISUP grade group by PRIMARY score and PI-RADS. Numbers within bar indicate percentage.

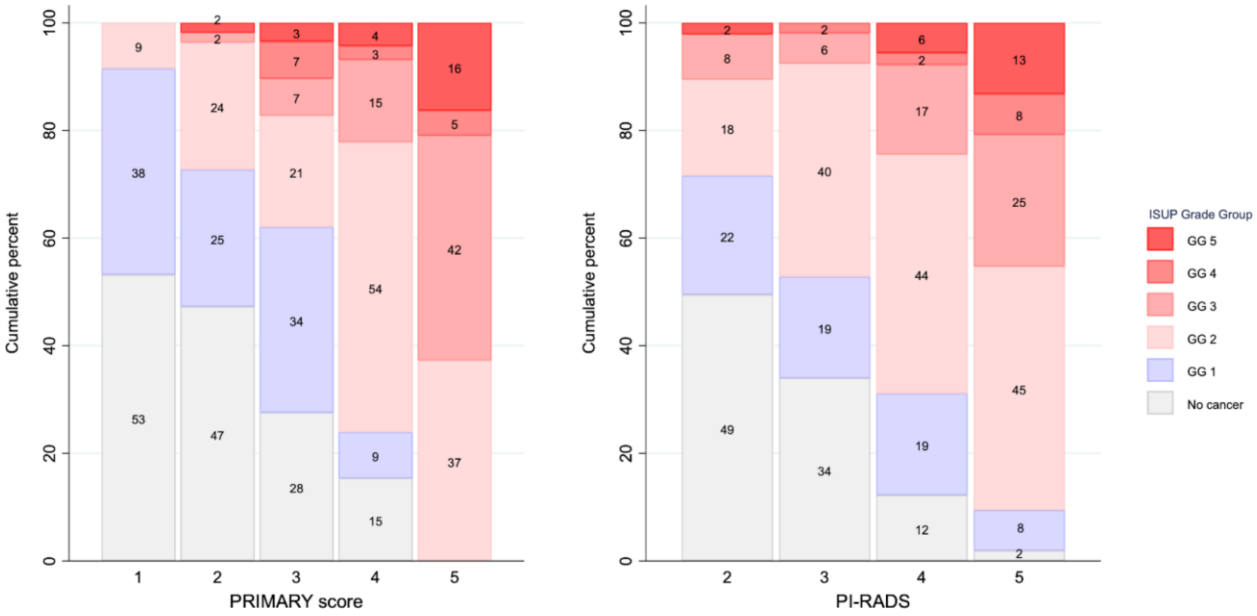
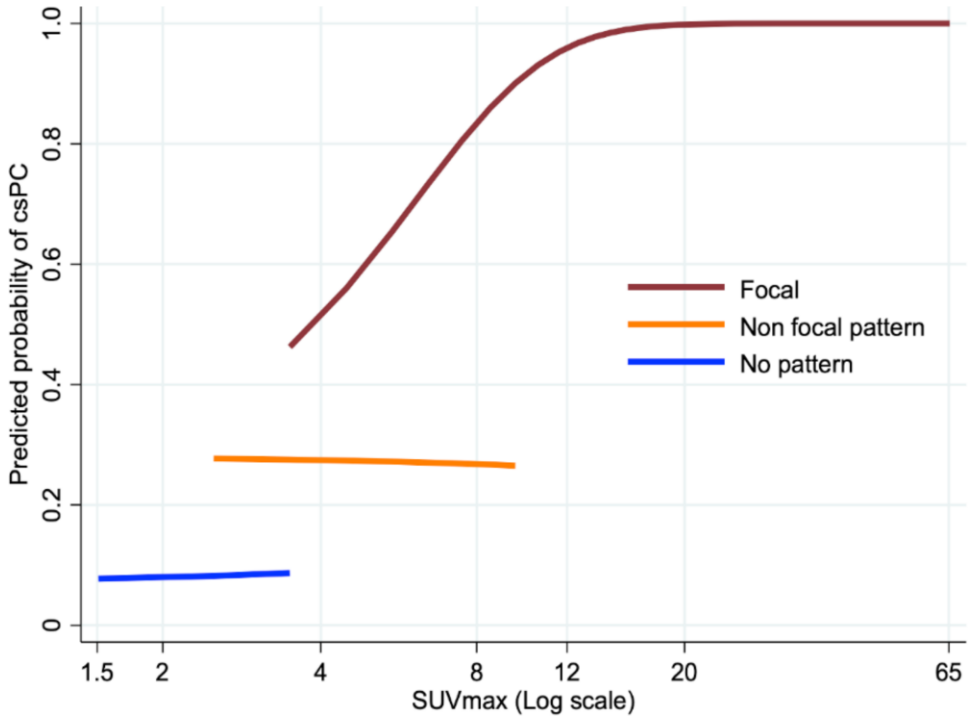


Figure 5. Predicted probability of csPCa vs SUVmax by pattern of uptake activity plotted for the range of SUVmax for that pattern



Graphical Abstract

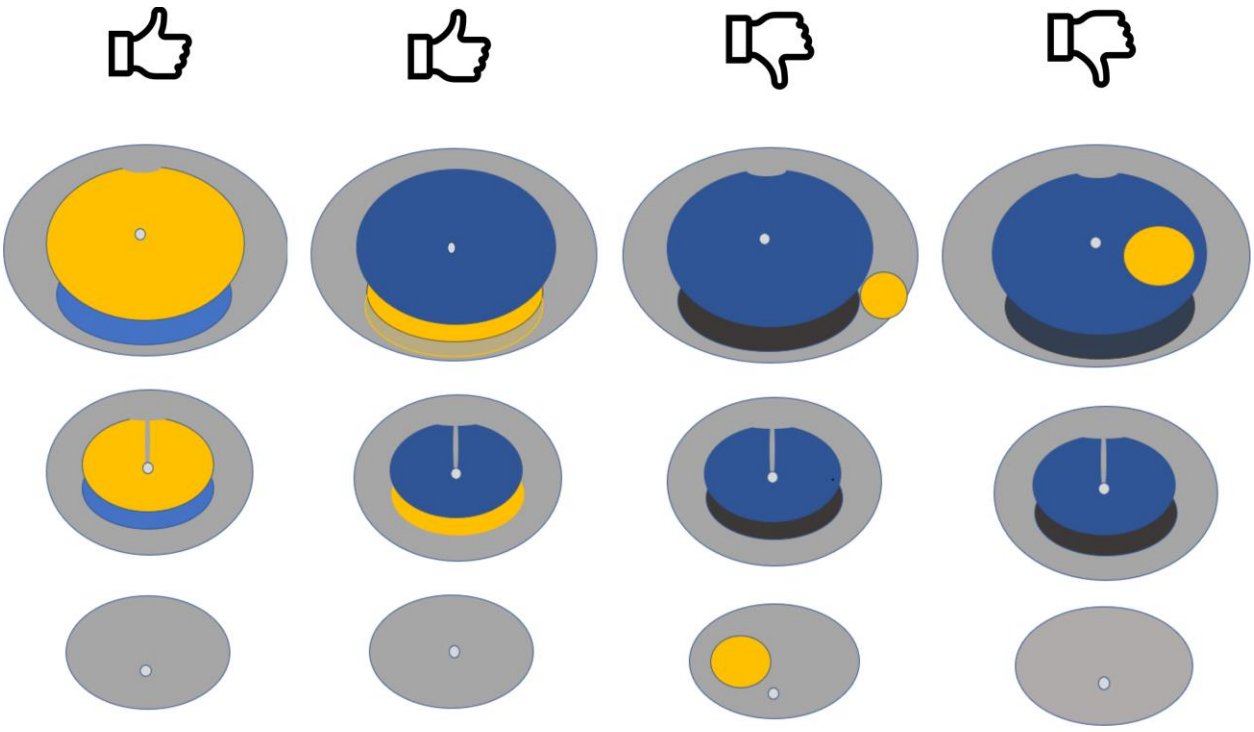


Table 1. Patient Characteristics

Variable	Median (IQR) or n (%)
Age at biopsy, years	64 (59 – 70)
Latest PSA *, ng/ml	5.6 (4.2 – 7.5)
Clinical T-stage	
TX	18 (6.2)
T1c	197 (68)
T2a	60 (21)
T2b	14 (4.8)
T2c	2 (0.7)
PI-RADS (mpMRI)	
2	95 (33)
3	53 (18)
4	90 (31)
5	53 (18)
Grade Group (biopsy)	
No cancer	77 (26)
1	52 (18)
2	102 (35)
3	39 (13)
4	7 (2.4)
5	14 (4.8)
**PSMA Pattern ** **	
No pattern	47 (16)
Diffuse TZ/ CZ	97 (33)
Focal TZ	53 (18)
Peripheral PZ	155 (53)

* One patient missing PSA ** Number exceeds sample size as a patient may exhibit more than one pattern simultaneously. CZ = central zone, PZ = peripheral zone, TZ = transition zone

Table 2: PRIMARY score.

	PRIMARY SCORE	n	% csPCa
1	No dominant intra-prostatic pattern on PSMA. Low grade activity.	47	8.5
2	Diffuse transition zone activity or symmetrical central zone activity that does not extend to the prostate margin on CT.	55	27
3	Focal TZ activity visually twice above background TZ activity.	29	38
4	Focal PZ activity (no minimum intensity)	117	76
5	PSMA SUVmax > 12	43	100

Table 3. Diagnostic performance (% and 95% CI) for PRIMARY score (1,2 vs 3-5) on PSMA reads and MRI PI-RADS (2 vs 3-5).

	PRIMARY score Central PET read	PI-RADS MRI read	PRIMARY score PET reader 1	PRIMARY score PET reader 2
All patients (n=291)				
Sensitivity	88 (82 – 93)	83 (77 – 89)		
Specificity	64 (55 – 73)	53 (44 – 62)		
PPV	76 (69 – 82)	69 (62 – 75)		
NPV	81 (72 – 88)	72 (61 – 80)		
Multiple readers (n=118)				
Sensitivity	88 (77 – 95)	82 (70 – 90)	83 (71 – 92)	92 (82 – 97)
Specificity	67 (54 – 79)	52 (38 – 65)	72 (59 – 83)	64 (50 – 76)
PPV	74 (62 – 83)	64 (52 – 74)	76 (64 – 85)	72 (61 – 82)
NPV	85 (71 – 94)	73 (57 – 85)	81 (67 – 90)	88 (74 – 96)
Kappa * PRIMARY score (1,2 vs 3-5)			0.76 (0.64 – 0.88)	0.64 (0.49 – 0.78)

Supplementary table 1. Cross tables for diagnostic performance statistics.

	PRIMARY score Central PET read		PI-RADS MRI read		PRIMARY score PET reader 1		PRIMARY score PET reader 2	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
All patients (n=291)								
csPCa	143	19	135	27				
No csPCa	46	83	61	68				
csPCa (n=162)								
MRI positive	119	16						
MRI negative	24	3						
No csPCa (n=129)								
MRI positive	22	39						
MRI negative	24	44						
Multiple readers (n=118)								
csPCa	53	7	49	11	50	10	55	5
No csPCa	19	39	28	30	16	42	21	37
csPCa (n=60)								
MRI positive	44	5			41	8	46	3
MRI negative	9	2			9	2	9	2
No csPCa (n=58)								
MRI positive	8	20			8	20	10	18
MRI negative	11	19			8	22	11	19