Risk Stratification of Prostate Cancer Utilizing Apparent Diffusion Coefficient Value and Lesion Volume on Multiparametric MRI

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Purpose: To evaluate the performance of apparent diffusion coefficient (ADC) and lesion volume in potentially risk-stratifying patients with prostate cancer (PCa).
Materials and Methods: Men with elevated prostate-specific antigen or abnormal digital rectal exam underwent a 3T multiparametric magnetic resonance imaging (mpMRI) with endorectal coil. ADC maps were calculated using b values of 0, 500, 1000, and 1500; additional images were obtained with b value of 2000. We prospectively enrolled 312 men with lesions suspicious for cancer (suspicion score 2–5) on mpMRI. MRI/ultrasound fusion-guided prostate biopsies were performed. Mean ADC of suspicious lesions were correlated against lesion volume, Gleason and D'Amico risk.
Results: The cancer detection rate of fusion biopsy per lesion was 45.6% (206/452). Cancerous lesions were larger (median volume: 0.40 vs. 0.30 cm^3; $P = 0.016$). The median ADC ($\times 10^{-6}$ mm^2/sec) for lesions negative and positive for PCa were 984.5 and 666.5, respectively ($P < 0.0001$). The AUC of ADC in predicting PCa was 0.79. Larger lesions were associated with higher risk PCa (Gleason and D'Amico) and lower ADC (all $P < 0.0001$).
Conclusion: The mean ADC of suspicious lesions on mpMRI was inversely correlated, while lesion volume had a direct correlation with PCa detection. Future follow-up studies are needed to assess longitudinal cancer risks of suspicious mpMRI lesions.
Level of Evidence: 2

J. MAGN. RESON. IMAGING 2017;45:610–616

The incidence of prostate cancer (PCa) in the United States was estimated at 220,800 cases in 2015.[1] Gleason score, D'Amico's, and Epstein's criteria are grading systems currently used to risk stratify men with newly diagnosed clinically localized PCa, and thus help determine those who may qualify for active surveillance rather than definitive treatment.[2–4] About 50% of men who elect active surveillance will eventually require treatment, especially younger men, those with higher clinical stage, higher Gleason score, and higher prostate-specific antigen at diagnosis.[5,6] Furthermore, up to 20% of those diagnosed with clinically localized low risk PCa may in fact harbor Gleason $\geq$7 disease at the time of diagnosis.[6] Hence, accurate risk stratification at the time of diagnosis is crucial to avoid overtreatment or potential delays in treatment.

Previous reports, using various definitions such as Gleason's score, D'Amico, and Epstein's criteria, have demonstrated an improved performance of multiparametric magnetic resonance imaging (mpMRI) in predicting clinically significant PCa, compared to traditional diagnostic tests such as prostate-specific antigen (PSA).[7–12] Increased utilization of mpMRI has led to the next logical clinical question: can one stratify patients into different PCa risk categories using mpMRI sequence-specific quantitative data?

View this article online at wileyonlinelibrary.com. DOI: 10.1002/jmri.25363

Received May 2, 2016, Accepted for publication Jun 15, 2016.

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The apparent diffusion coefficient (ADC) values calculated from diffusion-weighted imaging (DWI) has been shown to correlate with PCa aggressiveness.[13,14] In an initial report, Turkbey et al reported a significant "negative" (inverse) correlation between calculated ADC values of tumors and their Gleason risk or D'Amico risk scores.[13] However, only a relatively small sample of patients was evaluated and no comparisons were made with men without PCa on biopsy.[10] Herein, with a much larger cohort of patients, we report on the performance of ADC and lesion volume in potentially risk stratifying patients with PCa.

Materials and Methods

A retrospective analysis was performed in a cohort of men prospectively enrolled in an Institutional Review Board (IRB)-approved phase III trial "MRI/TRUS Fusion-Guided Prostate Biopsy – An Improved Way to Detect and Quantify Prostate Cancer" (NCT 01566045) at Hofstra Northwell School of Medicine. The details of this trial have been published in previous reports from our institution.[8,15,16] Briefly, men with clinical suspicion for PCa [elevated (>4 ng/mL) or rising PSA or abnormal digital rectal exam (DRE) between June 2012 and October 2014 were referred for mpMRI.[2] Multiparametric MRI of the prostate was performed using a 3T Verio MRI machine (Siemens, Erlangen, Germany), with a 16-channel cardiac coil (Sense, Invivo, Gainesville, FL) placed on the anterior pelvis, and an endorectal coil (ERC) (BPX-30, Medrad, Pittsburgh, PA) filled with FC-770 (3M, St. Paul, MN). MRI sequences obtained were: a tri-planar T_2-weighted imaging; DWI (b-values 0, 50, 500, 1000, 1500, 2000) with ADC mapping (b-values 0, 50, 500, 1000, 1500); and dynamic contrast-enhanced (DCE) MRI sequences using the European Society of Urogenital Radiology (ESUR) guidelines.[17] The MRI studies were reviewed and interpreted by three genitourinary radiologists (EB, RV, ARR), with more than 15 years' combined experience, in consensus. Lesions on mpMRI were graded on a 5-point Likert scale based on their suspicion for cancer, as described in the ESUR guidelines.[17] Lesion dimensions were measured individually based on 3D-region of interest segmentation on mpMRI and lesion volumes were estimated using the ellipsoid formula. ADC of each lesion was calculated as the mean ADC values measured in the whole lesion. The anatomic location of the lesions was reported using the NIH prostate zones, as previously reported.[8] Men with suspicious lesion on mpMRI of the prostate were consented and enrolled into the trial.

Demographic and clinical data were prospectively collected. The study protocol biopsies included fusion biopsy and a standard 12-core transrectal ultrasound (TRUS)-guided biopsy. The UroNav MRI/TRUS (end-fire iU22 ultrasound, Philips Healthcare, Best, Netherlands) fusion guided-prostate biopsy system (Invivo) was used to perform targeted biopsy of suspicious prostate lesion. A total of two biopsy cores (one each in the axial and sagittal planes) were obtained from each lesion, an approach shown to improve cancer detection by about 8%.[18] A standard 12-core biopsy was then performed using TRUS guidance, with the UroNav workstation (Invivo) turned off to blind the investigator to the anatomic location of the lesion. At our institution, a genitourinary pathologist (OY) reviewed all biopsy specimens.

These analyses were limited to men undergoing an initial or repeat biopsy with a suspicious lesion on mpMRI, no prior history of PCa, radiation to the pelvis, or inability to tolerate prostate biopsy under local anesthesia or mild sedation (Fig. 1).

Statistical Analysis

We compared demographic and clinical variables using Fisher's exact tests and Kruskal–Wallis test for categorical and continuous variables, respectively, between men diagnosed with cancer and those without cancer on protocol biopsies. We calculated and compared the cancer detection rate (CDR) of fusion, 12-core, and protocol biopsies. On fusion biopsy, clinically significant PCa was defined as any Gleason $\geq$7 or Gleason 6 with a lesion volume $>0.2\,cm^3$ based on Epstein criteria, which was developed using whole-mount prostatectomy specimens. The performance of mpMRI in predicting PCa was evaluated using logistic regression and by plotting receiver operating characteristic (ROC) curves, estimating AUCs and corresponding confidence intervals. Decision point analysis was performed to determine optimal cutoff values for ADC; sensitivity and specificity were reported for each cutoff point. Statistical level of significance was set at 0.05, and 2-sided *P*-values are reported.

Results

A total of 312 men with suspicious lesion on mpMRI were eligible for analysis (Fig. 1), of which 64.7% were diagnosed with PCa. The average number of suspicious mpMRI lesions was 1.45 (452/312); PCa was detected on fusion biopsy in 45.6% (206/452) of lesions. Demographic, clinical, and radiological characteristics of men with cancer compared with men without cancer are presented in Table 1. In summary, men with PCa were more likely to be older, have an abnormal DRE, elevated PSA and PSA density, smaller prostate volume, larger lesion volume, and lower ADC value.

As presented in Table 2, the CDRs of 12-core biopsy, fusion biopsy, and protocol biopsies (12-core + fusion) were significantly associated with level of suspicion on mpMRI ($P < 0.0001$), with 100% of those with suspicion level of 5 on mpMRI diagnosed with PCa and 98.0% with clinically significant PCa. The location of the lesion—peripheral zone or central gland—did not affect the performance of fusion biopsy in detecting all PCa and clinically significant PCa ($P < 0.0001$; Table 3).

The median ADC value of mpMRI lesions in men with cancer was 666.5×10^{-6} compared with 984.5×10^{-6} mm^2/sec in men without cancer (Table 1; $P < 0.001$). The AUC of ADC value in predicting PCa on fusion biopsy was 0.79 (95% confidence interval [CI]: 0.75, 0.83) at the lesion level (Fig. 2a). The optimal ADC cutoff for predicting PCa was 719×10^{-6} mm^2/sec, characterized by a sensitivity and specificity of 63.6% and 82.5%, respectively (Fig. 2b). In a subgroup analysis, the AUC of ADC for predicting cancer in lesions located in the central gland was 0.83 (95% CI: 0.76, 0.90), which was not significantly different from 0.81 (95% CI: 0.76, 0.86) for lesions located

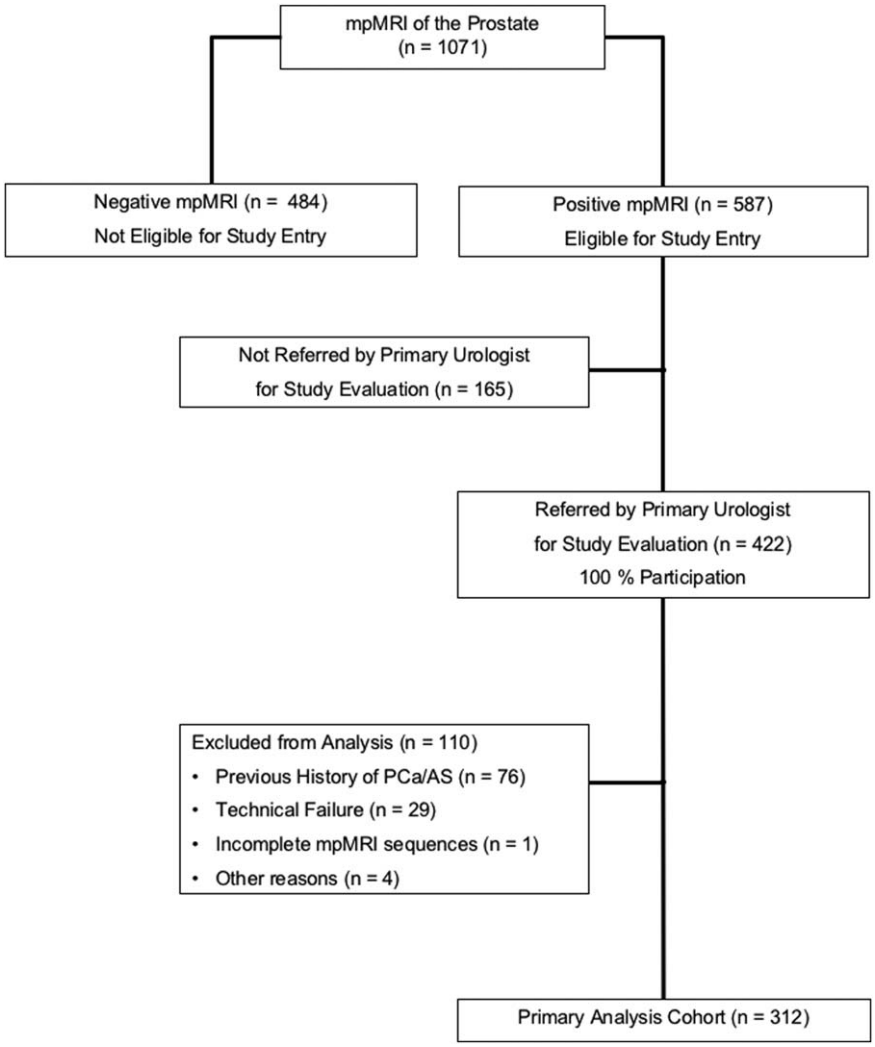

FIGURE 1: CONSORT diagram of the "MRI/TRUS Fusion-Guided Prostate Biopsy – An Improved Way to Detect and Quantify Prostate Cancer" trial. mpMRI, multiparametric magnetic resonance imaging; PCa, prostate cancer; AS, active surveillance.

TABLE 1. Demographic, Clinical, Radiological Characteristics of Men With and Without Prostate Cancer ($n = 312$)

Variable	Cancer ($n = 202$)	No Cancer ($n = 110$)	*P*-value
Age	66.0 [60.8–71.7]	63.9 [58.6–68.0]	0.142
African American	30 (14.9)	10 (9.1)	0.160
Family History of PCa	63 (31.2)	32 (29.1)	0.797
Abnormal DRE	35 (17.3)	7 (6.4)	0.009
PSA (ng/ml)	7.77 [5.5–12.5]	6.25 [4.6–8.9]	0.004
PSAD (ng/ml/cm^3)	0.18 [0.13–0.30]	0.10 [0.08–0.17]	<0.001
MRI Prostate Volume (cm^3)	43.0 [30.0–58.0)	57.0 [40.7–70.3]	<0.001
MRI Lesion Volume (cm^3)	0.37 [0.14–0.96]	0.25 [0.13–0.55]	0.016
ADC of Lesion (x10^{-6} x mm^2/sec)	666.5 [562.8–833.4]	984.5 [780.8–1160.2]	<0.001

Median [interquartile range] is reported for continuous variables and frequency (%) for categorical variables.PCa: Prostate cancer; DRE: Digital rectal examination; PSA: Prostate specific antigen; PSAD: PSA density; MRI: Magnetic resonance imaging; ADC: Apparent diffusion coefficient.

TABLE 2. Cancer Detection Rates of Fusion and 12-Core for Each Level of Suspicion on MRI (Patient Level Analysis; *n* = 312)

Level of Suspicion	N	Cancer detection rate (%)			
		12-Core only	Fusion only	Protocol	Clin. significant
2	12	2 (16.7)	2 (16.7)	3 (25.0)	2 (16.7)
3	135	53 (39.3)	36 (26.7)	60 (44.4)	38 (28.1)
4	115	77 (67.0)	80 (69.6)	89 (77.4)	81 (70.4)
5	50	36 (72.0)	48 (96.0)	50 (100.0)	49 (98.0)
Total	312	168 (53.8)	166 (53.2)	202 (64.7)	170 (54.5)

MRI: Magnetic resonance imaging; Protocol = Fusion + 12-core biopsy. All *P*-values of comparison of MRI suspicion with CDR <0.0001.

in the peripheral zone of the prostate. However, the optimal ADC cutoff for predicting PCa located in the central gland was 602 $\times$ 10^{-6} mm^2/sec (range = 286–1350 $\times$ 10^{-6} mm^2/sec; sensitivity = 64.6%; specificity = 89.4%) compared with 901 $\times$ 10^{-6} mm^2/sec (range: 207–1650 $\times$ 10^{-6} mm^2/sec; sensitivity = 75.2%; specificity = 76.1%) for lesions located in the peripheral zone of the prostate.

The mean ADC value of suspicious mpMRI lesions was inversely correlated with the probability of PCa detection on fusion biopsy as well as the Gleason and D'Amico risk stratification (Fig. 3). The mean (±SD) ADC value of men without PCa, men with low, intermediate, and high Gleason risk PCa were 976.6 (±252.1), 833.3 (±275.5), 685.1 (±196.6), and 596.0 (±153.9) $\times$ 10^{-6} mm^2/sec, respectively ($P < 0.0001$; Fig. 3a). Similarly, the mean (±SD) ADC value of men without PCa, men with low, intermediate, and high D'Amico risk PCa were 976.6 (±252.1), 826.7 (±277.2), 693.6 (±206.6), and 614.0 (±156.7) $\times$ 10^{-6} mm^2/sec, respectively ($P < 0.0001$; Fig. 3b).

The greater the volume of the suspicious lesion on mpMRI, the more likely it was to find a Gleason ≥7 PCa on fusion biopsy. For example, the detection rate of Gleason ≥7 PCa in lesions <0.20 cm^3 was 24.3% compared with 47.6% for lesions ≥1.0 cm^3 ($P < 0.001$; Table 4). We observed an inverse correlation of ADC value with lesion volume on mpMRI, with larger lesions associated with lower ADCs. In an exploratory multivariable analysis combining ADC value and lesion volume in addition to age, family history, DRE findings, PSA, prostate volume to predict PCa, however, only ADC value was statistically significant ($P < 0.0001$ vs. 0.3095).

Discussion

The most commonly used risk stratification systems for prostate cancer include Gleason score, D'Amico's criteria, Epstein's criteria, and the National Comprehensive Cancer Network's (NCCN's) risk groups.[2–4] Although several studies have reported on the ability of mpMRI of the prostate to enhance the detection of clinically significant PCa and improve risk stratification, incorporation of imaging findings in risk stratification is yet to be defined.[7–9] Compared to mpMRI without ERC, the use of ERC has been shown

TABLE 3. Cancer Detection Rates of Fusion Biopsy for Each Level of Suspicion on MRI (Lesion Level Analysis; *n* = 452)

Level of Suspicion	Cancer detection rate (%)					
	Peripheral zone			Central gland		
	N	All PCa	Clin Sig PCa	N	All PCa	Clin Sig PCa
2	23	2 (8.7)	1 (4.3)	1	0 (0)	0 (0.0)
3	170	42 (24.7)	26 (15.3)	61	13 (21.3)	10 (16.4)
4	102	72 (70.6)	65 (63.7)	43	26 (60.5)	26 (60.5)
5	26	25 (96.2)	25 (96.2)	26	26(100.0)	26 (100.0)
Total	321	144 (44.9)	117 (36.4)	131	65 (49.6)	62 (47.3)

MRI: Magnetic resonance imaging; PCa: Prostate cancer; All *P*-values of comparison of MRI suspicion with CDR <0.0001.

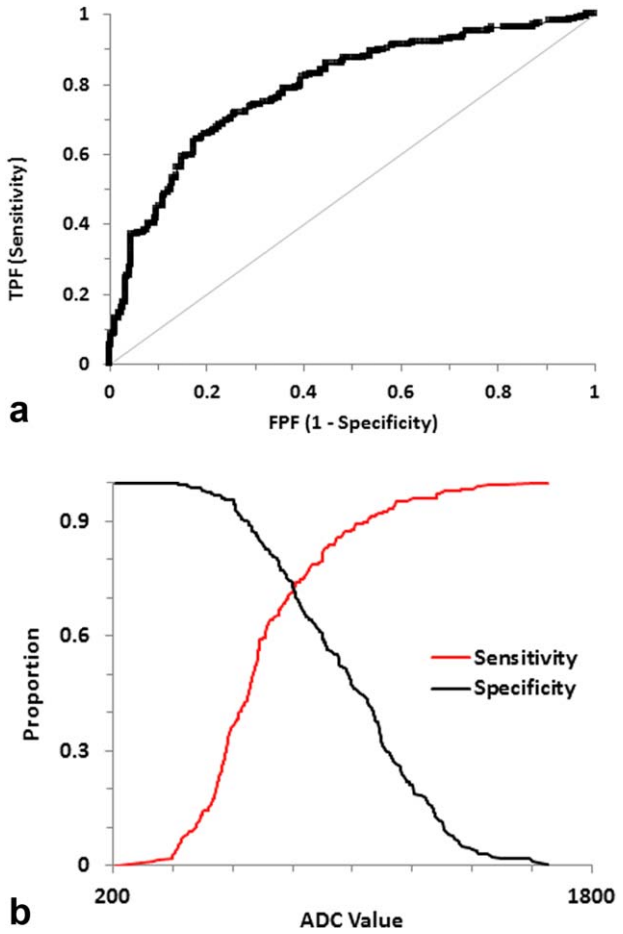

FIGURE 2: a: Receiver operating characteristic curve depicting the performance of ADC value in predicting prostate cancer (AUC = 0.79; 95% CI: 0.75, 0.83). b: Decision point analysis, Optimal ADC cutoff = 719 × 10^{-6} mm^2/sec (sensitivity = 63.6%, Specificity = 82.5%). ADC, apparent diffusion coefficient; TPF, true positive fraction; and FPF, false positive fraction

to increase the ability of mpMRI to detect more lesions including smaller lesions, with higher sensitivity and positive predictive value (PPV). The use of ERC improves image quality by increasing the signal-to-noise ratio and decreasing artifacts secondary to air in the rectum.[19]

ADC value was inversely correlated with PCa aggressiveness based on Gleason score or D'Amico's criteria, as previously reported by several research groups.[20–22] In an analysis of 48 patients who underwent MRI/TRUS-fusion-guided prostate biopsies, Turkbey et al reported a "negative" (inverse) correlation between calculated ADC values of tumors and Gleason scores.[13] The ADC value was found to accurately classify tumors into intermediate to high risk versus low risk in 73% of cases.[13] In a much larger cohort of patients, we similarly report an inverse relationship between ADC and clinical significance of PCa. We found that the AUC of ADC in predicting PCa did not differ between the central gland and peripheral zone of the prostate. The association between ADC and clinically significant PCa can be explained by the biology of PCa, characterized by impaired Brownian motion of water molecules due to hypercellularity, disorganized or complete loss of glandular architecture in higher-grade tumors, as previously hypothesized.[13,23,24] Similar findings have been reported by other investigators who found that lower ADC values were strongly associated with higher tumor aggressiveness.[22,25]

In defining the use of ADC value for PCa risk stratification, a cutoff point (s) needs to be defined. Kim et al[14] separated a cohort of patients with PCa into two groups using an ADC cutoff of 830 × 10^{-6} mm^2/sec, and reported that a higher ADC is predictive of insignificant PCa (Gleason ≤6). However, the method of determination of this cutoff point was not reported. In our cohort, we determined that the optimal ADC cutoff for defining cancerous versus benign lesions was 719 × 10^{-6} mm^2/sec, with a sensitivity and specificity of 63.6% and 82.5%, respectively. Furthermore, we found that the threshold ADC for PCa may differ between the central gland and peripheral zone: 602 × 10^{-6} mm^2/sec versus 901 × 10^{-6} mm^2/sec, respectively, which may reflect the varied cellularity of these zones of the prostate. Although analysis was limited to the peripheral zone only, Li et al reported a similar ADC threshold of 960 × 10^{-6} mm^2/sec for differentiating cancerous versus benign lesions.[26]

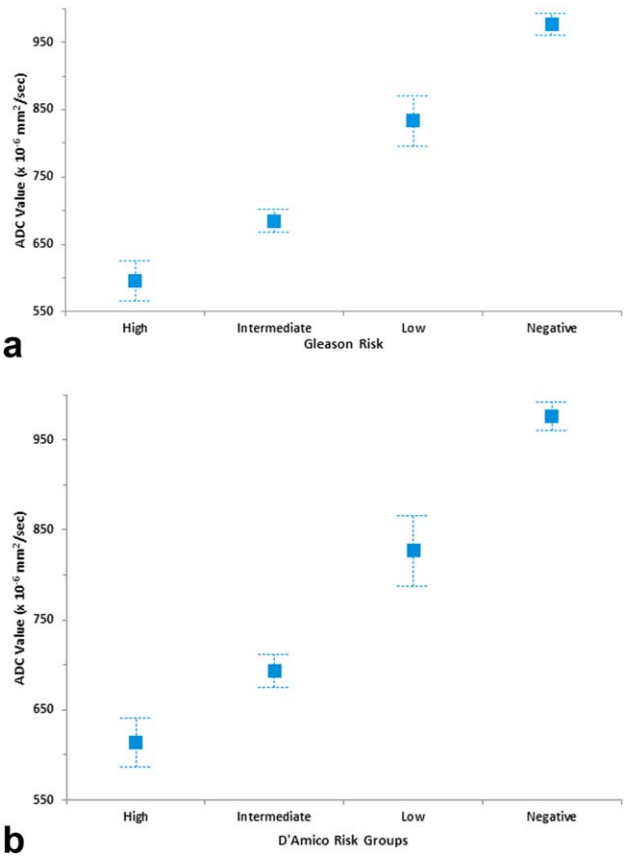

FIGURE 3: Correlation of ADC value of suspicious lesions with (a) Gleason risk stratification; and (b) D'Amico risk stratification ($P < 0.0001$). ADC, apparent diffusion coefficient.

TABLE 4. Correlation of Suspicious Lesion Volume on MRI With Gleason Risk Stratification on Fusion Biopsy (Lesion Level Analysis; $n = 452$)

Histology		Target lesion volume (cm^3)				Totals ($n = 452$)
		<0.20 ($n = 177$)	0.20–0.49 ($n = 126$)	0.50–0.99 ($n = 67$)	≥ 1.00 ($n = 82$)	
No Cancer		107 (60.4)	69 (54.8)	38 (56.7)	32 (39.0)	246 (54.4)
Gleason Risk	6	27 (15.3)	12 (9.5)	5 (7.5)	11 (13.4)	55 (12.2)
	7	39 (22.0)	36 (28.6)	23 (34.3)	25 (30.5)	123 (27.2)
	8–10	4 (2.3)	9 (7.1)	1 (1.5)	14 (17.1)	28 (6.2)

MRI: Magnetic resonance imaging; P-value of comparison < 0.0001.

Our analyses demonstrated other findings that may be useful in determining the clinical significance of PCa. We found an inverse correlation between mean ADC value of suspicious lesions and both the Gleason and D'Amico risk groups, with higher-risk lesions characterized by lower mean ADC values, which may be attributed to the more restricted diffusion of molecules in cancerous versus benign tissue. We also found that the larger the lesion volume, the higher the risk or aggressiveness of the PCa. For example, 47.6% of lesions $\geq 1.0\,cm^3$ were Gleason ≥ 7 tumors compared with 24.3% of lesions $<0.2\,cm^3$. In addition, we observed an inverse correlation between the ADC value of lesions and lesion volume, which again may be related to the hypercellularity of aggressive or larger tumors.[23,24] Although this association may be explained by the collinearity of ADC values and lesion volume, both mpMRI parameters (lesion volume and/or ADC value of suspicious lesion) may be useful in combination with clinical parameters to risk stratify men diagnosed with PCa.

Our study is not without limitations. First, for the purpose of these analyses, men with negative mpMRI were excluded since there was no lesion to target with fusion biopsy. However, mpMRI has been shown in multiple studies to select clinically significant PCa,[8,9,15,27,28] with a high negative predictive value (>90%).[29] Second, a negative fusion biopsy may be due to assignment of a falsely high suspicion score or targeting error.[30] In our study, a team of three radiologists interpreted the mpMRI images in a consensus format. As a result, we do not have data on interobserver variability, which may characterize routine clinical practice. Although current recommendations support the use of consensus reads when starting an imaging program, we continued our consensus reads as part of our normal workflow. Radiology–pathology correlation and imaging quality review allowed for ongoing improvements and collaborations between all departments.[31] In addition, two biopsy cores (one each in the axial and sagittal planes) were obtained from each lesion, an approach shown to improve cancer detection by about 8%.[18] Third, we do not have radical prostatectomy specimens to determine the true positivity rate of suspicious lesions on mpMRI, hence theoretically some lesions may have been misclassified. Lastly, lesion volumes were estimated using the ellipsoid formula. This approach, however, may overestimate the actual volume by 7% when compared to whole-mount histopathology without a shrinkage factor correction.[32] Nevertheless, the strength of this study lies in the prospective nature and comparatively larger sample size. In addition, the use of a 3T MRI magnet and endorectal coil may have improved image quality and signal-to-noise ratio, and as a result, the performance of ADC value in stratifying PCa. Research is currently ongoing to evaluate the utility of mpMRI and ADCs as a quantitative predictive parameter in the management of men with PCa on active surveillance.

In conclusion, the calculated mean ADC value of suspicious lesions on mpMRI has an inverse relationship with lesion volume and prostate cancer risk or aggressiveness. Our study validates the findings of other groups, showing that ADC may be a useful tool in predicting PCa and its clinical significance. Furthermore, we report that lesion volume may be a useful tool to determine the clinical significance of prostate cancer. ADC values, lesion volume, and its growth rate needs to be evaluated prospectively as parameters for monitoring eligible patients who elect active surveillance of their newly diagnosed low-risk clinically localized PCa and/or in making a decision to proceed to treatment.

Conflict of Interest

A.R.R.: Nonfinancial research equipment from Invivo.

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