Characterizing indeterminate (Likert-scored 3/5) peripheral zone prostate lesions with PSA density, PI-RADS scoring and qualitative descriptors on multi-parametric MRI

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ABSTRACT:

Objectives: To determine whether indeterminate (Likert-score 3/5) peripheral zone (PZ) multi-parametric MRI (mpMRI) studies are classifiable by Prostate-Specific Antigen (PSA), PSA density (PSAD), PI-RADS_v2 rescoring and morphological MRI features.

Methods:
Men with maximum Likert-score 3/5 within their PZ were retrospectively selected from 330 men who prospectively underwent prostate mpMRI (3T) without an endorectal coil, followed by twenty-zone trans-perineal template prostate mapping biopsies ± focal lesion-targeted biopsy. PSAD was calculated using pre-biopsy PSA and MRI-derived volume. Two readers A and B independently assessed included men with both subjective Likert-score and PI-RADS_v2. Both readers then classified mpMRI morphological features in consensus. Men were divided into two groups: significant cancer (≥Gleason 3+4) or insignificant cancer (≤Gleason 3+3)/no cancer. Comparisons between groups were made separately for PSA&PSAD using Mann-Whitney test and morphological descriptors with Fisher’s exact test. PI-RADS_v2 and
subjective Likert assessment were descriptively compared and percentage inter-reader agreement calculated.

**Results:**

76 men were eligible for PSA&PSAD analyses, 71 for PI-RADS scoring, and 67 for morphological assessment (excluding significant image artefacts). Unlike PSA ($p=0.915$), PSAD was statistically different ($p=0.004$) between the significant [$0.19 \text{ ng/ml}^2$ (IQR: 0.13-0.29)] and non-significant/no cancer [$0.13 \text{ ng/ml}^2$ (IQR: 0.10-0.17)] groups. Presence of mpMRI morphological features wasn’t significantly different between groups. Subjective Likert assessment discriminated patients with significant cancer better than PI-RADS_v2. Inter-reader percentage agreement was 83% for subjective Likert-scoring and 56% for PI-RADS_v2.

**Conclusion:**

PSAD may categorize presence of significant cancer in patients with Likert-scored 3/5 PZ mpMRI findings.

**Advances in knowledge:** PSAD may be used in indeterminate PZ mpMRI to guide decisions between biopsy versus monitoring.
Keywords

Multi-parametric MRI; Prostate-Specific Antigen Density; Likert; PI-RADS;
Prostatic Neoplasms; indeterminate.
INTRODUCTION:

Multi-parametric MRI (mpMRI) has the potential to be the modality of choice for ruling out clinically significant prostate cancer with reported negative predictive values as high as 89% (83-94%) (1, 2). However, prostate mpMRI is scored as indeterminate (Likert-score 3/5) in almost 1/3rd of cases (163 of 576 patients enrolled in the recent multi-centre prospective PROMIS study) where the radiologist is unable to confirm or refute the presence of clinically significant cancer.

Two scoring systems are commonly used to evaluate the likelihood of prostate cancer on mpMRI (3-6). First, the Prostate Imaging Reporting And Data System version 2 (PI-RADS_v2) which uses explicit criteria based on a zonal mpMRI dominant sequence (e.g. diffusion-weighted imaging in the peripheral zone and T2-weighted imaging in the transition zone) to rate the suspicion of prostate cancer on a five-point scale (7) and second, a subjective five-point Likert assessment (8), based on each mpMRI sequence equally (unlike the use of dominant sequence in PIRADS_v2) and adapted to the radiologist’s experience for overall impression. Both 5-point scales define the likelihood for the presence of prostate cancer, as follows 1: highly unlikely, 2: unlikely, 3: equivocal, 4: likely, 5: highly likely). Subjective Likert scoring has recently been prospectively validated in the multi-centre, multi-reader PROMIS trial (1). PI-RADS_v2 remains more widely accepted where prospectively scored cohorts have also been reported (9) but studies with head-to-head comparisons of PI-RADS_v2 and Likert-assessment as scoring systems are lacking.
Indeterminate mpMRI poses both a management dilemma and potential unnecessary increase in healthcare cost. If all patients within this group were biopsied, a majority of men without significant disease would be exposed to potentially unnecessary risks of haemorrhage and urinary tract infections, which can lead to hospitalization (10) further increasing healthcare costs; conversely, if all men were not biopsied then a significant proportion of men would have significant cancer missed. This cohort of patients has been scarcely studied as an independent group (11, 12) since most attention so far, has been focused on both extremes of the scale (13-16). Decreasing the number of equivocal mpMRI scans remains an unmet clinical challenge and represents a determinant factor for widespread global adoption of mpMRI.

The prevalence of prostate cancer is higher in the peripheral zone than the transition zone and zone-specific molecular and imaging phenotypes exist, prompting separate zonal assessment (17-19).

The aim of this work was to determine whether indeterminate (Likert-score 3/5) peripheral zone (PZ) multi-parametric MRI (mpMRI) studies can be categorized into significant/insignificant cancer by Prostate-Specific Antigen (PSA), PSA density (PSAD), PI-RADS_v2 rescoring and morphological MRI features.

MATERIALS AND METHODS
Local institutional review board waived the requirement for individual consent for this single-center retrospective analysis of prospectively enrolled patients from a previous study cohort (20) - Research Ethics Committee reference 11/LO/1657.

Patients

330 men (median age: 63 years, interquartile range, IQR [42-83]; median PSA: 7.4 ng/ml, IQR [0.7-58.05]), with prior negative/non-significant prostate disease on TRUS biopsies, but in whom a clinical suspicion of prostate cancer remained (elevated PSA or PSA kinetics, abnormal digital rectal examination, etc) were consecutively enrolled from January 2012-2014 (20). They all underwent prostate mpMRI without an endorectal coil at 3T (unless contraindicated). A radiologist (Reader A) with 10 years of experience in prostate imaging, blinded to histopathological results, prospectively reported mpMRI findings and scored the likelihood of significant cancer on a subjective 5-point Likert scale. All patients underwent 20-zone trans-perineal template prostate mapping (TPM) biopsies (21). In addition, when a focal lesion was identified on mpMRI, its location was mapped on a prostate gland representative diagram and its biopsy template grid co-ordinates noted (21). MR-guided targeted biopsies were performed by experienced urologists (≥ 10 years of experience), aware of the radiologist’s report, as described within the previous study protocol (20).

Men with complete 3T mpMRI datasets, full template biopsy ± targeted biopsy and maximum Likert-scored 3/5 PZ were eligible for inclusion. 107/330
patients fulfilled these criteria. Patients with a concurrent Likert-score 3/5 in
the transition zone (TZ) subsequently identified as clinically significant tumour
were excluded (n=6), men with a lack of complete gland sampling/ inadequate
sampling density were excluded (n=20), and five men who underwent 1.5T
scans were excluded. The final cohort comprised of 76/107 PZ Likert-scored
3/5 mpMRI studies for analysis. Figure 1 summarizes the patient selection.

MpMRI Protocol
The 3T mpMRI protocol for included men (Table 1) has been previously
described (22). All studies were performed with the same protocol on a single
3T scanner (Achieva®, Philips Healthcare, Netherlands) using a 32-channel
pelvic-phased array coil. Briefly, sequences included axial turbo spin echo
and coronal T₂W; axial DWI using a high b-value at 2000s/mm²; axial ADC
map generated by diffusion gradients b0, b150, b500, and b1000 (s/mm²) and
axial T₁W dynamic–contrast enhanced sequences before and after
intravenous administration of at least 0.1 mmol/kg gadolinium meglumine
contrast agent (Dotarem®, Guerbet, France) at a rate of 3ml/s via power
injector, followed by 20ml saline bolus at the same rate with a temporal
resolution of 15 seconds.

Cancer Significance
Histology results were reported by a uro-pathologist with 12 years of
experience. Recognizing that there still is an ongoing debate on what
constitutes clinically significant prostate cancer, for the purposes of this study,
the presence of any Gleason 7 pattern or higher (≥ 3+4), anywhere within the
PZ was considered as clinically significant (23). The maximum cancer core length (MCCL) was measured and categorized as <6mm or ≥6mm.

**Correlation of Trans-perineal Template Mapping Biopsies and MpMRI**

For mpMRI to histopathology matching, Likert-scores 3/5 at the apex and base were considered positive for significant cancer if the corresponding Barzell zone was positive on biopsy. Likert-scores 3/5 at the mid-gland level were considered positive if the corresponding apical or basal Barzell zone was positive on biopsy. A schema for correspondence of Barzell zones on TPM (21) and prostate mpMRI region is illustrated in Figure 2.

**Serum PSA and PSA Density**

PSA prior to entry of patients into the previous study (14) was recorded. To calculate PSA density, the prostate volume was measured on the mpMRI study. The maximum antero-posterior and latero-lateral diameters of the prostate were manually measured by Reader A on axial T₂W slices while its cranio-caudal diameter was measured on coronal T₂W slices as shown in Figure 3. Assuming an ellipsoid shape of the prostate, its volume was calculated by Reader A as the product of the three diameters and π/6 (24). PSAD was calculated by the quotient of serum PSA over the gland volume.

**Likert to PI-RADS Scoring**

Reader A, who reported the mpMRI of the prostate as Likert-score 3/5 in the previous study (22), rescored them with PI-RADS_v2 criteria (8). A second radiologist, Reader B (4 years of experience in reading prostate mpMRI)
independently rescored the scans, using first Likert scoring, then at different
time points with PI-RADS_v2. Both readers were blinded to histopathological
reports, unaware of each other’s scores.

**Peripheral Zone MpMRI Morphology**

As Likert-score 3/5 exhibit varied appearances on mpMRI, the
presence/absence of the morphological descriptors (described below and in
Figures 4A-4C) of PZ signal changes on all combined sequences were
considered by Readers A and B in consensus (as no pre-defined
morphological validated classification scheme has yet been reported for
Likert-score 3/5 cohorts). This was assessed only after the subjective Likert
and PI-RADS_v2 scores of both readers had been locked.

i) “discrete focal” – single or multiple focal changes occupying <50%
of PZ,

ii) “diffuse homogeneous” – uninterrupted signal changes occupying
>50% of PZ, and without focal intensity variation,

iii) “diffuse inhomogeneous” – signal changes occupying >50% of PZ
interrupted by focal intensity variation or stranded changes

**Statistical Analyses**

The Mann-Whitney tests were used to compare each PSA and PSAD
between clinically significant and non-significant/no cancer groups. From a
receiver-operating characteristic (ROC) curve, sensitivity and specificity of
various PSAD thresholds were obtained and the highest Youden’s J index
was determined to identify PSAD threshold for significant cancer in our cohort (25). Proportions of up-scored, down-scored and unchanged Likert and PI-RADS scores per reader were descriptively compared. Inter-reader percentage agreement for Likert and PI-RADS were calculated. The Kappa agreement coefficient, $\kappa$, between both readers was also computed for PI-RADS ($\kappa < 0.4$: fair, $0.4 < \kappa < 0.8$: moderate, $\kappa > 0.8$: strong agreement). PZ morphological descriptors were compared between significant and insignificant cancer groups with Fisher’s exact test. Statistical significance was set at $p<0.05$. GraphPad Prism statistitical software (version 6, GraphPad Software, San Diego, CA) was used.

RESULTS

Of 76 men (median age 61 years [IQR 57-66]; median PSA 7.2 ng/ml [IQR 4.9-10.3]; median gland volume 52 cc [IQR 33-63]), 21 (27%) had a clinically significant cancer at biopsy, 31 (41%) harbored low grade (Gleason 3+3) disease, and 24 (32%) had no cancer (including high-grade prostate intra-epithelial neoplasm, atypical acini, inflammation, atrophy, and/or benign cores).

**Serum PSA and PSA Density**

Median PSA and PSAD were 7.17 ng/ml (IQR: 5.55-8.69) and 0.19 ng/ml$^2$ (IQR: 0.13-0.29) in the significant cancer group while in the non-significant/no cancer group, these were 7.20 ng/ml (IQR: 4.31-10.7) and 0.13 ng/ml$^2$ (IQR: 0.10-0.17) respectively. PSAD was significantly higher in the significant cancer group ($p=0.004$) as represented in Figure 5; PSA was not significantly
different between the two groups (p=0.915). A PSAD threshold of >0.17 ng/ml² [sensitivity: 67% (95CI: 43-85%), specificity: 75% (95CI: 61-85%), NPV: 85% (95%CI: 72-94%) for significant cancer was identified in our cohort with the Youden’s index. To maximize sensitivity, the use of >0.10 ng/ml² as PSAD threshold would yield 90% sensitivity (95CI: 70-99%), a reduced specificity of 36% (95CI: 23-50%) but NPV would increase to 89% (95CI: 67-99%).

Likert to PI-RADS Rescoring

Of 76 patients, five had extensive post-biopsy artefact, leaving 71 patients eligible for PZ PI-RADS scoring. Among them, four had non-diagnostic quality DWI, due to air in the rectum, and PI-RADS ‘Assessment without adequate DWI’ was applied (8).

The set of 71 patients all scored as Likert 3 by Reader A comprised of eighteen (18/71, 25%) clinically significant cancer at biopsy. Reader B scored 59/71 patients as Likert 3, of whom fifteen (15/59, 25%) had clinically significant cancer; four were scored Likert 2 and none had clinically significant cancer; eight were scored Likert 4, three of which had clinically significant cancer (3/8, 38%) where two had Gleason 3+4 pattern and MCCL≤6mm, one man had Gleason 4+3, MCCL≥6mm.

On PI-RADS_v2 rescoring, Readers A and B down-scored to PI-RADS≤2, 34/71 (48%) and 34/59 (58%) patients respectively; with 27/34 (79%) and 26/34 (76%) demonstrating non-significant/no cancer at biopsy. For reader A,
6/34 (18%) PI-RADS ≤2 scored men had Gleason 3+4 disease, MCCL < 6mm and 1/34 man Gleason 3+4, MCCL ≥ 6mm. For Reader B, 7/30 (23%) PI-RADS ≤2 scored men had Gleason 3+4 pattern with MCCL < 6mm, 1/34 man Gleason 3+4, MCCL ≥ 6mm, and 1/34 Gleason 4+3 disease.

Readers A and B up-scored to PI-RADS4 in 31/71 (44%) and 20/59 (34%) patients respectively, and none to PI-RADS5; with 23/31 (74%) and 13/20 (65%) demonstrating non-significant/no cancer at biopsy. For Reader A, 6/31 (19%) PI-RADS4 scored men had Gleason 3+4 and MCCL < 6mm, 1/31 had a Gleason 3+4 with MCCL ≥ 6mm, and 1/31 had Gleason 4+3 pattern. For Reader B, 5/20 (25%) PI-RADS 4 scored men had Gleason 3+4 and MCCL < 6mm, and 2/20 men had Gleason 3+4, MCCL ≥ 6mm. Reader B scored five patients PI-RADS3 (none with significant cancer) while Reader A scored six patients PI-RADS3 where three had clinically significant cancer (3/6, 50%) - two of which were Gleason 3+4, MCCL < 6mm and one Gleason 3+4, MCCL ≥ 6mm. These results are summarized in Figure 6.

The percentage agreement between Readers A and B for Likert-score 3/5 was (59/71) 83% and (40/71) 56% for PI-RADS_v2. The latter had an inter-reader agreement coefficient Kappa of 0.27 (95% CI 0.10-0.44).

Peripheral Zone mp-MRI Morphology

Sixty-seven men were included in this analysis after excluding non-diagnostic DWI studies. Results of qualitative mpMRI assessment are summarized in Table 2. Thirteen of 47 (28%) patients with discrete focal change [median
volume 0.17 cc (IQR: 0.05-0.16) demonstrated significant cancer; and 3/10 patients with diffuse homogeneous changes also demonstrated significant cancer. No patient with diffuse inhomogeneous signal changes had significant cancer. However, differences between groups did not reach statistical significance (p=0.21 to 1.00).

**DISCUSSION**

This paper assessed whether serum PSA & PSAD, PI-RADS_v2 rescoring and morphological features of Likert-scored 3/5 PZ signal changes could help identify patients harbouring significant cancer.

Firstly, we found serum PSA level by itself, was not able to identify patients with significant cancer. Yet, when combined with gland volume assessment, PSAD was the best predictor of patients with significant cancer. Rais-Bahrami *et al* reported that PSAD coupled to the number of MR suspicious lesions on bi-parametric MRI (T$_2$W and DWI) improve categorization of Gleason score $\geq 7$ upon TRUS or MR/US fusion biopsies (26). Recently, the use of PSA density with mpMRI has gained further interest in improving mpMRI accuracy (27-29). Our study complements this work, and provides evidence that PSAD can specifically address the problem of indeterminate mpMRI studies.

Furthermore, we reported two thresholds of PSAD for classification of patients with Likert-score 3/5. Various PSAD thresholds have been previously proposed to select patients with significant disease (27, 28, 30-33). Epstein *et al* found $>0.15$ng/ml$^2$ to be associated with significant disease upon
prostatectomy with a 66% NPV (21). The National Comprehensive Cancer
Network (NCCN) has adopted this value (34) while the Prostate Cancer
Research International Active Surveillance (PRIAS) program has adopted
>0.2ng/ml\(^2\) (33) as predictors of significant disease. In our study, Youden’s
cut-off of PSAD>0.17 ng/ml\(^2\) in determining the presence of significant cancer
offers a 75% specificity (95CI: 61-85%) and 85% NPV (95%CI: 72-94%). This
would provide a prudent approach to management by accepting a higher
number of patients to be biopsied to minimize the chances of missing patients
with significant tumour. Were this threshold applied to our cohort of 76
patients, it would have correctly avoided biopsy in 40/76 (53%) and led to 7/76
(9%) patients with cancer not being immediately diagnosed.

Secondly, we found a relatively poor performance of PI-RADS\(_v2\) as a
classifier of Likert 3/5 patients. PI-RADS\(_v2\) rescoring from both readers, up
or downscored almost all patients into PI-RADS≤2 and PI-RADS4 score
groups. However, as approximately ¾ of men up-scored to PI-RADS4 had no
significant disease (and hence would undergo unnecessary biopsy) and
almost ¼ of men down-scored to PI-RADS≤2 had significant cancer (and
hence significant cancer would be missed if no biopsy was performed) we
conclude that within our patient cohort PI-RADS scoring was not a good
classifier of patients. Our results are not unique in highlighting some current
deficiencies within PI-RADS\(_v2\) reporting schema (35); Besides, Vargas \textit{et al}
have also reported that it offered limited assessment of Gleason 4+3 pattern
of volume ≤0.5ml (36).
Interestingly, whilst Likert scoring demonstrated 83% inter-reader concordance, PI-RADS_v2 showed only 56% concordance – in line with Greer et al who reported an overall inter-observer concordance of 58% for PI-RADS_v2 (37) while Renard-Penna et al reported higher concordance values (92%) for Likert scoring (5). While no other study has compared Likert and PI-RADS_v2 yet, some studies have compared Likert scoring to PI-RADS_v1 (4, 5) with Vaché et al showing a more accurate performance of Likert scores (4).

For PI-RADS_v2, Rosenkrantz et al found expert inter-reader agreement, \( \kappa \) in the PZ score groups of \( \geq 4 \) and \( \geq 3 \) to be 0.59 and 0.53 respectively (38).

Muller et al (39) showed an overall \( \kappa=0.47 \) for PI-RADS_v2 scoring with mixed reader experience. Within our study, we found a smaller \( \kappa \) of 0.27 for PI-RADS_v2. We do not believe this to be surprising as we specifically assessed a subgroup (Likert 3/5) of patients where radiological assessment is inherently more challenging.

Finally, we investigated whether any particular pattern of PZ signal change could help classify patients. We found the group of patients with ‘diffuse inhomogeneous’ pattern did not include any patient with significant cancer. However, the number of patients within our cohort was too small to confirm the statistical significance of this observation.

The results of our study are relevant to directing clinical practice following the recent PROMIS study publication with Likert-scored mpMRI (1). When 3/5-scores are classified as positive, the specificity of the mpMRI study is reduced (5, 40). If these scores are classified as negative, the sensitivity of the mpMRI
test reduces. We would advocate that the Likert 3/5 score should be treated as a separate indeterminate group which needs further classification with secondary features. Using PSAD provides a simple method to manage patients with indeterminate scores: men with high PSAD would undergo biopsy; those with low PSAD may benefit from further observation (perhaps PSA surveillance) as our results suggest that some of them (albeit a small percentage) will have significant tumour. Our results support the necessity for continued iteration of PI-RADS reporting schema based on ongoing research to improve classification, minimise subjectivity and promote inter-reader agreement.

Our study has several limitations. Firstly, it was necessary to use a template biopsy based reference in our cohort as it comprised many patients without significant cancer/any cancer and therefore could not have a prostatectomy. We acknowledge the limitations of template biopsy – (which has a 95% detection rate for significant tumours against 100% at prostatectomy (41)) – nevertheless unavoidable within our cohort. Secondly, although we propose PSAD thresholds to aid management of Likert-score 3/5 patients, the clinical impact of these thresholds should be prospectively validated. Thirdly, it would be prudent to replicate our study in other cohorts to confirm generalizability of our findings, both in terms patient cohorts being imaged with mpMRI (e.g. pre-biopsy vs delayed post-biopsy) and also different MRI scanning platforms (e.g. 1.5T vs 3T).

CONCLUSIONS
MR-adjusted PSAD may help classify patients with PZ Likert-scored 3/5 on mpMRI who have clinically significant cancer and could be used to select patients for biopsy over observation. Prospective studies are further required to validate the use of PSA density in indeterminate mpMRI cohorts.
REFERENCES


### TABLES

#### Table 1

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<th>Echo Time (ms)</th>
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<th>Slice thickness (mm)</th>
<th>Matrix size</th>
<th>Field of view (mm)</th>
<th>Fat suppression</th>
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<td>90</td>
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<td>3</td>
<td>300x290</td>
<td>180</td>
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<td>05:13</td>
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<td>90</td>
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Note:

- DWI: Diffusion-weighted imaging
- DCE: Dynamic Contrast-Enhanced imaging
- SPAIR: Spectral Attenuated Inversion Recovery
- SPIR: Spectral Pre-saturation with Inversion Recovery
Table 2

Table 2: Qualitative mpMRI Assessment

<table>
<thead>
<tr>
<th>Qualitative mpMRI descriptor</th>
<th>Significant Cancer</th>
<th>Non-significant cancer/no cancer</th>
<th>Total</th>
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<tr>
<td>Focal lesion</td>
<td>13 (28%)</td>
<td>34 (72%)</td>
<td>47 (70%)</td>
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<tr>
<td>Diffuse homogeneous changes</td>
<td>3 (30%)</td>
<td>7 (70%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Diffuse inhomogeneous changes</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
<td>10 (15%)</td>
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Table 2 shows the number of significant cancer and non-significant cancer/no cancer, in each of the qualitative mpMRI descriptor groups.
FIGURES

Figure 1. Flowchart diagram illustrating the patient selection process for this study.
Figure 2.

Figure 2 shows the correlation of the 20 Barzell zones from template mapping biopsy to the corresponding regions on mpMRI.
Figure 3.

Figure 3 illustrates T2-weighted MRI images where the antero-posterior ($D_{a-p}$) and latero-lateral diameters ($D_{l-l}$) of the prostate gland are measured on the axial plane and the cranio-caudal diameter or height ($D_{c-c}$) is measured on the coronal plane to calculate the volume of the prostate gland by using the prolate ellipse formula ($D_{a-p} \times D_{l-l} \times D_{c-c} \times 0.52$).
Figures 4A-4C. Illustrations of morphologic mpMRI descriptors for PZ scored 3/5

4A. A schematic representation and example of a focal lesion (occupying <50% of the slice) in the PZ (axial plane) in a 70 year old man with PSA of 13 ng/ml and PSAD of 0.14 ng/ml^2. The lesion is seen at 6 o’clock, hypointense on T2, and enhances on DCE. Histology results were benign.

4B. A schematic representation and example of diffuse homogeneous signal changes in a 51 year old man with PSA of 6 ng/ml and PSAD of 0.25 ng/ml^2. The signal changes seen are hypointense on axial T2 and the whole PZ enhances uninterruptedly on axial DCE. Histology results revealed Gleason 3+4 with MCCL <6mm on the right lateral side whereas the left PZ was benign.

4C. A schematic illustration and example of diffuse inhomogeneous changes in the axial plane in a 66 year old man with PSA of 5 ng/ml and PSAD of 0.09 ng/ml^2. Areas of low T2 signal interspersed by normal high T2 signal intensities are observed. The low T2 signal intensities of the PZ are seen to enhance (on > 50% of the gland) from 1 to 5 o’clock and 7 to 8 o’clock on DCE. Histology results were benign.
Figure 5.

Figure 5. Bar-charts showing the median PSA density comparison between the significant cancer and non-significant/no cancer groups with a statistical difference of $p < 0.01$. 
Figure 6. Bar-charts illustrating the results of Likert and PI-RADS scoring of the PZ by Readers A and B. PI-RADS segregate Likert-score 3/5 lesions mostly into PI-RADS ≤2 and PI-RADS 4 by both Readers A and B. The number of Likert-indeterminate lesions decreased from 71 to 6 (8%) by Reader A and 5 (7%) by Reader B with PI-RADS scoring. Readers A and B respectively up-scored 31/71 (44%) and 20/59 (34%) to PI-RADS 4; eight of 31 (26%) and seven of 25 (28%) had significant cancer. They down-scored 34/71 (48%) and 34/59 (58%) to PI-RADS ≤2; seven of 34 (24%) and eight of 31 (26%) had significant cancer.
330 patients

314 patients

Exclusions:
- due to incomplete mpMRI datasets: 11
- 1.5 T scans: 5

Prospectively assigned Likert score

1/5 & 2/5
n = 33

3/5
n = 113

4/5
n = 69

5/5
n = 99

TZ
n = 11

PZ
n = 102

Exclusions: 26
- Inadequate TPM biopsy sampling: 20
- Associated TZ tumour (6)

Eligible for QUANTITATIVE PSA and PSA density analysis
N = 76

Exclusions due to post-biopsy artefact: 5

Eligible for PI-RADS rescorning
N = 71

Exclusions due to distorted DWI: 4

Eligible for qualitative mpMRI analysis
N = 67
Transperineal Template Mapping Biopsies

Modified D'Azza Zones

1. Left Parasagittal Anterior Apex
2. Left Parasagittal Anterior Base
3. Right Parasagittal Anterior Apex
4. Right Parasagittal Anterior Base
5. Midline Apex
6. Midline Base
7. Left Medial Anterior Apex
8. Left Medial Anterior Base
9. Right Medial Anterior Apex
10. Right Medial Anterior Base
11. Left Lateral
12. Right Lateral
13. Left Parasagittal Posterior Apex
14. Right Parasagittal Posterior Base
15. Midline Apex
16. Midline Base
17. Left Medial Posterior Apex
18. Left Medial Posterior Base
19. Right Medial Posterior Apex
20. Right Medial Posterior Base

Multi-parametric MRI

Base

Mid

Apex

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MR-based volume of the prostate, \( V (\text{cc}) = D_{a-p} (\text{cm}) \times D_{l-l} (\text{cm}) \times D_{c-c} (\text{cm}) \times 0.52 \)
Mann-Whitney test of unpaired data for PSA density

Non-significant/no cancer

Significant cancer

PSA density (ng/ml^2)

p = 0.0040

**

Significant cancer

Non-significant/no cancer