Radiology

ORIGINAL RESEARCH • GENITOURINARY IMAGING

Avoiding Unnecessary Biopsy after Multiparametric Prostate MRI with VERDICT Analysis: The INNOVATE Study

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This work was directly supported by Prostate Cancer UK:Movember Targeted Call 2014: Translational Research St.2, project reference PG14-018-TR2, and further supported by the National Institute for Health and Care Research, University College London Hospitals Biomedical Research Centre, and Cancer Research UK National Cancer Imaging Translational Accelerator. D.C.A. and E.P. supported by Engineering and Physical Sciences Research Council.

Conflicts of interest are listed at the end of this article.

Radiology 2022; 000:1–8 • https://doi.org/10.1148/radiol.212536 • Content code: GU

Background: In men suspected of having prostate cancer (PCa), up to 50% of men with positive multiparametric MRI (mpMRI) findings (Prostate Imaging Reporting and Data System [PI-RADS] or Likert score of 3 or higher) have no clinically significant (Gleason score ≤3+3, benign) biopsy findings. Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumor (VERDICT) MRI analysis could improve the stratification of positive mpMRI findings.

Purpose: To evaluate VERDICT MRI, mpMRI-derived apparent diffusion coefficient (ADC), and prostate-specific antigen density (PSAD) as determinants of clinically significant PCa (csPCa).

Materials and Methods: Between April 2016 and December 2019, men suspected of having PCa were prospectively recruited from two centers and underwent VERDICT MRI and mpMRI at one center before undergoing targeted biopsy. Biopsied lesion ADC, lesion-derived fractional intracellular volume (FIC), and PSAD were compared between men with csPCa and those without csPCa, using nonparametric tests subdivided by Likert scores. Area under the receiver operating characteristic curve (AUC) was calculated to test diagnostic performance.

Results: Among 303 biopsy-naive men, 165 study participants (mean age, 65 years ± 7 [SD]) underwent targeted biopsy; of these, 73 had csPCa. Median lesion FIC was higher in men with csPCa (FIC, 0.53) than in those without csPCa (FIC, 0.18) for Likert 3 ($P = .002$) and Likert 4 (0.60 vs 0.28, $P < .001$) lesions. Median lesion ADC was lower for Likert 4 lesions with csPCa (0.86×10^{-3} mm^2/sec) compared with lesions without csPCa (1.12×10^{-3} mm^2/sec, $P = .03$), but there was no evidence of a difference for Likert 3 lesions (0.97×10^{-3} mm^2/sec vs 1.20×10^{-3} mm^2/sec, $P = .09$). PSAD also showed no difference for Likert 3 (0.17 ng/mL^2 vs 0.12 ng/mL^2, $P = .07$) or Likert 4 (0.14 ng/mL^2 vs 0.12 ng/mL^2, $P = .47$) lesions. The diagnostic performance of FIC (AUC, 0.96; 95% CI: 0.93, 1.00) was higher ($P = .02$) than that of ADC (AUC, 0.85; 95% CI: 0.79, 0.91) and PSAD (AUC, 0.74; 95% CI: 0.66, 0.82) for the presence of csPCa in biopsied lesions.

Conclusion: Lesion fractional intracellular volume enabled better classification of clinically significant prostate cancer than did apparent diffusion coefficient and prostate-specific antigen density.

Clinical trial registration no. NCT02689271

Online supplemental material is available for this article.

Multiparametric MRI (mpMRI) is now established as the first-line investigation for suspected prostate cancer (PCa) (1), but overall specificity for clinically significant cancer (csPCa) (Gleason score ≥3+4) is reported at a modest 37% (2,3). This results in one in two men with positive mpMRI findings undergoing biopsy, the results of which were negative for significant cancer, with associated morbidity and a health economic cost (4–6).

Adjunct markers have been proposed to complement mpMRI to assist in the decision to biopsy. Several prostate-specific antigen (PSA) density (PSAD) thresholds (ranging from 0.08–0.15 ng/mL^2) are commonly used for men with indeterminate mpMRI findings, but no consensus exists on the optimal threshold (7,8). The apparent diffusion coefficient (ADC) is the most often investigated quantitative marker derived from mpMRI results and has shown value in differentiating significant PCa, but it can cause false-positive findings (9–11).

Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumor (VERDICT) MRI is a

Abbreviations

ADC = apparent diffusion coefficient, AUC = area under the receiver operating characteristic curve, csPCa = clinically significant PCa, FIC = fractional intracellular volume, mpMRI = multiparametric MRI, PCa = prostate cancer, PI-RADS = Prostate Imaging Reporting and Data System, PSA = prostate-specific antigen, PSAD = PSA density, VERDICT = Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumor

Summary

Fractional intracellular volume–derived Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumor analysis of multiparametric MRI findings resulted in better classification of clinically significant prostate cancer than did analysis of prostate-specific antigen density or lesion apparent diffusion coefficient.

Key Results

- In a prospective study of 165 participants, fractional intracellular volume (FIC) derived from Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumor analysis of multiparametric MRI findings (area under the receiver operating characteristic curve [AUC], 0.96) was superior to apparent diffusion coefficient (AUC, 0.85; $P < .001$) and prostate-specific antigen density (AUC, 0.74; $P < .001$) in the identification of lesions with clinically significant prostate cancer (csPCa).
- For indeterminate (Likert 3) lesions, only FIC differed ($P = .002$) between lesions with (median FIC = 0.53) and those without (median FIC, 0.18) csPCa.

multicompartmental diffusion-based method that has been tailored for the prostate and produces estimates of histopathologic features (12,13). Initial results show that VERICT-derived fractional intracellular volume (FIC) can be used to differentiate lesions with from lesions without csPCa and correlates with the cellular fraction in prostatectomy specimens (14,15). This study is called "CombIning advaNces in imagiNg With biOmarkers for improVed Diagnosis of Aggressive prosTate cancer" (or INNOVATE) and represents the largest clinical evaluation of this imaging biomarker thus far in which men underwent VERDICT MRI and mpMRI before targeted biopsy of lesions identified on mpMRI scans (16).

Our objective was to compare quantitative parameters derived from mpMRI and VERDICT MRI results in biopsied lesions in a prospective cohort. We hypothesized that FIC enables better differentiation of which mpMRI-identified lesions have csPCa than does ADC or PSAD.

Materials and Methods

Trial Design and Participants

Ethical approval for the prospective two-center INNOVATE study (ClinicalTrials.gov: NCT02689271) was granted by the UK Research Ethics Committee (ref: 15/LO/0692). The study protocol has been published previously (16). Study participants provided written informed consent. The current study represents a primary analysis of a prospective two-center trial. Data generated or analyzed during the study are available from the corresponding author by request.

Men suspected of having csPCa (raised PSA level or suspicious digital rectal examination findings) referred for further evaluation between April 2016 and December 2019 were recruited from two tertiary centers (Barts Health London and University College London Hospital). Figure 1 outlines the inclusion and exclusion criteria. Men referred with clinical suspicion of PCa were included, and men who were unable to undergo MRI, those who were unable to give informed consent, those who were undergoing treatment for PCa, and those who had undergone previous biopsy were excluded. There is an overlap of 20 participants with a previously published study, which included men who had undergone a previous biopsy (14). The clinical outcomes of the cohort excluding VERDICT MRI results have been published recently (17).

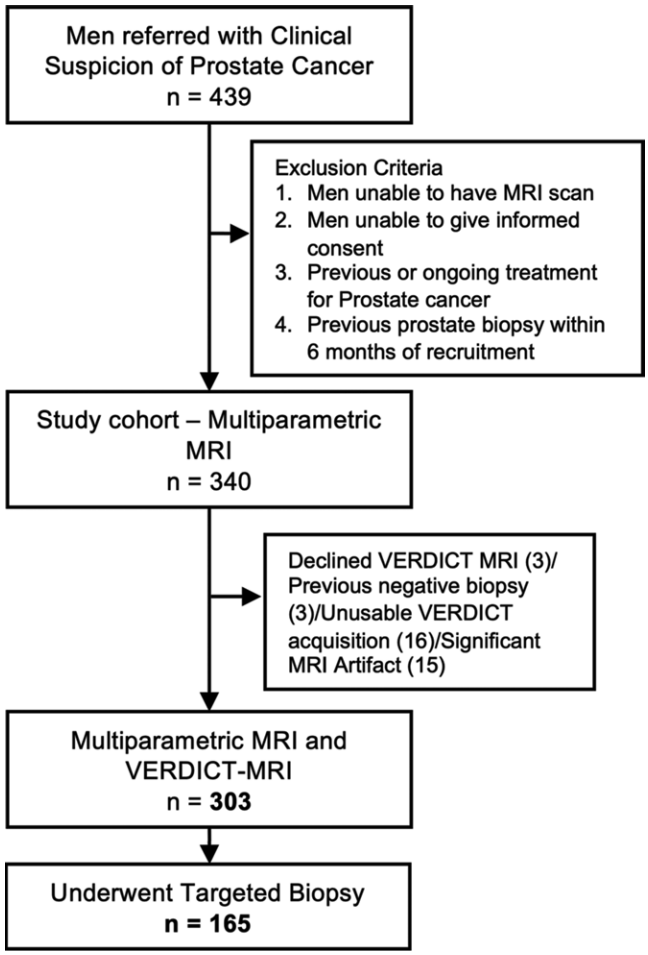

Figure 1: Flowchart of study cohort and participant selection. VERDICT = Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumor.

MRI Examination

Biopsy-naive participants underwent prebiopsy mpMRI and VERDICT MRI. Multiparametric MRI was performed in compliance with the Prostate Imaging Reporting and Data System (PI-RADS) version 2.1 standards on three scanners (Achieva and Ingenia, Philips Healthcare; Avanto, Siemens Healthcare) (18). The protocol included T2-weighted imaging in two planes, diffusion-weighted imaging (b value, 0–1000 sec/mm^2), separate high-b-value acquisition (b value = 1400 sec/mm^2 or b value = 2000 sec/mm^2), and dynamic contrast-enhanced imaging (ProHance; Bracco Diagnostics) (Table E1 [online]). ADC maps were

derived from *b* values (0, 150, 500, and 1000 sec/mm^2). VERDICT MRI was performed with one scanner (Achieva) using five *b* values of 0–3000 sec/mm^2 (Table E2 [online]).

Image Analysis

The index lesion was defined as the highest scoring lesion based on a first read by a clinical radiologist and an independent second read by a study radiologist (S.P., with 12 years of mpMRI experience). Lesions were scored using the Likert system, which ascribes a score from 1 to 5 for the likelihood of csPCa, as recommended by United Kingdom guidelines (1). Disagreements between readings were resolved by consensus in a multidisciplinary meeting involving urologists and radiologists. If more than one lesion had the same highest Likert score, then the larger lesion was selected. Lesions were indicated on a pictorial diagram that was used by a board-certified radiologist (S.S., with 4 years of mpMRI experience) blinded to histologic results to draw a region of interest around the lesion on FIC and ADC maps (Fig 2). The mean ADC (from clinical mpMRI) and FIC were recorded. To assess interrater reliability, a random sample (n = 30) of index lesions was contoured by another board-certified radiologist (F.G., with 7 years of mpMRI experience). Regions of interest were drawn using the Multi-Image Analysis Graphical User Interface (Mango; Research Imaging Institute, University of Texas Health Science Center at San Antonio) (19). PSAD was calculated by dividing the PSA by the MRI-calculated prostate volume using the ellipsoid method (18).

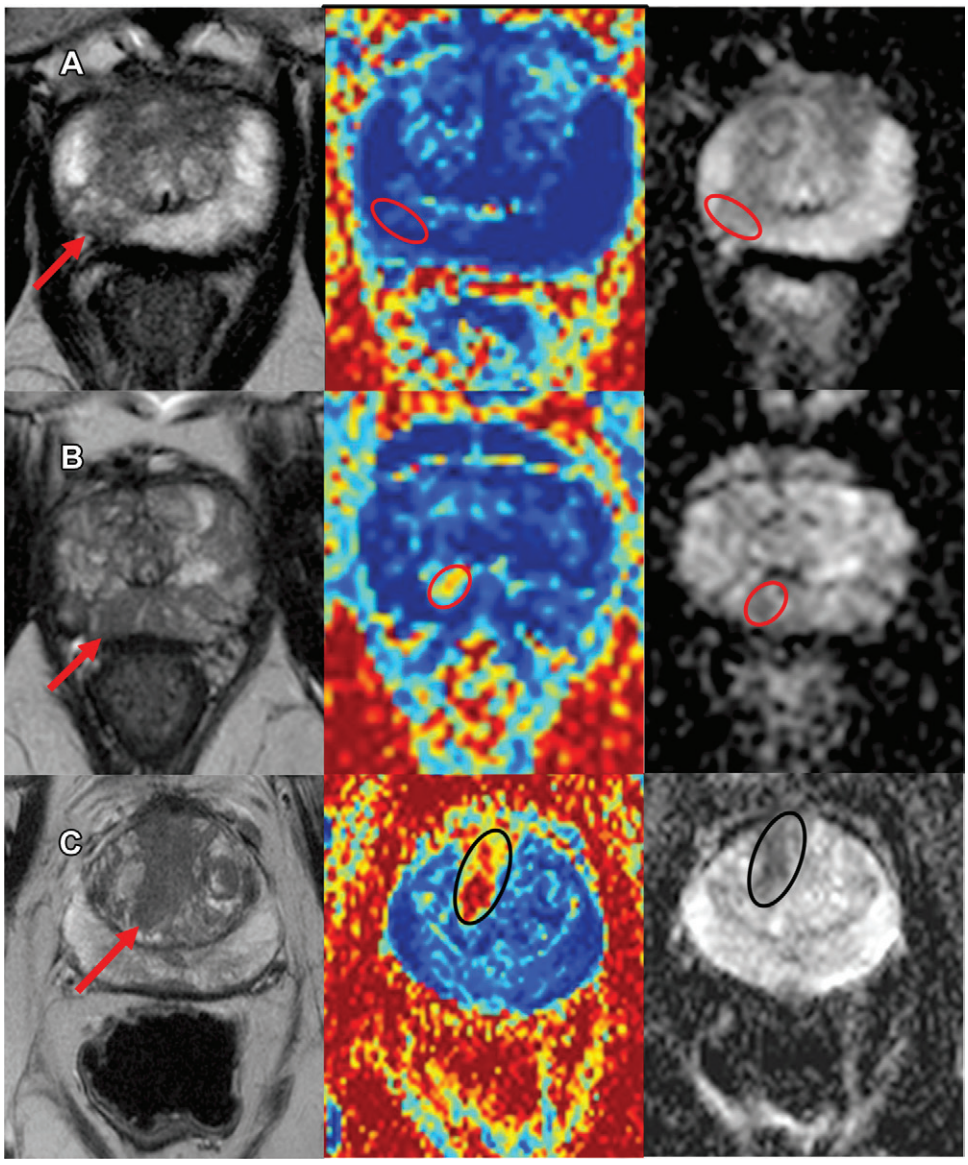

Figure 2: MRI scans in three participants in the study. Left: Axial T2-weighted scan. Middle: Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumor MRI fractional intracellular volume (FIC) map. Right: Apparent diffusion coefficient (ADC) map. The region of interest, indicated as an ellipse on the FIC and ADC maps and as a red arrow on the T2-weighted image, delineates the biopsied lesions. **(A)** Images in a 64-year-old man with a prostate-specific antigen (PSA) level of 5.93 ng/mL and a Likert 3 and Prostate Imaging Reporting and Data System (PI-RADS) 3 MRI lesion in the right basal posterolateral peripheral zone, which was negative for prostate cancer (PCa) at targeted biopsy. **(B)** Images in a 61-year-old man with a Likert 4 and PI-RADS 4 MRI lesion (PSA, 9.80 ng/mL) in the right apical posterolateral peripheral zone, which was positive for Gleason 3+4 PCa at targeted biopsy. **(C)** Images in a 67-year-old man with a Likert 5 and PI-RADS 5 MRI lesion (PSA, 7.83 ng/mL) in the anterior basal transition zone, which was positive for Gleason 5+4 PCa on targeted biopsy.

Biopsy

The decision to offer biopsy was based on mpMRI Likert score and PSAD and not on VERDICT MRI results. Lesions were targeted with transperineal or transrectal biopsy, as well as systematic biopsies, at the two recruiting centers. Biopsies were performed by urologists using cognitive fusion or technology-assisted fusion. Each target was biopsied, and three to six biopsy cores were obtained. Histopathologic assessment was performed at the two recruiting sites, with histopathologists blinded to the results of image analysis. Clinically significant cancer was defined as the presence of one biopsy core containing a lesion with a Gleason score of 3+4 or higher (10).

Statistical Analysis

The study was designed to achieve a power of 90% to detect a 20% reduction in the proportion of false-positive biopsies

(negative or clinically insignificant cancer) in men with positive mpMRI results. This resulted in a sample size of 130 participants using a two-sided χ^2 test with a significance level of .05 and 95% CI. An estimated insignificant biopsy rate of 0.6 was used based on the Prostate MRI Imaging Study trial (2).

Two groups were defined for the primary outcome: *(a)* no cancer or clinically insignificant cancer and *(b)* clinically significant cancer. For Gleason score analysis, four groups were defined: no cancer, Gleason score of 3+3, Gleason score of 3+4, and Gleason score of 4+3 or higher based on previous studies (2). Lesions were retrospectively rescored by a reader (S.S.) using PI-RADS 2.1 and blinded to the histology results to assess generalizability to centers that use PI-RADS (18). Nonparametric tests were used to compare the differences between groups. For the primary outcome, the difference in the median value between two groups was analyzed with the independent samples median test with Yate continuity correction. The Kruskal-Wallis test with Bonferroni multiple comparison correction was used for Gleason groups. CIs were derived by bootstrapping based on 10 000 samples. Post hoc subgroup analyses were performed for men with Likert 3 and Likert 4 lesions, those with PI-RADS 2.1 rescoring, and those who underwent mpMRI performed with the 3.0-T Achieva imager. Receiver operating characteristic curve analysis was performed to compare the classification ability of the three parameters, and a χ^2 test was used to compare the area under the receiver operating characteristic curve (AUC), specificity, and false-negative rates. The highest value of the Youden statistic was calculated from the coordinates of the receiver operating characteristic curve to obtain a threshold. To assess clinical utility, thresholds were applied to Likert 3 or 4 lesions. Likert 5 lesions were excluded, as the positive predictive value of mpMRI is near 100% (2,17). Interrater variability of FIC and ADC maps was assessed with Bland-Altman analysis and the intraclass correlation coefficient. Supplemental analyses were performed to compare AUC for minimum and 10th percentile ADC. Logistic regression models were constructed using lesion FIC, lesion ADC, and PSAD, and they were compared using decision curve analysis.

Statistical analyses were performed using statistical software (SPSS, version 26, IBM; GraphPad Prism, version 9, GraphPad; Stata, version 17, StataCorp). The *P* value threshold for significance was set at $P < .05$.

Results

Participant Characteristics

Among 340 enrolled study participants, three declined VERDICT MRI, three had previous negative biopsy results, 15 had unusable results of VERDICT acquisition (incomplete data sets), and 15 had a substantial artifact on MRI scans (Fig 1). A total of 303 biopsy-naive men were included and underwent mpMRI and VERDICT MRI (Table). Among these men, 165 underwent targeted biopsy (mean age, 65 years ± 7 [SD]). Among the 138 men who did not undergo biopsy, 43 had negative mpMRI findings (Likert 2), 78 had a Likert 3 lesion and low PSAD (<0.15), 12 had a Likert 3 lesion and high PSAD (>0.15), and five had a Likert 4 lesion. The men with a Likert 3 lesion and high PSAD and those with a Likert 4 lesion were recommended for biopsy but opted for PSA and mpMRI surveillance. The median PSA level in the biopsied group was 6.48 ng/mL (range, 0.83–141 ng/mL; IQR, 4.6 ng/mL), and the median prostate volume was 46 mL (range, 12–150 mL; IQR, 30 mL).

Participant Characteristics

Parameter	Finding
Total no. of participants	303
Median age (y)	64 (47–81) [10]
Median PSA (ng/mL)	6.48 (0.83–141) [4.6]
Median prostate volume (mL)	46 (12–150) [30]
Median PSA density (ng/mL^2)	0.14 (0.02–2.36) [0.10]
No. of participants biopsied	165
Mean age ±SD of biopsied participants (y)	65 ± 7
Median maximum cancer core length (mm)	8 (1–20)
Benign biopsy	76
Gleason 3+3	16
Gleason 3+4	46
Gleason ≥4+3	27

Note.—Unless otherwise indicated, data are numbers of participants. Data in parentheses are ranges, and data in brackets are IQRs. PSA = prostate-specific antigen.

MRI Evaluation

Most study participants underwent MRI on the Achieva 3.0-T scanner (78 of 165 men) or the Avanto 1.5-T scanner (79 of 165 men), with a few (eight of 165 men) undergoing imaging with the Ingenia 3.0-T MRI scanner. The Likert scores for the biopsied lesions were as follows: 46% (76 of 165 men) had a Likert score of 3; 30% (49 of 165 men) had a Likert score of 4; and 24% (40 of 165 men) had a Likert score of 5 (Fig 3). Most index lesions were in the peripheral zone (78%, 129 of 165 men) or transition zone (15%, 24 of 165 men) but were rarely in the central zone (1%, two of 165 men). Some lesions spanned both the peripheral zone and the transition zone (5%, nine of 165 men). Retrospective PI-RADS scoring led to a change in score for 52 Likert 3 lesions. A total of 42 lesions were rescored as PI-RADS 2, and 10 were upgraded to PI-RADS 4. Two Likert 5 lesions were reclassified as PI-RADS 4 (Fig 3).

Biopsy Results

Most men (82%, 136 of 165) underwent targeted transperineal biopsy at one center (University College London NHS Foundation Trust), whereas 18% (29 of 165) underwent targeted transrectal biopsy at the other (Barts Health NHS Trust). All biopsies at the first center and most (27 of 29 biopsies, 93%) at the second center were performed using cognitive fusion, except for two biopsies that used technology-assisted fusion. Biopsy was performed a median of 28 days (IQR, 32 days) after imaging, with most lesions (87%, 144 of 165) biopsied within 3 months. For some participants (*n* =

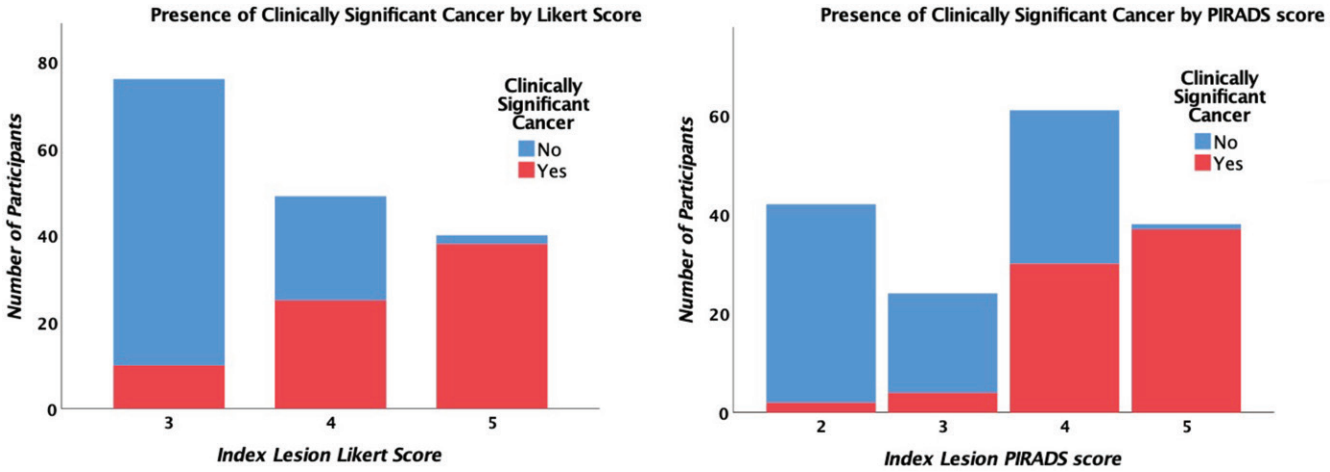

Figure 3: Presence of clinically significant cancer (csPCa) in biopsied lesions by Likert and Prostate Imaging Reporting and Data System (PI-RADS) score. Bar graphs show the proportion of biopsied lesions that had csPCa (red) and those that did not (blue), subdivided by lesion Likert and PI-RADS score.

21), biopsy was performed more than 3 months after research imaging after a period of PSA surveillance.

A total of 73 of 165 lesions (44%) were positive for csPCa, 16 lesions had a Gleason score of 3+3, and 76 lesions were negative. Most lesions with csPCa (63%, 46 of 73 lesions) had 3+4 disease, followed by 4+3 (18 of 73 lesions), 4+5 (three of 73 lesions), 3+5 (two of 73 lesions), 4+4 (two of 73 lesions), 5+4 (one of 73 lesions), and 5+5 (one of 73 lesions) disease. The proportion of lesions with csPCa for each Likert score was as follows: Likert 3, 10 of 76 lesions; Likert 4, 25 of 49 lesions; and Likert 5, 38 of 40 lesions. For PI-RADS rescored lesions, the proportions were as follows: PI-RADS 2, two of 42 lesions; PI-RADS 3, four of 24 lesions; PI-RADS 4, 30 of 61 lesions; and PI-RADS 5, 37 of 38 lesions.

PSAD Analysis

The median PSAD level for men with csPCa was 0.21 ng/mL^2 (IQR, 0.23 ng/mL^2; 95% CI: 0.27, 0.49), and that for men without csPCa was 0.12 ng/mL^2 (IQR, 0.07 ng/mL^2; 95% CI: 0.12, 0.17) ($P < .001$). The distribution of PSAD subdivided by Likert score is shown in Figure 4. For Likert 3 lesions, the median PSAD showed no evidence of a difference ($P = .074$) between lesions with csPCa (0.17 ng/mL^2) and those without csPCa (0.12 ng/mL^2).

There was no evidence of a difference in the median PSAD ($P = .47$) for Likert 4 lesions with csPCa (0.14 ng/mL^2) compared with lesions without csPCa (0.12 ng/mL^2). The same relationship was seen when lesions were scored with PI-RADS, version 2.1 (Fig E1 [online]). PSAD was higher in lesions with a Gleason score of 3+4 ($P = .002$) or a Gleason score of 4+3 or higher ($P < .001$) compared with lesions without csPCa (Fig 5). PSAD was higher in lesions with a Gleason score of 4+3 or higher ($P = .02$) compared with lesions with a Gleason score of 3+3. There was no evidence of a difference between lesions with a Gleason score of 3+4 and those with a Gleason score of 4+3 or higher ($P = .16$), nor was there a difference between lesions with a Gleason score of 3+3 and those with a score of 3+4 ($P = .93$).

ADC Analysis

The median lesion ADC was 0.83 × 10^{-3} mm^2/sec (IQR, 0.29 × 10^{-3}; 95% CI: 0.77, 0.89 × 10^{-3}) in lesions with csPCa and 1.17 × 10^{-3} mm^2/sec (IQR, 0.36 × 10^{-3}; 95% CI: 1.13, 1.24 × 10^{-3}) in lesions without csPCa ($P < .001$). For Likert 3 lesions, the median lesion ADC showed no evidence of a difference ($P = .09$) between lesions with csPCa (0.97 × 10^{-3} mm^2/sec) and those without csPCa (1.20 × 10^{-3} mm^2/sec) (Fig 4).

There was a difference in the median lesion ADC ($P = .03$) between lesions with csPCa (0.86 × 10^{-3} mm^2/sec) and lesions without csPCa (1.12 × 10^{-3} mm^2/sec) for Likert 4 lesions. A similar relationship was observed when lesions were scored with PI-RADS, version 2.1 (Fig E1 [online]). Lesion ADC was lower in Gleason 3+4 lesions ($P < .001$) or Gleason 4+3 lesions ($P < .001$) compared with lesions without csPCa. There was a difference between Gleason 3+3 lesions and Gleason 3+4 lesions ($P < .001$) and between Gleason 3+3 and Gleason 4+3 or greater lesions ($P < .001$), but there was no evidence of a difference between Gleason 3+4 lesions and Gleason 4+3 or greater lesions ($P > .99$) or between negative lesions and Gleason 3+3 lesions ($P > .99$).

In participants (47%, 78 of 165 men) who underwent clinical diffusion-weighted imaging on the scanner used for VERDICT MRI (3.0-T Achieva imager), lesion ADC was lower for Likert 4 lesions that had csPCa ($P = .005$) compared with lesions without csPCa. There was no evidence of a difference in lesion ADC for Likert 3 lesions ($P = .06$) (Fig E2 [online]). The analysis of lesion ADC for each Gleason score in this subgroup is shown in Figure E3 (online).

FIC Analysis

The median lesion FIC in lesions with csPCa was higher at 0.61 ($P < .001$) (IQR, 0.17; 95% CI: 0.56, 0.63) than that in lesions without csPCa at 0.22 (IQR, 0.19; 95% CI: 0.22, 0.27). For Likert 3 lesions, FIC was higher ($P < .001$) in lesions with csPCa (0.53; 95% CI: 0.47, 0.59) compared with

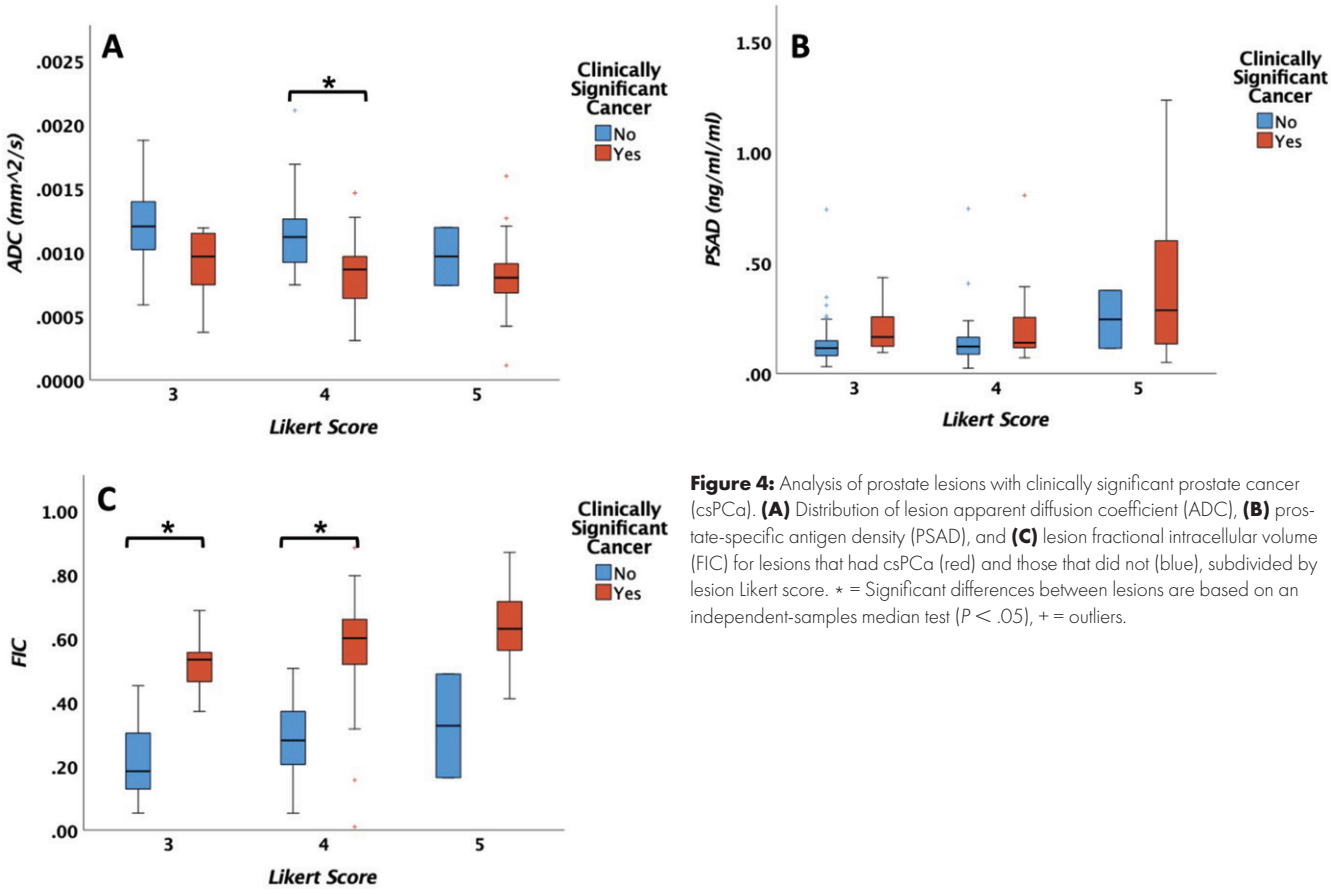

Figure 4: Analysis of prostate lesions with clinically significant prostate cancer (csPCa). **(A)** Distribution of lesion apparent diffusion coefficient (ADC), **(B)** prostate-specific antigen density (PSAD), and **(C)** lesion fractional intracellular volume (FIC) for lesions that had csPCa (red) and those that did not (blue), subdivided by lesion Likert score. * = Significant differences between lesions are based on an independent-samples median test ($P < .05$), + = outliers.

lesions without csPCa (0.18; 95% CI: 0.19, 0.25) (Fig 4). There was a difference in median lesion FIC ($P < .001$) for Likert 4 lesions with csPCa (0.60; 95% CI: 0.48, 0.63) and those without csPCa (0.28; 95% CI: 0.24, 0.34). A similar relationship was seen when lesions were scored with PI-RADS, version 2.1 (Fig E1 [online]).

Lesion FIC was higher in PCa lesions with a Gleason score of 3+4 ($P < .001$) or a score of 4+3 or higher ($P < .001$) compared with negative lesions (Fig 5). There was also a difference between lesions with a Gleason score of 3+3 or 3+4 ($P < .001$) and those with a score of 4+3 or greater ($P < .001$). There was no evidence of a difference in lesion FIC between lesions that were negative and PCa lesions with a Gleason score of 3+3 ($P > .99$) or between lesions with a Gleason score of 3+4 or 4+3 or higher ($P > .99$).

Diagnostic performance of PSAD and MRI analysis receiver operating characteristic curves for PSAD, lesion ADC, and lesion FIC are shown in Figure 6. The AUC was higher for lesion FIC at 0.96 (95% CI: 0.93, 1.00) compared with ADC at 0.85 ($P = .016$; 95% CI: 0.79, 0.91) and PSAD at 0.74 ($P < .001$; 95% CI: 0.66, 0.82).

The Youden index was determined to provide optimal sensitivity and specificity thresholds. The thresholds were as follows: PSAD of 0.18 ng/mL^2 (sensitivity, 59%; specificity, 83%), lesion ADC of 1.00×10^{-3} mm^2/sec (sensitivity, 83%; specificity, 77%), and lesion FIC of 0.41 (sensitivity, 95%; specificity, 90%). Thresholds based on the highest Youden statistic were retrospectively applied in men with Likert 3 or Likert 4 lesions ($n = 125$), of which 35 of 125 lesions (28%) were positive for csPCa and 90 of 125 lesions (72%) were negative for csPCa.

The lesion FIC threshold of 0.41 for participants with Likert 3 or 4 lesions (ie, participants with a lesion FIC of 0.41 or less would not be biopsied) would result in a higher specificity (number of participants who could avoid a negative biopsy) of 91% (82 of 90 participants, $P = .01$) compared with 78% (70 of 90 participants) for the lesion ADC threshold of 1.00×10^{-3} mm^2/sec. The PSAD threshold of 0.18 ng/mL/mL would result in a specificity of 83% (75 of 90 participants), with no evidence of a difference compared with the FIC threshold ($P = .12$). The false-negative rate (number of participants with csPCa who would be undetected) is lower for the FIC threshold at 11% (four of 35 participants, $P < .01$) compared with PSAD at 54% (19 of 35 participants) and with no evidence of a difference compared with lesion ADC at 23% (eight of 35 participants, $P = .12$).

The AUC was 0.84 (95% CI: 0.78, 0.90) for minimum ADC and 0.84 (95% CI: 0.77, 0.90) for 10th percentile ADC, which was lower than that of mean ADC (0.85; 95% CI: 0.79, 0.91) (Fig E4 [online]). In a logistic regression model with all three parameters, only lesion FIC ($P < .001$) was significant and provided the most net benefit (Fig E5 [online]).

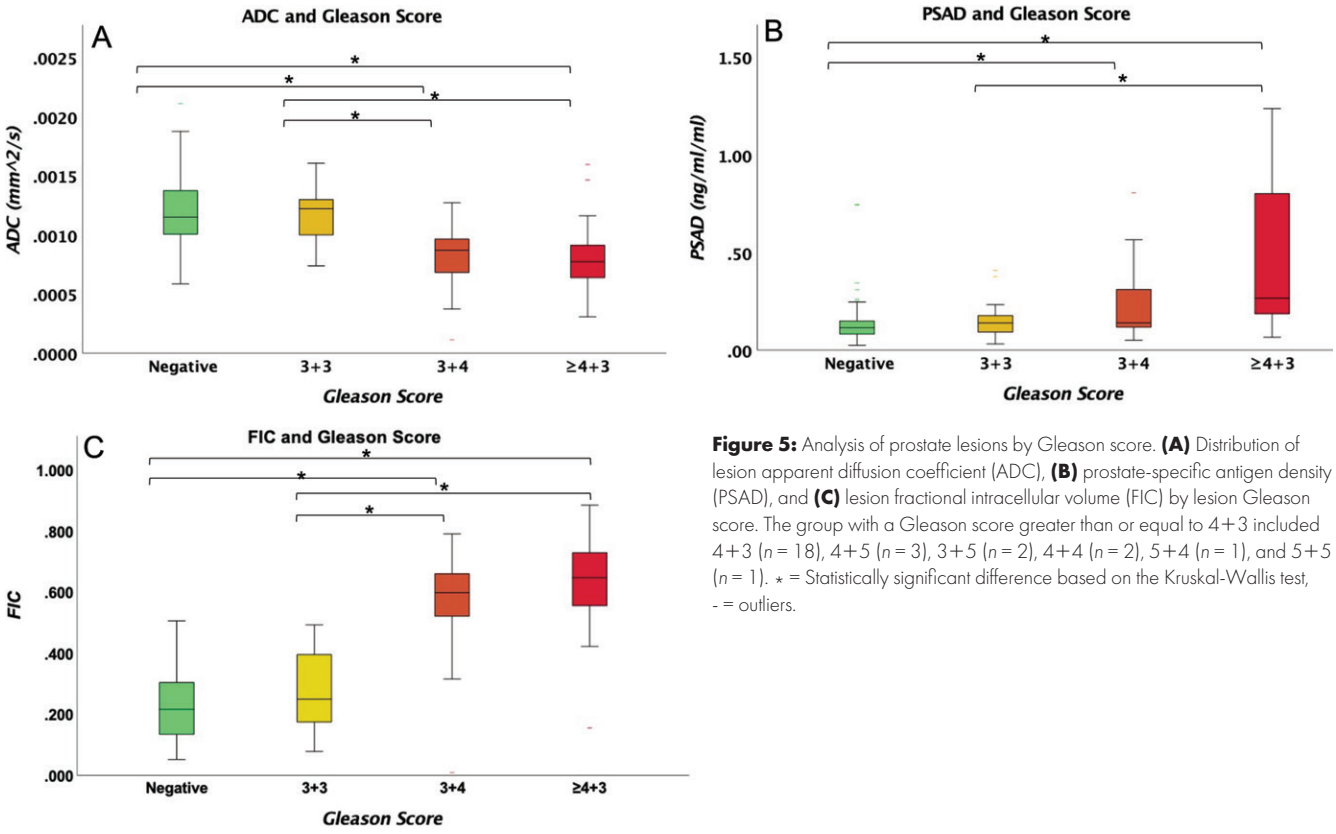

Figure 5: Analysis of prostate lesions by Gleason score. **(A)** Distribution of lesion apparent diffusion coefficient (ADC), **(B)** prostate-specific antigen density (PSAD), and **(C)** lesion fractional intracellular volume (FIC) by lesion Gleason score. The group with a Gleason score greater than or equal to 4+3 included 4+3 (*n* = 18), 4+5 (*n* = 3), 3+5 (*n* = 2), 4+4 (*n* = 2), 5+4 (*n* = 1), and 5+5 (*n* = 1). ⋆ = Statistically significant difference based on the Kruskal-Wallis test, - = outliers.

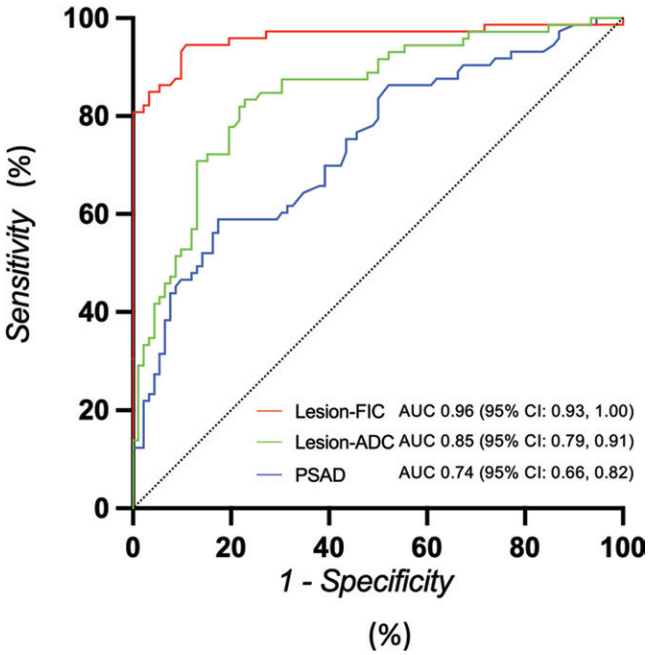

Figure 6: Graph shows receiver operating characteristic curves for lesion apparent diffusion coefficient (ADC) (green), prostate-specific antigen density (PSAD) (blue), and lesion fractional intracellular volume (FIC) (red) for all lesions. Areas under the receiver operating characteristic curve (AUCs) and 95% CIs are indicated.

Interreader Variability

The intraclass correlation coefficient for lesion FIC was 0.93, and the intraclass correlation coefficient for lesion ADC was 0.89. The Bland-"Altman analysis plot showed no evidence of proportional bias in the two measurements (Fig E6 [online]).

Discussion

In this prospective trial, we found that a quantitative imaging marker derived from Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumor MRI, called fractional intracellular volume (FIC), enabled better classification (area under the receiver operating characteristic curve [AUC], 0.96; 95% CI: 0.93, 1.00) of lesions that had clinically significant prostate cancer (csPCa) than did apparent diffusion coefficient (AUC, 0.85; 95% CI: 0.79, 0.91) and prostate-specific antigen density (AUC, 0.74; 95% CI: 0.66, 0.82) derived from multiparametric MRI. For indeterminate lesions, only lesion FIC was significantly higher in lesions with csPCa ($P < .001$). The FIC threshold, when retrospectively applied to men with Likert 3 or 4 disease, could have allowed 91% of men (82 of 90) within this subgroup to avoid biopsy at the cost of not detecting csPCa in 11% (four of 35).

The performance of PSAD and ADC in lesion stratification was comparable to reported metrics in previous studies. The AUC for ADC has been reported to range from 0.7 to 0.72 (5,20), and the AUC for PSAD has been reported to range from 0.68 to 0.75 (5,8). Lesion FIC outperformed both for the classification of

csPCa, in keeping with a previous study in a smaller cohort (14). Interreader variability was similar for both ADC and FIC and comparable to published values for region of interest analysis (14).

In our center and in others in the United Kingdom, scoring of mpMRI studies is performed using the Likert system, as recommended by UK guidelines (1). Scoring of lesions with PI-RADS, version 2.1, was performed retrospectively within our study and did not influence biopsy decisions. Nonetheless, lesion FIC enabled differentiation between lesions with and those without csPCa in the PI-RADS 3 and 4 scored groups. This rescored analysis implies potential generalizability of our results to centers that exclusively use PI-RADS scoring.

Our study had limitations. First, although recruitment was performed at two centers, imaging was performed at one specialist center; therefore, generalizability has not been investigated. Second, ADC was derived from mpMRI performed with three different scanners and from VERDICT MRI performed with one scanner; therefore, the results for ADC may be affected by interscanner variability. However, in the subgroup analysis of ADC produced by the same scanner as that used for VERDICT, the results were comparable to the whole sample. The third limitation is that only participants who underwent biopsy were included in this analysis; therefore, the prevalence of csPCa in this cohort might be higher. Finally, due to the smaller number of lesions in the transition zone compared with the peripheral zone in this cohort, we cannot fully assess the impact of VERDICT for transition zone tumors.

In conclusion, lesion fractional intracellular volume enabled excellent classification of clinically significant prostate cancer and offers men with positive multiparametric MRI findings who are likely to have clinically insignificant biopsy results the opportunity to potentially avoid unnecessary biopsy. Prospective multicenter evaluation of the thresholds derived in our study remains the next step.

Author contributions: Guarantors of integrity of entire study, **S.S., B.K., S.P.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **S.S., S.H., D.C.A., S.P.**; clinical studies, **S.S., J.C., E.W.J., A.G., E.D., S.H., A.F., F.G., C.M.M., S.P.**; statistical analysis, **S.S., H.R., T.P., D.C.A., S.P.**; and manuscript editing, **S.S., H.R., B.K., H.P., E.W.J., E.D., S.H., A.H., A.F., F.G., D.A., C.M.M., H.C.W., D.C.A., E.P., S.P.**

Data sharing: Data generated or analyzed during the study are available from the corresponding author by request.

Disclosures of conflicts of interest: S.S. No relevant relationships. **H.R.** No relevant relationships. **B.K.** No relevant relationships. **J.C.** No relevant relationships. **H.P.** No relevant relationships. **E.W.J.** No relevant relationships. **T.P.** No relevant relationships. **A.G.** Spoke for Angiodynamics at Nanoknife meeting; support from Angiodynamics for travel to and accommodations at Nanoknife training course. **E.D.** No relevant relationships. **G.S.** No relevant relationships. **S.H.** No relevant relationships. **U.S.F.** No relevant relationships. **A.H.** No relevant relationships. **A.F.** No relevant relationships. **F.G.** 2020 PCF Young Investigator Award; consulting fees from Lucida Medical. **D.A.** University College London has a patent pending that used some data collected during this study for verification but did not use VERDICT scans. **C.M.M.** Grants from NIHR, PCUK, Movember, CRUK, MRC, and Spectracure; consulting fees from Sonablate; honoraria from Astellas Janssen; unpaid board membership on the EAU Foundation Research Board, Movember advisory boards, and BMJ Open editorial board. **H.C.W.** Centre of Excellence funding from Prostate Cancer UK; support for attending meetings and/or travel from Cancer Research UK Medical Research Council; Medical Research Council DPFS committee and Cancer Research UK funding committees. **D.C.A.** No relevant relationships. **E.P.** No relevant relationships. **S.P.** Patent for luminal index MRI is pending; chair of the Governance Group for the National Cancer Imaging Translational Accelerator.

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