

Title:

The added value of diffusion-weighted images and dynamic contrast-enhancement in multi-parametric MRI for the detection of clinically significant prostate cancer in the PICTURE trial

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/BJU.14953](https://doi.org/10.1111/BJU.14953)

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Article type : Original Article

Article category: Urological Oncology

Abstract

Objective: To determine the additional diagnostic value of diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging in men requiring a repeat biopsy within the PICTURE study.

Patients and Methods: PICTURE was a paired-cohort confirmatory study in which 249 men who required further risk stratification following a previous non-MRI guided TRUS biopsy underwent a 3-Tesla mpMRI consisting of T2W, DWI and DCE followed by transperineal template prostate mapping (TPM) biopsy. Each mpMRI was reported using a LIKERT score in a sequential blinded manner to generate scores for T2W, T2W+DWI and T2W+DWI+DCE. Area under the receiver operating characteristic (AUROC) analysis was performed to compare the diagnostic accuracy of each combination. The threshold for a positive mpMRI was set as a LIKERT score ≥ 3 . Clinically significant prostate cancer was analysed across a range of definitions including UCL/Ahmed Definition 1 (primary definition), UCL/Ahmed Definition 2, any Gleason $\geq 3+4$ and any Gleason $\geq 4+3$.

Results: Of 249, sequential MRI reporting was available for 246. There was a higher rate of equivocal lesions (44.6%) using T2W alone compared to the addition of DWI (23.9%) and DCE (19.8%). Using the primary definition of clinically significant disease, there was no significant difference in the

overall accuracy between T2W at AUROC 0.74 (95% CI 0.68-0.80), T2W+DWI at 0.76 (95% CI 0.71-0.82) and T2W+DWI+DCE at 0.77 (95% CI 0.71-0.82) ($p=0.55$). The AUROCs remained comparable using other definitions of clinically significant disease including UCL/Ahmed 2 ($p=0.79$), Gleason $\geq 3+4$ ($p=0.53$) and Gleason $\geq 4+3$ ($p=0.53$).

Conclusions: Using a 3T MRI, a high level of diagnostic accuracy can be achieved using T2W as a single parameter in men with a prior biopsy. However, such a strategy can lead to a higher rate of equivocal lesions.

Introduction

Multi-parametric magnetic resonance imaging (mpMRI) has become an important test for the detection and ruling out of clinically significant prostate cancer (1-3). There has been increased standardisation of the sequences following the technical parameters described in expert consensus guidelines (4, 5). The standard acquisition parameters combine anatomical T1-weighted (T1W) and T2-weighted (T2W) imaging with functional sequences. The standard functional sequences are diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging which provide additional information on cellular density and tissue vascularity.

Uncertainty remains on whether this entire combination of sequences is necessary to rule-out and detect clinically significant prostate cancer. In early guidelines there was a similar level of importance given to each T2W, DWI and DCE sequences (6). The current version of the Prostate Imaging Reporting-Data System (PI-RADSv2) has limited the role of DCE to a binary score which can only differentiate equivocal lesions in the peripheral zone (PZ) (7). It also recommends dominant sequences based on zonal anatomy so that DWI is dominant in the PZ and T2W is dominant in the transition zone (TZ). Recent systematic reviews have indicated that DCE may not be necessary (8, 9) supported by results from paired cohort studies from expert centres (10, 11).

This study evaluates the diagnostic accuracy of combining T2W with functional sequences on a 3 Tesla (3T) MRI against transperineal prostate template mapping (TPM) biopsy within the PICTURE trial. TPM biopsy provides a robust reference standard for clinically significant prostate cancer due to the fixed 5mm sampling of the entire prostate. This approach minimises the methodological limitations from alternative reference tests such as transrectal ultrasound-guided (TRUS) 10-12 core systematic non-MRI guided biopsy which have an inherent random error and whole-mount radical prostatectomy specimens which have an inherent selection bias.

Patients and Methods

Study Design: The PICTURE trial was a paired-cohort validating confirmatory study designed to provide level 1 evidence on the diagnostic accuracy of mpMRI in men who required further biopsy. The study was approved by the National Research Ethics Committee London (reference 11/LO/1657) and the full trial protocol has been previously published (12). The primary outcomes on accuracy of mpMRI, Prostate Histoscanning and image-targeted biopsies were recently reported (13-15). This PICTURE analysis is Standards for Reporting Diagnostic Accuracy (STARD) compliant(16).

Participants: Participants were recruited in outpatient clinic and were eligible for enrolment if they had undergone prior TRUS-biopsy and been advised as part of standard of care to undergo a repeat biopsy for further risk stratification. Participants were excluded if they had previous treatment for prostate cancer; a contraindication to MRI or artefact which would reduce MRI quality; a prostate gland volume ≥ 80 ml or other medical conditions meaning they were unable to have general or regional anaesthesia.

Imaging Protocol: mpMRI was performed using a 3T scanner with a pelvic-phased array coil. The acquisition protocol consisted of T1W and T2W sequences, DWI with high b-value ($b=2000$) and apparent diffusion coefficient (ADC) map using multiple b-values ($b=0,150,500,1000$) and DCE with gadopentetate dimeglumine (Magnevist, Bayer AG, Leverkusen, Germany). The full acquisition parameters are listed in the supplementary appendix.

Image Interpretation: MRI scans were reported in a sequential blinded fashion so that three sets of reports were generated; T2W alone, T2W+DWI and T2W+DWI+DCE. Reporting was completed in a single session with each sequential report locked after being issued. The reporting was completed by a board-certified radiologist with over 10 years of experience in prostate MRI interpretation and reporting a high volume of MRIs per annum (>1500 scans/year). To assess inter-observer agreement, 50 (20%) of mpMRI consisting of all sequences were randomly selected for re-reporting by a second expert radiologist blinded to the original reports.

A 5-point Likert Assessment System was used to rate the likelihood of clinically significant disease as highly unlikely (1), unlikely (2), equivocal (3), likely (4) or highly likely (5). This scoring system has been prospectively validated in the PROMIS trial(1) and has been recommended for use by our national consensus meeting(17). Comparative studies have shown that it provides similar results to PI-RADS (18, 19).

Reference test: All participants underwent TPM biopsy irrespective of the findings on mpMRI. Participants were blinded to the mpMRI results to reduce selection bias and increase non-compliance with TPM biopsy. The mapping procedure followed a pre-defined protocol in which biopsy cores were taken every 5mm using a brachytherapy grid. Additional targeted cores could also be taken within the biopsy protocol which were processed and reported separately. As per the original analysis plan and the primary outcomes of mpMRI validation (13) only the TPM biopsies were used in this report. All biopsies were reported in accordance with the 2005 International Society of Urological Pathology (ISUP) recommendations (20) by one of two expert uropathologists blinded to the mpMRI images. Any negative biopsy was double reported as part of a quality control process.

Outcomes: The definition of clinically significant disease was set using validated criteria which have been developed for TPM biopsy (21). The primary definition (UCL/Ahmed definition 1) was the presence of dominant Gleason pattern 4 or greater and/or a cancer core length (CCL) involvement of ≥ 6 mm of any Gleason score. The secondary definitions were a) UCL/Ahmed 2 (any Gleason score 7 and/or CCL involvement of ≥ 4 mm of any Gleason score), b) any Gleason $\geq 3+4$ and c) any Gleason $\geq 4+3$.

Statistics

The study sample size had been calculated based on the negative predictive value (NPV) of mpMRI as the primary objective of the PICTURE trial (12), so the current manuscript is not specifically powered to compare the additional diagnostic value of functional sequences and T2W alone. Descriptive statistics were used for baseline characteristics, distribution of LIKERT scores and cancer detection rates. The index test was considered positive for an mpMRI score of 3 or greater in any sector. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated for each of the three sequences with binomial 95% confidence intervals, with a score of 3 or above designated a suspicious/positive MRI. Receiver–operator curves (ROC) were constructed and DeLong’s test was used to compare the area under the ROC (AUROC) (22).

The inter-observer agreement was calculated using weighted kappa and proportion of agreement and assessed using AUROC. The weighted kappa allows for the magnitude of the disagreements to be taken into account. The weighting system used resulted in the weights 0.75, 0.5, 0.25 and 0 for MRI ratings scores that differed by 1, 2, 3 and 4 respectively. All analyses were conducted using

STATA version 11.0 software (Stata Corporation, College Station) with any tests of significance using 2-sided $p=0.05$ as the threshold for statistical significance.

Results

Baseline Characteristics

A total of 330 participants were enrolled into the study. There were 81 withdrawals, 249 participants underwent both mpMRI and TPM-biopsy and 246 had a full set of sequential mpMRI reports (Figure 1 and Table 1). Previous TRUS biopsy results included no cancer in 76 (30.5%), Gleason 6 in 121 (48.6%) and low volume Gleason 7 in 52 (21.1%).

A median (IQR) 49 (40-50) cores were taken at TPM-biopsy. Any cancer was detected on TPM-biopsy in 209 (83.9%) of 249. Using definition 1, clinically significant cancer was detected on TPM-biopsy in 103 (41%) of 249 (Table 2). A non-suspicious MRI (LIKERT score ≤ 2) occurred for T2W in 18.5%, TW2+DWI 12.6% and TW2+DWI+DCE 8.9% (Figure 2).

Diagnostic Accuracy

For the primary definition, T2W alone had sensitivity 96% (90-99), specificity 29% (22-37), positive predictive value (PPV) 49% (42-56) and negative predictive value (NPV) 91% (79-98). For T2W+DWI, sensitivity was 96% (90-99), specificity 29% (22-37), (PPV) 49% (42-56) and (NPV) 91% (79-98). For T2W+DWI+DCE, sensitivity was 96% (90-99), specificity 29% (22-37), PPV 49% (42-56) and NPV 91% (79-98) (Table 3). The diagnostic performance for each set of sequences was evaluated for other definitions of clinical significance on TPM-biopsy as presented in Table 4.

Overall accuracy for definition 1, as assessed by area under the receiver operating characteristic curve (AUROC), for T2W, T2W+DWI and T2W+DWI+DCE were 0.74 (95% CI 0.68-0.80), 0.76 (95% CI 0.71-0.82) and 0.77 (95% CI 0.71-0.82), respectively ($p=0.55$) (Figure 3). There were no significant differences in overall accuracy when comparing AUROC for other definitions of clinically significant disease (Tables 5) (Figure 4).

Inter-observer variability

The weighted agreement on the double-read of the full mpMRI sequence was 87.0% ($K=0.52$, standard error [se] =0.10) indicating good agreement. When the mpMRI scores for each reporter were compared to TPM-biopsy histology, there were minimal differences between each reporter in terms of AUROC analyses (reporter one AUROC 0.76 [0.63-0.90] versus reporter two 0.75 [0.61-0.89]).

Discussion

In summary, our PICTURE study results showed that the added diagnostic value of functional sequences was marginal using a 3T MRI scanner in men requiring a repeat biopsy. To our knowledge, this is the first study that presents the diagnostic accuracy of combining T2W and functional sequences against TPM-biopsy as an accurate reference standard. The overall accuracy of mpMRI was high across all combinations of sequences and definitions of clinically significant disease.

In this study, an abbreviated MRI protocol could still function as a triage test to rule-out clinically significant prostate cancer in men requiring repeat biopsies, but the number of men avoiding biopsies as a result of using more sequences decreased from 18.5% (T2W alone) to 12.6% (T2W+DWI) and 8.9% (T2W+DWI+DCE). The number of biopsy would increase but without adding significant utility as no additional cases of significant disease were identified with DWI and only one extra case was identified with DCE.

Rather surprisingly, our findings suggest that it may be feasible using T2W images alone on a 3T MRI to achieve a high level of diagnostic accuracy. Similar findings have been previously reported by Mertan et al (23) in a prospective study of 62 patients which also used a 3T MRI. The findings of both studies should be interpreted cautiously as the results are derived from single high-volume centres using a 3T MRI scanner in a patient population that does not represent biopsy-naïve men. In contrast, the majority of previous studies have demonstrated improved accuracy for detection of prostate cancer using functional sequences in combination with T2W imaging (24, 25).

Our study serves to highlight that specific sequences might be safely omitted without impacting diagnostic accuracy. With recent guidelines issued by NICE in the UK (26) as well as the European Association of Urology (27), there will be rapid uptake of pre-biopsy mpMRI, resulting in increasing pressures on limited capacity. Endeavours that shorten the sequences without significantly compromising the triage role of pre-biopsy MRI and detection rates of clinically significant prostate cancer might improve on cost-efficiency and throughput.

There is reason to be cautious in moving towards a stripped-down version of only T2W. Although the supplementary information provided by DWI and DCE did not improve AUROC, there was a shift in the distribution of LIKERT scores. The functional sequences had a useful role upgrading LIKERT 3 lesions and improving the reporter's scoring confidence for other lesions (Figure 5). The addition of DWI and DCE led to a reduction in LIKERT 3 lesions from 44.6% to 33.5% and a corresponding

increase in LIKERT 5 lesions from 12.0% to 37.9%. This shift has also been observed in similar studies using PIRADSV2 where DCE has a role distinguishing equivocal lesions in the PZ (28). It has been suggested that the higher proportion of equivocal lesions could be addressed by only performing the additional sequences in those cases where such a lesion is identified. However, this would require scans to be immediately reported or the patient to return for a second scan at a later date.

Given our findings, a protocol using T2W and DWI may be a reasonable approach to balance the number of men avoiding an immediate biopsy and the reduction in equivocal lesions. The removal of contrast has advantages in terms of patient acceptability as well as reducing scanning time. The safety of gadolinium-based contrast has been questioned following reports that it can form depositions within the dentate nucleus and globus pallidus(29).

This approach is supported by recent systematic reviews and meta-analyses comparing standard mpMRI with biparametric MRI (bpMRI) defined as consisting of T2W and DWI sequences without DCE. In this meta-analysis the pooled summary statistics had no significant difference in sensitivity (mpMRI: 86%, 95% confidence interval [CI] 81-90; bpMRI: 90%, 95% CI 83-94) or specificity (mpMRI: 73%, 95% CI 64-81; bpMRI: 70%, 95% CI 42-83) with the summary AUROCs being comparable for mpMRI (0.87) and bpMRI (0.90) (8). Subsequent to this, van der Leest et al (10) have shown that sensitivity for high-grade prostate cancer for both bpMRI and mpMRI was 95% (95% CI 91-97%) with specificity 69% (95% CI 64-73%). In this study biopsy could be avoided in 49% for the bpMRI and mpMRI protocol. The recently published Danish BIDOC paired cohort clinical utility study in over one thousand men has also shown that bpMRI has good performance characteristics but was unable to compare their findings to mpMRI (11).

Our study has several limitations. First, these findings relate to an expert centre using a 3T MRI producing high-quality T2W images. We acknowledge that this limits the reproducibility of our findings given that 1.5T is commonly used. Second, this represents a whole-gland analysis and regional analysis differentiating PZ and TZ may highlight an added value of DWI and/or DCE. Third, the study had a heterogeneous patient population and we acknowledge that these findings may not relate to a biopsy-naïve population. Fourth, TPM is not a suitable reference standard for evaluation of extraprostatic extension so the impact of bp-MRI on staging has not been assessed in this study. Last, and importantly, we cannot test the clinical utility of a bpMRI pathway compared to a mpMRI based pathway in which decisions on biopsy are made without use of DCE in the bpMRI pathway.

This is necessary since radiologists may score differently when they know that patients have not had the DCE sequences.

In conclusion, the present study showed that a high level of diagnostic accuracy can be achieved using T2W as a single parameter with a 3T MRI in men with a prior biopsy. However, such a strategy can lead to a higher rate of equivocal lesions so a protocol including T2W and DWI may offer the optimal balance in this population.

Acknowledgements

David Eldred-Evans receives funding from The Urology Foundation, the BMA Foundation and Imperial Health Charity.

Joana B. Neves receives funding from the Medical Research Council (MRC Clinical Research Training Fellowship).

Taimur Shah would like to acknowledge funding from Prostate Cancer UK and the St Peters Trust for clinical research.

Shonit Punwani would like to acknowledge sessional funding from UCLH BRC

Hashim Ahmed's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) Imperial Biomedical Research Centre. Hashim Ahmed receives funding from the Wellcome Trust, Prostate Cancer UK, Medical Research Council (UK), Cancer Research UK, The Urology Foundation, the BMA Foundation and Imperial Health Charity. Hashim Ahmed receives funding from Sonacare Inc., Sophiris Bio and Trod Medical for other trials and studies. Travel allowance was previously provided from Sonacare Inc.

Mark Emberton's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre. He was awarded NIHR Senior Investigator in 2015. Mark Emberton has stock interest in Nuada Medical Ltd. He is also a consultant to Steba Biotech and GSK. He receives travel funding from Sanofi Aventis, Astellas, GSK and Sonacare. He previously received trial funding or resources from GSK, Steba Biotech and Angiodynamics and currently receives funding for trials from Sonacare Inc, Sophiris Inc and Trod Medical.

Alex Freeman has stock interest in Nuada Medical Ltd.

Caroline Moore receives funding from ProfBiotics and GSK.

Emberton, Arya, Moore and Ahmed are proctors for HIFU with Sonacare Inc. Arya and Ahmed are proctors for Boston Scientific for cryotherapy. Ahmed is a proctor for Rezum with Boston Scientific.

All others have no conflicts of interest

Figures

Figure 1: PICTURE trial flowchart compliant with STARD

Figure 2: Distribution of LIKERT Scores across each three sequences

Figure 3: AUROC curve for UCH definition1 for clinically significant cancer

Figure 4: AUROC curve for UCH definition2 for clinically significant cancer

Figure 5: Equivocal lesion upgraded on functional sequences

Tables

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Table 2: Histological Characteristics on TPM Biopsy

Table 3: Diagnostic accuracy of different mpMRI sequences using UCH 1 Definition for clinically significant cancer

Table 4: Diagnostic accuracy of different mpMRI sequences using alternative secondary definitions of clinically significant cancer

Table 5: Comparison of Area under receiver operating characteristic curve across definitions of clinically significant disease

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Table 1: Characteristics of participants at baseline

Age, years (SD)	62 (7.0)
PSA (ng/ml), Median (IQR)	6.8 (4.8-9.8)
Prostate volume, median (IQR)	37.0 (26.8-50.0)
Number of previous biopsies, median (IQR)	1 (1-2)
Previous TRUS biopsy result (%)	
- Benign	76 (30.5)
- Gleason 3+3	121 (48.6)
- Gleason \geq 3+4	52 (21.1)

IQR = Interquartile range

Table 2: Histological Characteristics on Transperineal Template Mapping biopsy

TPM biopsy outcome (%)	
Benign	40 (16.1)
Gleason score	
3+3	66 (26.5)
3+4	110 (44.2)
4+3	29 (11.7)
4+4	3 (1.2)
3+5	1 (0.4)
Maximum cancer core length mm, median (IQR)	4 (2-7)
Cores positive for cancer, median (IQR)	6 (2-11)
Total number of cores, median (IQR)	45 (40-55)

IQR = Interquartile range

Table 3: Diagnostic accuracy of different combinations of MRI sequences using UCL/Ahmed Definition 1 for clinically significant cancer

Primary Definition (UCL/Ahmed 1): Dominant Gleason pattern 4 or greater and/or a cancer core length (CCL) involvement of ≥ 6mm of any Gleason score				
T2W	96 (90-99)	29 (22-37)	49 (42-56)	91 (79-98)
T2W + DWI	96 (90-99)	19 (13-26)	45 (39-52)	87 (70-96)
T2W + DWI + DCE	97 (92-99)	13 (8-20)	44 (37-51)	86 (65-97)

PPV = Positive Predictive Value; NPV = Negative Predictive Value

Table 4: Diagnostic accuracy of different MRI sequences using other definitions of clinically significant prostate cancer

UCL/Ahmed 2: Any Gleason score 7 and/or CCL involvement of ≥ 4 mm of any Gleason score				
T2W	92 (87-96)	41 (30-52)	76 (70-82)	72 (57-84)
T2W + DWI	95 (90-98)	27 (18-38)	73 (66-79)	71 (52-86)
T2W + DWI + DCE	96 (92-99)	20 (12-30)	71 (65-77)	73 (50-89)
Any Gleason score $\geq 3+4$				
T2W	93 (88-97)	34 (25-44)	66 (59-72)	78 (64-89)
T2W + DWI	95 (90-98)	23 (15-32)	63 (56-69)	77 (59-90)
T2W + DWI + DCE	97 (92-99)	16 (10-24)	61 (54-67)	77 (55-92)
Any Gleason score $\geq 4+3$				
T2W	94 (79-99)	20 (15-26)	15 (10-20)	85 (96-100)
T2W + DWI	97 (84-100)	14 (10-19)	14 (10-20)	97 (83-100)
T2W + DWI + DCE	97 (84-100)	10 (6-15)	14 (10-19)	77 (96-100)

PPV = Positive Predictive Value; NPV = Negative Predictive Value

Table 5: Comparison of Area under receiver operating characteristic curve (AUROC) across definitions of clinically significant disease

T2W	0.74 (0.68-0.80)	0.77 (0.71-0.83)	0.72 (0.66-0.78)	0.68 (0.59-0.77)
T2W + DWI	0.76 (0.71-0.82)	0.78 (0.72-0.84)	0.73 (0.67-0.79)	0.71 (0.62-0.80)
T2W + DWI + DCE	0.77 (0.71-0.82)	0.79 (0.73-0.84)	0.74 (0.68-0.80)	0.71 (0.63-0.79)
p value	0.55	0.79	0.53	0.53

Figure 1: Standards for reporting of diagnostic accuracy (STARD) flowchart

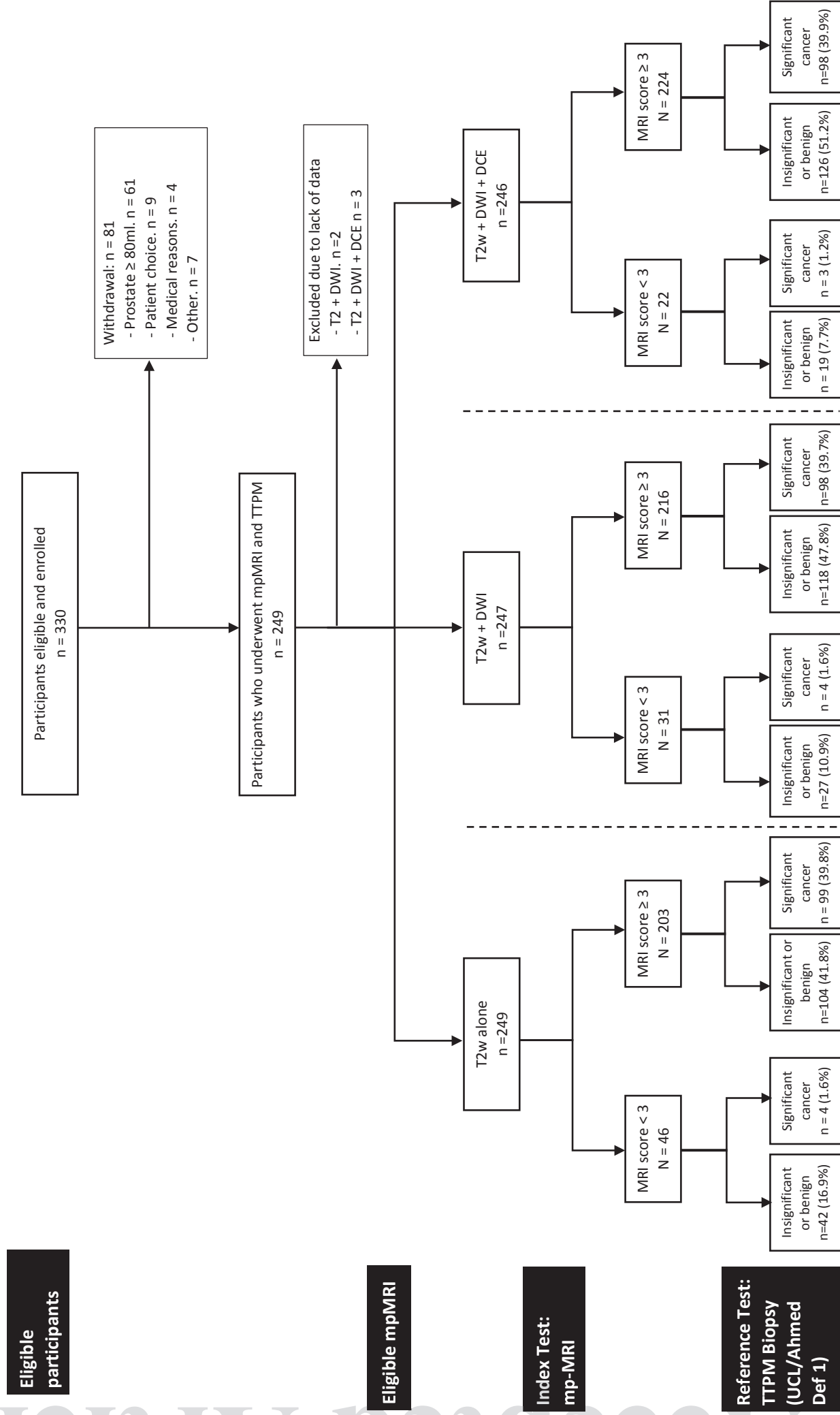


Figure 2: Distribution of LIKERT Scores across each three sequences

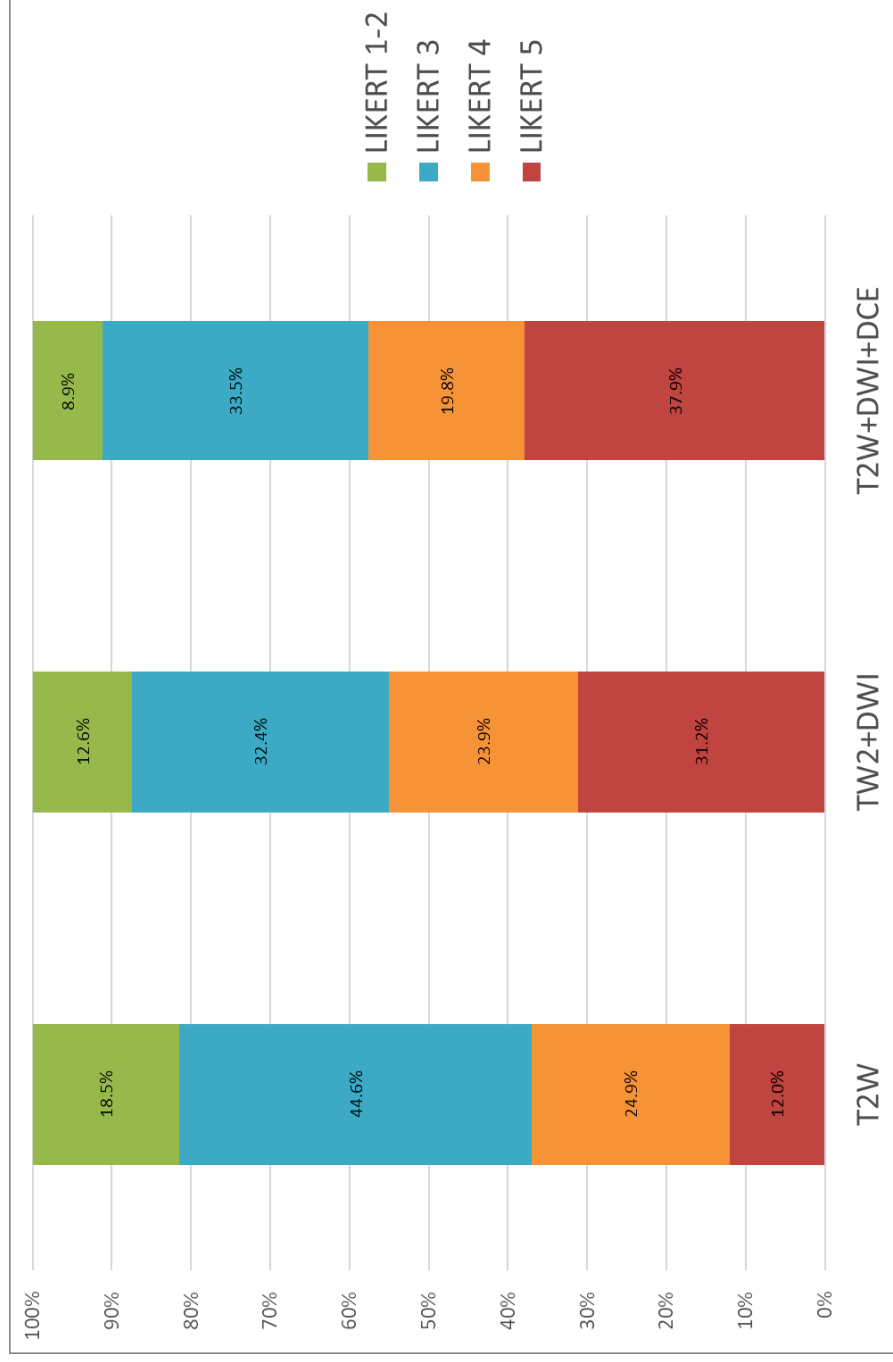


Figure 3: AUROC curve for UCL/Ahmed definition1 for clinically significant cancer

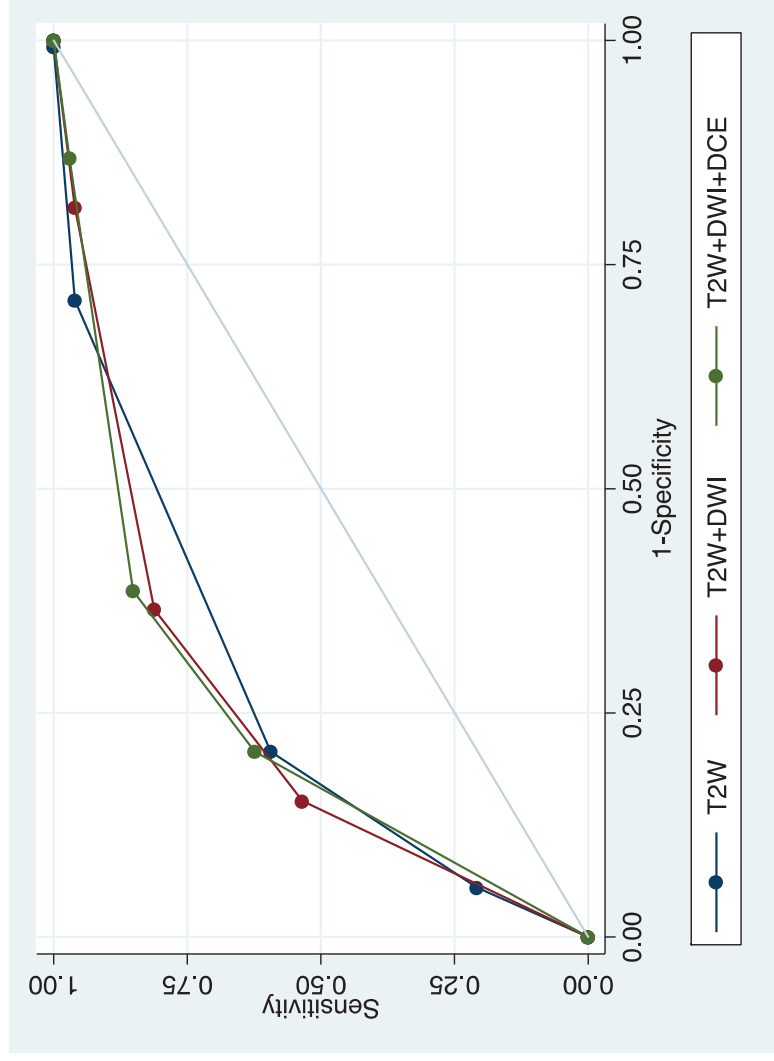
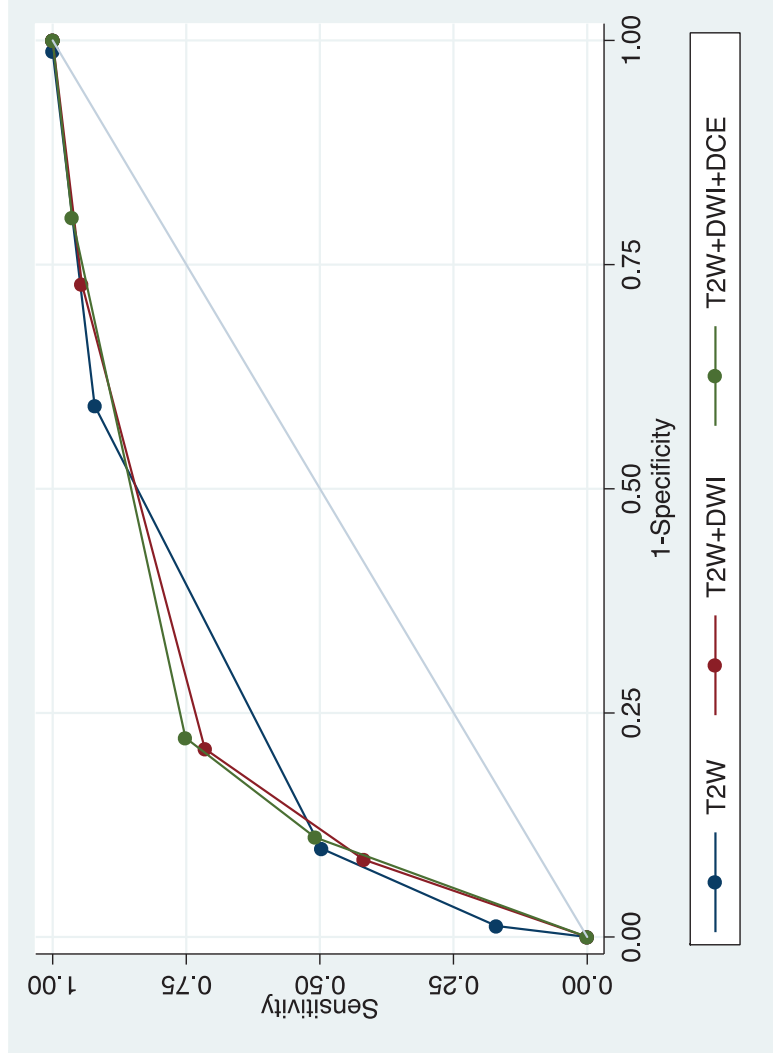


Figure 4: AUROC curve for UCL/Ahmed definition 2 for clinically significant cancer



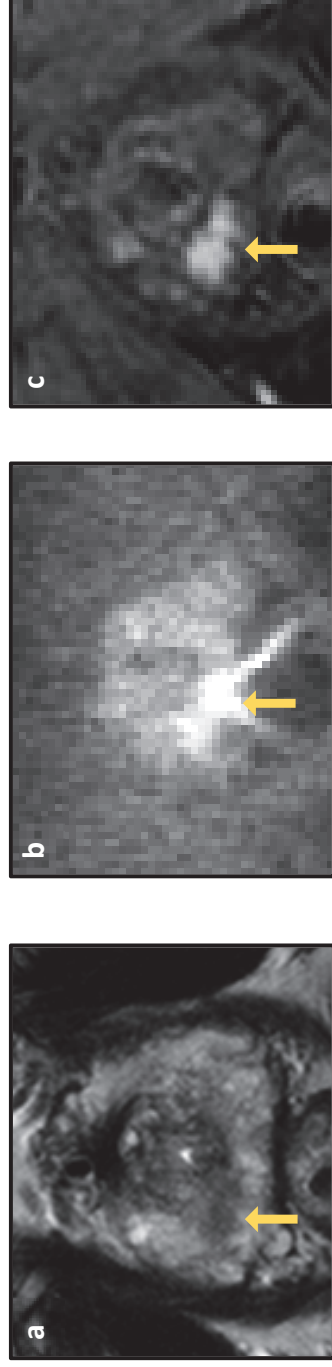


Figure 5: Equivocal lesion upgraded on functional sequences in a 65-yr-old man with PSA 9.3ng/ml and known Gleason 3+3 on previous TRUS biopsy. (a) Axial T2-weighted images shows a diffuse area with low signal intensity in the right peripheral zone scoring 3 out of 5. (b) A focal area of restricted diffusion on diffusion weighted imaging (DWI) scoring 4 out of 5. (c) There is avid enhancement on dynamic contrast enhanced (DCE) imaging scoring 5 out of 5. The transperineal template prostate mapping confirmed Gleason 4+3 (ISUP 3) with maximum cancer core length 6mm.