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Utility of Restriction Spectrum Imaging Among Men Undergoing First-Time Biopsy for Suspected Prostate Cancer

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Abstract

OBJECTIVE.—The purpose of this article is to evaluate restriction spectrum imaging (RSI) in men undergoing MRI-ultrasound fusion biopsy for suspected prostate cancer (PCa) and to compare the performance of RSI with that of conventional DWI.

MATERIALS AND METHODS.—One hundred ninety-eight biopsy-naïve men enrolled in a concurrent prospective clinical trial evaluating MRI-targeted prostate biopsy underwent multiparametric MRI with RSI. Clinical and imaging features were compared between men with and without clinically significant (CS) PCa (MRI-ultrasound fusion biopsy Gleason score ≥ 3 + 4). RSI *z* score and apparent diffusion coefficient (ADC) were correlated, and their diagnostic performances were compared.

RESULTS.—CS PCa was detected in 109 of 198 men (55%). Using predefined thresholds of ADC less than or equal to 1000 $\mu m^2/s$ and RSI *z* score greater than or equal to 3, sensitivity and specificity for CS PCa were 86% and 38%, respectively, for ADC and 61% and 70%, respectively, for RSI. In the transition zone ($n = 69$), the sensitivity and specificity were 94% and 17%, respectively, for ADC and 59% and 69%, respectively, for RSI. Among lesions with CS PCa, RSI *z* score and ADC were significantly inversely correlated in the peripheral zone ($\rho = -0.4852$; $p < 0.01$) but not the transition zone ($\rho = -0.2412$; $p = 0.17$). Overall diagnostic accuracies of RSI and DWI were 0.70 and 0.68, respectively ($p = 0.74$).

CONCLUSION.—RSI and DWI achieved equivalent diagnostic performance for PCa detection in a large population of men undergoing first-time prostate biopsy for suspected PCa, but RSI had superior specificity for transition zone lesions.

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Keywords

biopsy; DWI; prostate cancer

DWI has been shown to be an integral component of contemporary prostate multiparametric MRI protocols [1–3], although it does suffer from a few notable limitations: information from the T2 component of the signal is underutilized, signal from extracellular and intracellular water is mixed, and the quantitative representation of tissue diffusivity, the apparent diffusion coefficient (ADC), is technique and scanner dependent and, thus, not easily generalizable across institutions and imaging platforms [4].

Restriction spectrum imaging (RSI) is a novel diffusion-based technique developed initially for neuroimaging that uses data from a broader range of b values obtained in multiple directions to model a distribution, or spectrum, of the anisotropic and isotropic tissue water compartments [5]. In so doing, RSI is thought to be able to isolate signal from intra-cellular restricted water and simultaneously minimize signals from extracellular hindered and free water, which currently confound conventional DWI [6]. In addition, the RSI z score inherently normalizes across the patient population studied and is, thus, potentially more comparable across different scanners and institutions, unlike the ADC value [7].

Existing data regarding the utility of RSI for PCa detection and characterization are largely limited to a few small proof-of-concept studies [8–10], which were limited by selection bias and small sample size. In addition, none of the existing studies evaluated the diagnostic performance of RSI in the transition zone, which is notable given the inherent limitations of conventional DWI in this region due to benign prostatic hyperplasia. The purpose of our study was to evaluate the diagnostic performance of RSI among a large cohort of men undergoing 3-T MRI for initial evaluation of suspected prostate cancer (PCa) and to compare the performance of RSI with that of conventional DWI, in both the peripheral zone and the transition zone.

Materials and Methods

Patients

This retrospective study was approved by the University of California Los Angeles institutional review board with a waiver of informed consent. The study cohort is composed of a subgroup of men enrolled in a National Cancer Institute–funded prospective phase 2 clinical trial, Prospective Assessment of Image Registration for the Diagnosis of Prostate Cancer (PAIREDCAP; R01CA195505), which recently completed enrollment. Briefly, this study concerned biopsy-naïve men 45–80 years old with PCa suspected on the basis of elevated prostate-specific antigen level with at least one Prostate Imaging–Reporting and Data System version 2 (PI-RADSv2) category 3 or higher lesion seen at MRI. Most study participants underwent RSI as part of their multiparametric MRI, followed by prostate biopsy, which included conventional 12-core systematic transrectal ultrasound–guided biopsy and targeted biopsy using both visual (cognitive) and a previously described commercially available MRI-ultrasound (software) fusion technique (Artemis, Eigen) [11].

All PI-RADSv2 category 3 or higher lesions underwent targeted biopsy. Between September 8, 2015, and March 29, 2018, 248 men were enrolled in PAIREDCAP. Among these men, RSI could not be performed in 39 (16%) and was technically inadequate in an additional 11 (4%), leading to the current study cohort of 198 patients evaluated here.

Imaging Technique

Multiparametric MRI examinations were performed on one of several 3-T MRI platforms (Magnetom Trio, Verio, Skyra, or Prisma, all from Siemens Healthineers) with a pelvic phased-array coil. The protocol included multiplanar high-resolution T2-weighted imaging, DWI, dynamic contrast-enhanced imaging [12], and RSI. The imaging protocol was adherent to PI-RADSv2 technical recommendation criteria [13] and is provided in full in Table 1.

Image Analysis

All multiparametric MRI examinations were prospectively evaluated by one of three experienced genitourinary radiologists, each of whom has interpreted more than 2000 prostate MRI examinations. Reporting and assessment were consistent with PI-RADSv2. RSI cellularity maps were retrospectively evaluated separately by one of three abdominal imaging fellows. Any lesion assigned a PI-RADSv2 overall assessment category of 3 or higher was contoured on the RSI cellularity map (overlaid on axial T2-weighted images). Using the predefined lesion contour, as determined by the initial interpreting radiologist, an ROI between 10 and 50 mm^2 in size was drawn corresponding to the region of greatest restricted diffusivity on the single axial slice, which depicted the lesion most clearly. For quality control purposes, 25 cases (12%) were randomly selected and measured by two separate observers. All RSI image analysis was done without knowledge of clinical data and biopsy results.

Statistical Analysis

Clinical and imaging features were compared between men with and without clinically significant (CS) PCa, which was defined as a biopsy Gleason score greater than or equal to 3 + 4 from within the targeted lesions. Multivariate logistic regression was performed for CS PCa, and the diagnostic performances of RSI and ADC were evaluated for all patients and by lesion location. The diagnostic test threshold for detection of CS PCa for DWI was set as an ADC value less than or equal to 1000 $\mu m^2/s$, according to previous work from our institution [14, 15]. The RSI threshold for CS PCa was set to a z score greater than or equal to 3, as shown elsewhere [10]. Because both of these tests are continuous variables, however, additional thresholds were also tested. Finally, ROC analysis of CS PCa for RSI and DWI were performed, and RSI z score and ADC were correlated using Spearman rank tests.

Results

Patient demographics stratified by MRI-ultrasound fusion biopsy–derived histopathologic analysis are presented in Table 2. CS PCa was detected in 109 of 198 men (55%). Thirty-four of 69 (49%) transition zone index lesions and 75 of 129 (58%) peripheral zone index lesions contained CS PCa. No significant difference in CS PCa frequency was observed

according to the zone of origin ($p = 0.23$). Higher prostate-specific antigen level, prostate-specific antigen density, overall PI-RADSv2 assessment category, lesion diameter, RSI *z* score, and lower ADC were all significantly associated with CS PCa. Controlling for PI-RADSv2 overall assessment category, lesions with an RSI *z* score greater than or equal to 3 were 2.69 times more likely to be associated with CS PCa than were lesions with an RSI *z* score less than 3 (95% CI, 1.43–5.04; $p = 0.0021$). In the 25 cases randomly selected for repeat measurement, the mean difference between the new RSI *z* score and the original RSI *z* score was 0.2983, which was not statistically significantly different ($p = 0.16$).

Using the predefined thresholds of RSI *z* score greater than or equal to 3 and ADC less than or equal to 1000 $\mu m^2/s$, the overall sensitivities of RSI and ADC for the detection of CS PCa were 61% and 86% with specificities of 70% and 38%, respectively. These differences were exaggerated in the transition zone, where the sensitivity and specificity of RSI for CS PCa were 59% and 69%, respectively, compared with sensitivity and specificity of 94% and 17%, respectively, for DWI. Sensitivity and specificity of DWI in the transition zone using a threshold of ADC less than or equal to 900 $\mu m^2/s$ were 74% and 54%, respectively. Sensitivity and specificity of RSI in the transition zone using a threshold of *z* score greater than or equal to 2.5 were 71% and 57%, respectively. Complete diagnostic performances are shown in Table 3.

Among patients with CS PCa, RSI *z* score and ADC were significantly inversely correlated with one another in the peripheral zone ($\rho = -0.4852$; $p < 0.01$) but not in the transition zone ($\rho = -0.2412$; $p = 0.17$). Spearman rank correlation plots stratified by biopsy histopathologic analysis are presented in Figure 1.

Overall diagnostic accuracies, determined by ROC analysis, were 0.70 and 0.68 for RSI and DWI, respectively ($p = 0.74$), as shown in Figure 2. In the peripheral zone, accuracies for RSI and DWI were 0.72 and 0.73, respectively ($p = 0.76$). In the transition zone, accuracies for RSI and DWI were 0.67 and 0.61, respectively ($p = 0.55$). A PI-RADSv2 over-all category greater than or equal to 4 had accuracies of 0.62, 0.62, and 0.61 for all lesions, peripheral zone lesions, and transition zone lesions, respectively. A PI-RADSv2 T2 score greater than or equal to 4 had accuracies of 0.63, 0.62, and 0.64 for all lesions, peripheral zone lesions, and transition zone lesions, respectively (Fig. 3). Logistic regression results are presented in full in Table 4.

Discussion

Multiple prior studies have documented the utility of DWI in PCa detection and characterization [16–19]. Although these studies have shown that the ADC value is currently the most useful quantitative parameter (imaging biomarker) for PCa assessment, it does have some notable limitations. Because of technique and scanner dependence, reproducibility across institutions and different MRI platforms is limited. Diagnostic performance is consistently lower in the transition zone relative to the peripheral zone [20]. In initial pilot studies, RSI has been shown to be a promising independent biomarker; however, these studies have been limited by small sample size and selection bias, applied only to surgical populations that underwent radical prostatectomy [8–10]. Thus, results reported to date may

not be applicable to patients with suspected PCa in a screening population undergoing systematic and targeted biopsy. It is in this context that the current study was undertaken.

In this study, when applied to a large biopsy-naïve cohort of men with clinically suspected PCa, we report for the first time a small but nonsignificant improvement in diagnostic performance of RSI compared with conventional DWI on 3-T MRI. Although the results presented here differ from those of previously reported series, which showed a clear superiority of RSI relative to DWI for PCa detection and characterization [8, 10], this is likely a reflection of the broader patient population and range of PCa grades evaluated in our study.

To determine whether RSI provides unique information compared with DWI, we correlated the two imaging techniques in both the peripheral and transition zones. There was a significant inverse correlation between RSI *z* score and ADC in the peripheral zone, but this relationship did not hold in the transition zone, which suggests that the two techniques do in fact provide distinct information for transition zone lesions. Moreover, the specificity of RSI for CS PCa in the transition zone was far superior to that of DWI (69% vs 17%); even when we lowered the ADC threshold to 900 $\mu m^2/s$ to improve the specificity of DWI, the specificity of RSI was superior (69% vs 54%). To our knowledge, these findings have not yet been reported in the literature. A possible explanation for the superior specificity achieved with RSI in the transition zone is that it can isolate signal from intracellular tumor cells (restricted diffusion), as seen in CS PCa, while simultaneously minimizing contributions from extra-cellular processes (hindered diffusion), such as may occur with stromal benign prostatic hyperplasia, which is the biggest confounder in the transition zone. This would be clinically useful, because DWI is quite sensitive, as shown in our study, but not very specific for CS PCa in the transition zone.

Strengths of this study include the large sample size, the inclusion of a large number of PCa lesions within both the peripheral and transition zones of varying grades, the exploration of the correlation between RSI *z* score and ADC, and the rigorous quality control, including confirmation of interreader validity of RSI *z* score measurements. The RSI *z* score validity was likely bolstered by the measurement technique used here, in which only the portion of the lesion with the greatest degree of restricted diffusivity was measured, because this has previously been shown to be more reproducible in multiple studies evaluating quantitative tumor ADC [21, 22].

There are also a few notable limitations. MRI-ultrasound fusion biopsy, rather than radical prostatectomy, served as the reference standard in this study; this was necessary because one of the primary aims of the study was to evaluate RSI in a general screening population, the majority of whom do not undergo radical prostatectomy. We did not evaluate PI-RADSv2 category 2 lesions, the vast majority of which would be expected to be benign; exclusion of these lesions from analysis may have resulted in a slight overestimate of diagnostic test sensitivity and a slight underestimate of diagnostic test specificity. Image acquisition, interpretation, and prostate biopsy were all conducted by a specialized team of experienced radiologists and urologists and, thus, may not be directly applicable to community practices. The ROI placement may have differed slightly between RSI and DWI, because our standard

practice is to draw the ROI separately on T2-weighted images, the ADC map, and the RSI map, to accommodate geometric distortion on the standard ADC map. T2-weighted imaging was necessarily used as an anatomic reference when evaluating both DWI and RSI, and this could have affected the image interpretation, although it would be expected to do so equally for both techniques. Finally, the ADC was calculated using a low b value of 0 s/mm^2 rather than 50 s/mm^2 which may have introduced some perfusion effects into the calculation, potentially undermining its performance.

In conclusion, RSI and DWI achieved equivalent overall diagnostic performance for PCa detection in a large population of men undergoing first-time biopsy for suspected PCa. However, elevated RSI *z* score is a more specific imaging finding than reduced ADC for CS PCa in the transition zone, adding supporting initial experience for its use as a possible new MRI biomarker in the transition zone. These results will need to be confirmed in larger future studies.

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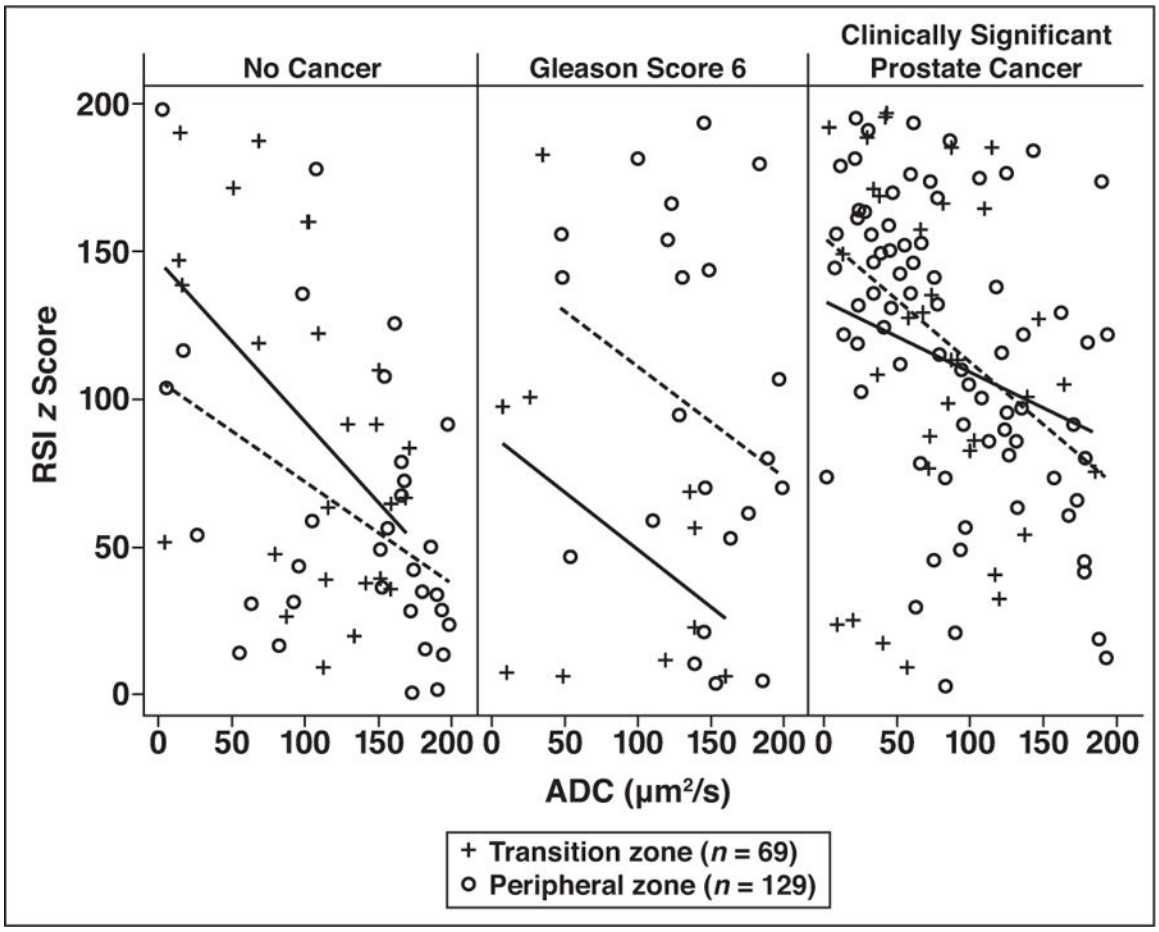

Fig. 1.

Spearman rank plots. Graph shows data for correlation between apparent diffusion coefficient (ADC) and restriction spectrum imaging (RSI) *z* score, stratified by prostate zone and biopsy findings. Solid lines denote transition zone. Dashed lines denote peripheral zone.

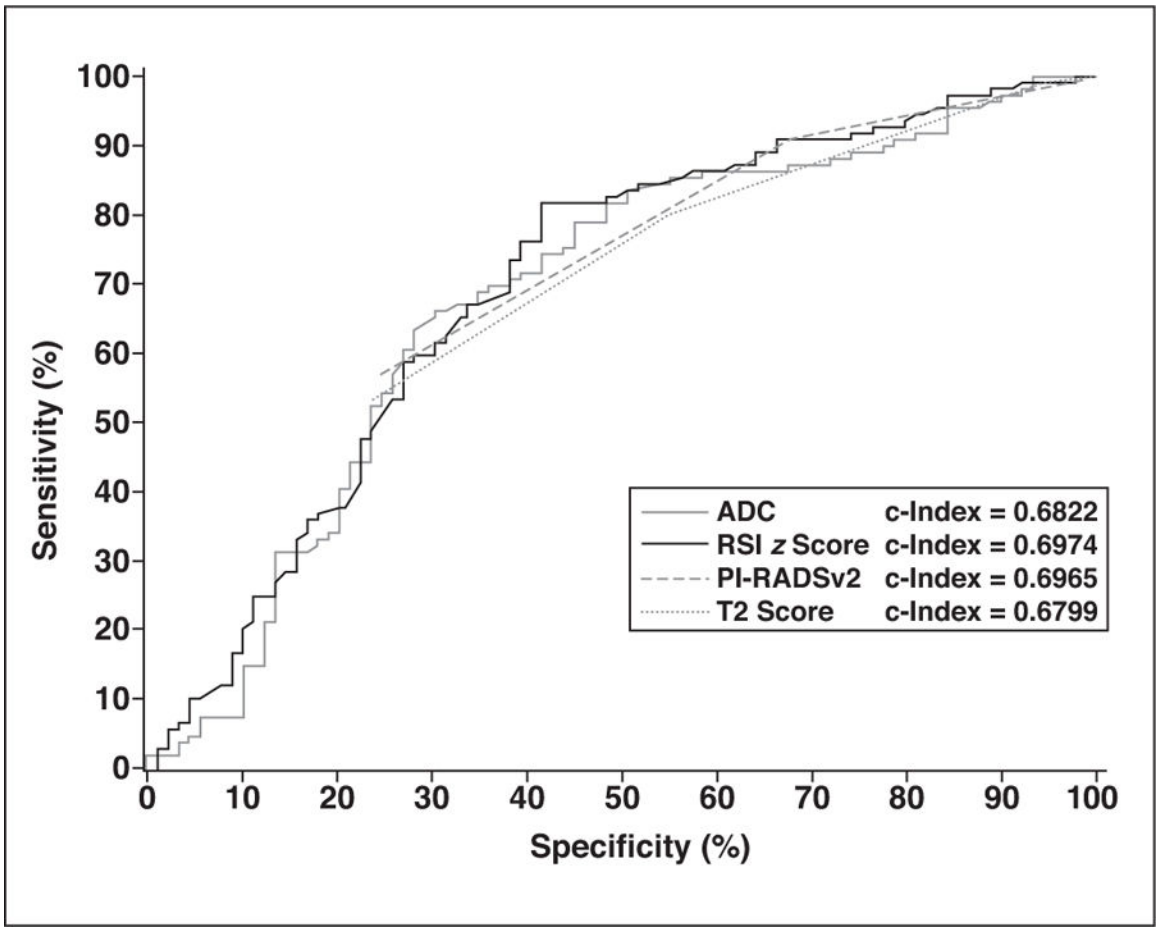

Fig. 2.

Graph of ROC curves for clinically significant prostate cancer detection parameters, including apparent diffusion coefficient (ADC), restriction spectrum imaging (RSI) *z* score, Prostate Imaging–Reporting and Data System version 2 (PI-RADSv2) category, and T2-weighted imaging score, along with corresponding c-indexes.

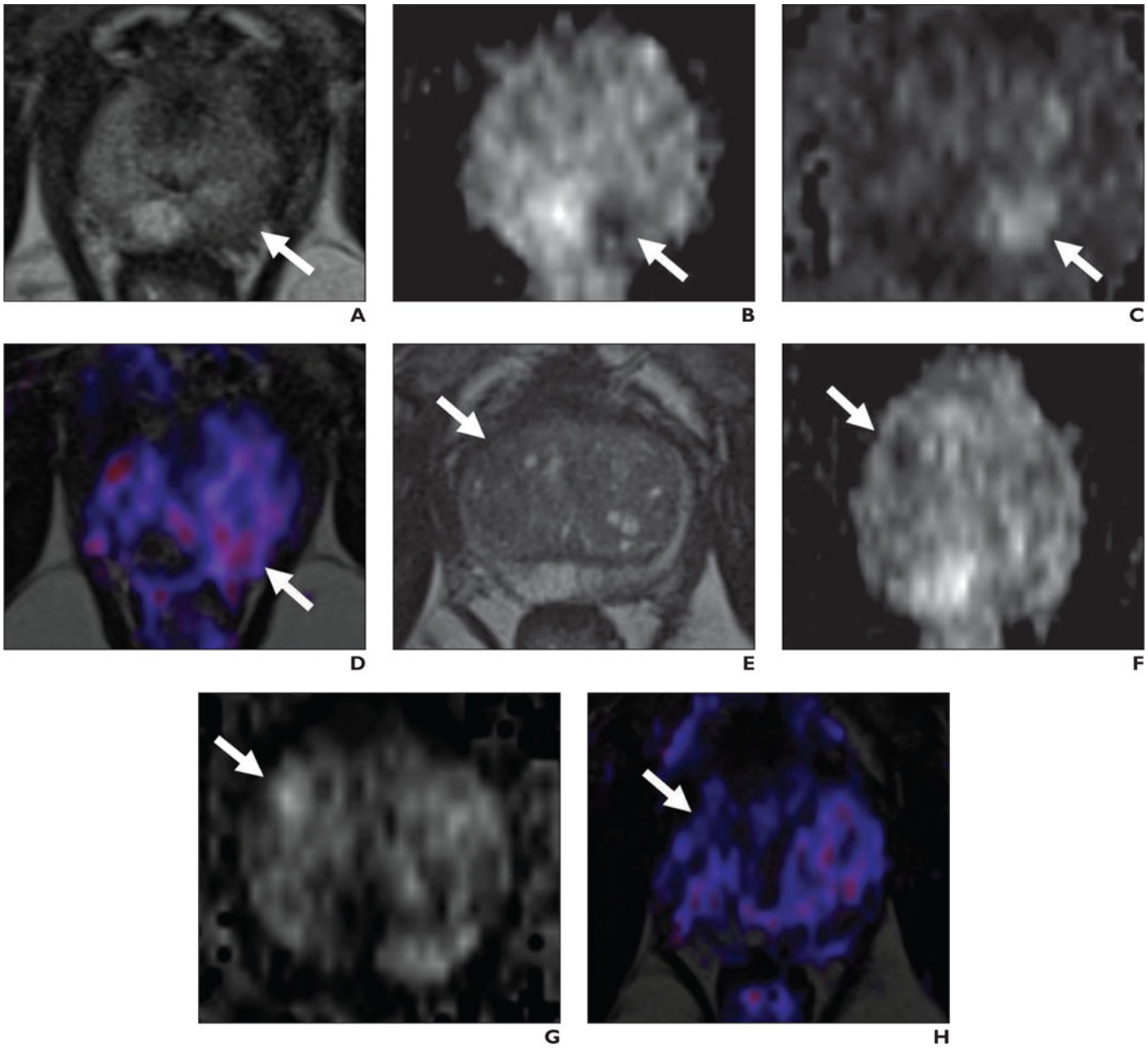

Fig. 3.

65-year-old man with prostate-specific antigen level of 5.5 ng/mL and no prior prostate biopsy. Prebiopsy multiparametric MRI with restriction spectrum imaging (RSI) identified two suspicious lesions.

A–D, T2-weighted MR image (**A**), apparent diffusion coefficient (ADC) map (**B**), DW image (**C**), and restriction spectrum image (**D**) show 1.8-cm lesion (*arrows*) in left posterior peripheral gland. ADC was 880 $\mu m^2/s$, RSI *z* score was 3.6, and overall Prostate Imaging–Reporting and Data System version 2 (PI-RADSv2) assessment was category 5. MRI-ultrasound fusion targeted biopsy (not shown) determined Gleason score of 4 + 3 in multiple cores.

E–H, T2-weighted MR image (**E**), ADC map (**F**), DW image (**G**), and restriction spectrum image (**H**) show 1.3-cm lesion (*arrows*) in right anterior transition zone. ADC was 888 $\mu m^2/s$, RSI *z* score was 1.0, and overall PI-RADSv2 assessment was category 3. MRI-ultrasound fusion targeted biopsy (not shown) revealed benign glands and stroma.

TABLE 1:

MRI Pulse Sequence Parameters

Sequence	TR/TE	Flip Angle (°)	Slice Thickness (mm)	FOV (mm)	Matrix Size (mm)	No. of Averages	Acquisition Time
2D T2-weighted turbo spin-echo	4000/109	160	3	200 × 200	320 × 310	2	4 min 10 s
DWI[a]	4800/80	Echo-planar imaging	3.6	210 × 260	160 × 94	7	5 min 50 s
Dynamic contrast-enhanced imaging	3.89/1.52	12	3.6	260 × 260	160 × 160	1	6 min 00 s
Restriction spectrum imaging[b]	5500/84	90	3.6	210 × 260	128 × 96	1	5 min 00 s

Note—Temporal resolution was 4.75 seconds.

[a]b Values were 0, 100, 400, 800, and 1400 s/mm^2.

[b]Sensitizing diffusion gradients were applied sequentially in 30 directions with b values of 800, 1500, and 4000 s/mm^2. Reference scans with b values of 0 were obtained with both forward and reverse phase encoding. The parallel imaging factor was 2.

TABLE 2:

Patient Characteristics by Gleason Score From Fusion Biopsy (n = 198)

Characteristic	Gleason Score < 7 (n = 89)	Gleason Score ≥ 7 (n = 109)	p
Age at biopsy (y)			
Mean ± SD	64.9 ± 6.8	66.2 ± 8.0	0.2593
< 60	25 (22)	26 (28)	0.0335
60–64	33 (29)	16 (17)	
65–69	19 (17)	24 (26)	
≥ 70	24 (21)	35 (38)	
Gleason score			
Benign	64 (57)		
3 + 3	36 (32)		
3 + 4		53 (58)	
4 + 3		27 (29)	
4 + 4		10 (11)	
4 + 5		10 (11)	
HGPIN and ASAP			
Positive for both HGPIN and ASAP	1 (1)		
Positive for HGPIN only	11 (10)		
Positive for ASAP only	0 (0)		
Negative for both	88 (78)		
PSA level (ng/mL), median (IQR)	5.7 (4.4–7.0)	7.2 (5.5–9.4)	0.0007[a]
MRI prostate volume, geometric (cm^3)	47.0 (36.0–60.8)	38.0 (31.0–52.0)	0.0028[a]
Median (IQR)			
20–356	24 (21)	42 (46)	0.0198
36–54	43 (38)	35 (38)	
55–99	34 (30)	23 (25)	
PSA density (ng/mL^2)			
Median (IQR)	0.12 (0.08–0.16)	0.19 (0.14–0.25)	< 0.0001[a]

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Characteristic	Gleason Score < 7 (*n* = 89)	Gleason Score ≥ 7 (*n* = 109)	*p*
< 0.15	69 (61)	27 (29)	< 0.0001
≥ 0.15	31 (28)	73 (80)	
PI-RADSv2 category			
3	33 (29)	9 (10)	< 0.0001
4	43 (38)	34 (37)	
5	25 (22)	57 (62)	
Maximum ROI diameter (mm)			
Median (IQR)	12.0 (10.0–19.0)	16.0 (12.0–21.0)	< 0.0001[a]
< 11	37 (33)	17 (19)	0.0066
11–18	37 (33)	45 (49)	
≥ 19	26 (23)	38 (41)	
RSI *z* score			
Median (IQR)	1.5 (0.3–3.5)	3.6 (2.3–5.5)	< 0.0001[a]
RSI ≥ 3	30 (27)	61 (67)	< 0.0001
RSI ≥ 4	22 (20)	41 (45)	0.0050
ADC (10^{-6} $\mu m^2/s$)			
Median (IQR)	971 (835–1076)	803 (727–941)	< 0.0001[a]
Range	480–1354	450–1188	

Note—Except where noted otherwise, data are percentage (number) of patients. HGPIN = high-grade prostatic intraepithelial neoplasia, ASAP = atypical small acinar proliferation, PSA = prostate-specific antigen, PI-RADSv2 = Prostate Imaging–Reporting and Data System version 2, IQR = interquartile range, RSI = restriction spectrum imaging, ADC = apparent diffusion coefficient.

[a]Kruskal-Wallis median test.

TABLE 3:

Diagnostic Performance of Restriction Spectrum Imaging (RSI) and DWI, Stratified by Lesion Location

Threshold and Parameter	Overall (*n* = 198)		Peripheral Zone (*n* = 129)		Transition Zone (*n* = 69)	
	RSI	DWI	RSI	DWI	RSI	DWI
ADC ≤ 1000 μm2/s and RSI *z* score ≥ 3						
Sensitivity	61	86	63	83	59	94
Specificity	70	37	70	50	69	17
PPV	71	63	75	70	65	52
NPV	60	69	58	68	63	75
ADC ≤ 900 μm^2/s and RSI *z* score ≥ 2.5						
Sensitivity	73	68	75	65	71	74
Specificity	62	65	65	72	57	54
PPV	65	62	75	77	62	61
NPV	70	70	65	60	67	68

Note—Data are percentages. Diagnostic performance of RSI (restriction spectrum imaging) and DWI is presented, each using two different thresholds. ADC = apparent diffusion coefficient, PPV = positive predictive value, NPV = negative predictive value.

TABLE 4:

Logistic Regression Analysis AUC Values for Restriction Spectrum Imaging (RSI), Apparent Diffusion Coefficient (ADC), Prostate Imaging–Reporting and Data System Version 2 (PI-RADSv2) **Overall Category, and PI-RADSv2 T2 Category**

Region	RSI ≥ 3	ADC ≤ 1000 μm^2/s	PI-RADSv2 Overall Category ≥ 4	PI-RADSv2 T2 Category ≥ 4	*p*[a]
Overall (*n* = 198)[b]	0.67	0.62	0.62	0.63	> 0.05
Peripheral zone (*n* = 129)	0.67	0.67	0.61	0.62	> 0.05
Transition zone (*n* = 69)	0.64	0.56	0.61	0.64	> 0.05

[a]When comparing AUC within each zone and overall, we found no statistically significant differences between the four measures (overall *p* value range, 0.11–0.79; transition zone *p* value range, 0.42–0.99; peripheral zone *p* value range, 0.11–0.96).

[b]Overall AUCs differ slightly from optimal test performance, as reported in the results, given that clinically relevant thresholds were preselected for measurements in this table.