Targeted Biopsy Validation of Peripheral Zone Prostate Cancer Characterization With Magnetic Resonance Fingerprinting and Diffusion Mapping

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Objective: This study aims for targeted biopsy validation of magnetic resonance fingerprinting (MRF) and diffusion mapping for characterizing peripheral zone (PZ) prostate cancer and noncancers.

Materials and Methods: One hundred four PZ lesions in 85 patients who underwent magnetic resonance imaging were retrospectively analyzed with apparent diffusion coefficient (ADC) mapping, MRF, and targeted biopsy (cognitive or in-gantry). A radiologist blinded to pathology drew regions of interest on targeted lesions and visually normal peripheral zone on MRF and ADC maps. Mean T1, T2, and ADC were analyzed using linear mixed models. Generalized estimating equations logistic regression analyses were used to evaluate T1 and T2 relaxometry combined with ADC in differentiating pathologic groups.

Results: Targeted biopsy revealed 63 cancers (low-grade cancer/Gleason score \(3 + 3\)) and 20 noncancers (low-grade cancer/Gleason score \(3 + 4\)) and 20 negative biopsies. Low-grade cancer T2 and ADC (mean ± SD, 75 ± 29 milliseconds, 1.00 ± 0.30 \(\times 10^{-3}\) mm\(^2\)/s) were significantly lower than prostatitis (mean ± SD, 1730 ± 350 milliseconds, 77 ± 36 milliseconds, 1.00 ± 0.33 \(\times 10^{-3}\) mm\(^2\)/s). For cancer versus prostatitis, ADC was sensitive and T2 specific with comparable area under curve (AUC; AUC\(\text{T2} = 0.71\), AUC\(\text{ADC} = 0.79\), difference between AUCs not significant \(P = 0.37\)). T1 + ADC (AUC\(\text{T1} + \text{ADC} = 0.83\)) provided the best separation between cancer and negative biopsies. Low-grade cancer T2 and ADC (mean ± SD, 75 ± 29 milliseconds, 0.96 ± 0.34 \(\times 10^{-3}\) mm\(^2\)/s) were significantly higher than clinically significant cancers (mean ± SD, 52 ± 16 milliseconds, 0.65 ± 0.18 \(\times 10^{-3}\) mm\(^2\)/s), and T2 + ADC (AUC\(\text{T2} + \text{ADC} = 0.91\)) provided the best separation.

Conclusions: T1 and T2 relaxometry combined with ADC mapping may be useful for quantitative characterization of prostate cancer grades and differentiating cancer from noncancers for PZ lesions seen on T2-weighted images.

Key Words: magnetic resonance fingerprinting, prostate cancer, peripheral zone, relaxometry, quantitative MRI

Interpretation of prostate multiparametric MRI sequences as guided by PIRADS v2 (Prostate Imaging, Reporting, and Data System version 2) is currently qualitative.1 However, there is increasing interest in quantitative evaluation for more objective lesion assessment.2–4 Prior studies have shown that the histological differences between normal prostate tissue, prostate cancers, and inflammation are associated with measurable differences in T2 and T2* relaxation times and apparent diffusion coefficient (ADC).5–14 In clinical practice, ADC mapping is the only technique used quantitatively in prostate magnetic resonance imaging (MRI) and has been shown to reflect cancer aggressiveness.14–19 and partially separate cancer from prostatitis.20,21 Magnetic resonance fingerprinting (MRF) represents another framework for performing relaxometry and allows simultaneous measurement of T1 and T2 relaxation times in a clinically feasible time.22,23 In MRF, user controllable system parameters such as flip angle, time of echo (TE), time of repetition (TR), and so on are allowed to vary in a pseudorandom manner such that unique signal evolutions are produced for each combination of tissue properties (T1, T2, etc) and a dictionary of all possible signal evolutions is computed for that sequence. Obtained signal evolutions are matched against the best entry in the dictionary on a pixel-by-pixel basis, with relaxation properties used to generate the matched entry assigned to that pixel as the measured T1 and T2. This yields simultaneous, rapid, and coregistered T1 and T2 maps that provide combined quantitative information,22 with several potential advantages over traditional mapping methods that typically measure either T1 or T2 relaxation times per acquisition.24,25 Although relaxation property measurements will necessarily vary slightly based on the system imperfections and confounders that are accounted for in the dictionary,26–29 MRF-based relaxometry has been found to be repeatable and reproducible in both phantom and in vivo assessment.30 Initial application to prostate imaging showed excellent separation between normal peripheral zone (PZ) and cancer or prostatitis using a combined quantitative protocol composed of MRF-relaxometry and echo planar imaging (EPI)-based diffusion-weighted imaging.31 That study also showed moderate accuracy for separating low-grade (Gleason score 6) from intermediate- to high-grade (Gleason score 7 and above) prostate cancers using quantitative criteria.32 However, these results were based on transrectal ultrasound (TRUS)-guided biopsy as a pathology reference and a small dataset with cognitive targeting. Transrectal ultrasound-guided biopsy is prone to sampling errors and can either underestimate the grade of cancer or miss cancer altogether,33 whereas targeted biopsy methods can produce better correlation with the actual pathology.34,35 The purpose of this study was to provide targeted biopsy validation of combined MRF-based relaxometry and diffusion mapping for characterizing prostate cancer grades and differentiating prostate cancer from prostatitis and negative biopsies in the PZ of prostate.
MATERIALS AND METHODS

Patients
This institutional review board–approved and Health Insurance Portability and Accountability Act–compliant study is a retrospective evaluation of MRF data collected prospectively between September 2014 and April 2018 from patients with suspected prostate cancer who had MRI followed by targeted biopsy (either cognitive or in-gantry biopsy). Written informed consent was obtained from all participants. Exclusion criteria included previous history of prostatectomy, pelvic radiation, chemotherapy, or hormonal therapy.

Diagnostic MRI scans and in-gantry biopsies were performed at 3 T (Verio or Skyra; Siemens, Erlangen, Germany) using a body array coil and no endorectal coil. The diagnostic MRI protocol is given in Table 1 and in-gantry biopsy protocol in a Supplementary Table (Supplementary Digital Content 1, http://links.lww.com/RLI/A433). Magnetic resonance fingerprinting acquisitions and b-values for diffusion were kept constant to ensure consistency in quantitative MRI evaluation.

Cognitive biopsies of cancer-suspicious lesions were performed in combination with 12-core TRUS biopsies. Targeted lesions were localized based on MRI reads and visualized on TRUS using a prostate sector map and internal landmarks for reference. In-gantry biopsies were performed with a dedicated MR-compatible biopsy device (DynaTRIM; In Vivo, Gainesville, FL) using the assisted planning software (DynaLOC; In Vivo) for guiding biopsy needle placement. For in-gantry biopsies, needle placement in the lesion was confirmed with a scan before taking biopsy samples. The median interval between MRF and cognitive biopsy was 21 days (range, 6–133 days). For in-gantry biopsy, MRF with ADC mapping were performed at the time of biopsy.

One hundred forty-one patients (median, 64 years; range, 42–81 years) underwent clinical MRI with MRF and targeted biopsy (84 cognitive and 57 in-gantry biopsy). All cognitive biopsy patients were biopsy-naive, whereas 35/57 in-gantry patients had previous TRUS biopsies. The median time interval between prior TRUS and in-gantry biopsy was 16.5 months (2–132 months). Eleven patients were excluded from quantitative analysis due to technical limitations (artifacts on MRF maps [n = 4], lesion not visualized on MRF maps [n = 5], and failed reconstruction of MRF maps [n = 2]) and if they had only transition zone lesions (n = 41). Lesions with histopathologic diagnosis other than cancer, prostatitis, or benign prostatic tissue were further excluded from corresponding region of interest (ROI) analysis (Fig. 1). None of the targeted lesions had visible postbiopsy hemorrhage to preclude analysis. Part of the dataset (37 patients with 27 prostate cancer lesions) used in this study was also used in a previous publication. However, that study did not evaluate lesions with negative biopsies, and the results of TRUS biopsy were used as final reference standard for MRF values in cases of discordance.

MRF Acquisition and Postprocessing
Magnetic resonance fingerprinting with FISP (fast imaging with steady-state precession) was used, and the whole prostate was covered. The acquisition time was 39 seconds per slice, and the total scan time was 5 to 10 minutes, depending on prostate size. A dictionary containing expected MRF signal evolutions was calculated with T1 20 to 2950 milliseconds and T2 9 to 500 milliseconds, and MRF maps obtained by template matching the signal time-course in each pixel, as described previously. For patients recruited between September 2014 and September 2017, the raw MRF data were processed offline on Matlab (Matlab 2014a; MathWorks, Natick, MA) with offline reconstruction time of 190 seconds per slice. For patients recruited after October 2017, a Gadgetron-based framework was used for rapid online reconstruction of MRF data and quantitative T1 and T2 maps in DICOM format were directly available real-time on the MR scanner. A prior comparison of offline and online reconstruction methods showed that MRF T1 and T2 values were similar for both reconstruction methods.

Clinical Interpretation and Quantitative ROI Analysis
Targeted biopsy lesions were evaluated based on PIRADS v2 by a fellowship-trained body radiologist (18 years radiology experience) who also performed all in-gantry targeted biopsies with 1 to 6 cores obtained per lesion (median, 3 cores). Another radiologist (8 years experience) who was blinded to the clinical information and pathology diagnosis but aware of the locations of the targeted lesions retrospectively drew ROIs on suspicious focal lesions and on the contralateral visually normal peripheral zone (NPZ) on both MRF and ADC maps. As a part of acquisition scheme, both T2-weighted and ADC slices were anatomically coregistered, whereas MRF T1 and T2 maps were anatomically coregistered. The T2-weighted slice with the largest lesion area and used for biopsy planning was taken as the reference slice, and the T2 MRF slice anatomically corresponding to this T2-weighted slice was selected. Lesions and NPZ ROIs were drawn on the selected T2 MRF slice, and both T1 and T2 were obtained simultaneously from these ROIs. Again using T2-weighted slice and T2 map as the reference, lesion and NPZ ROIs were replicated independently at the corresponding locations on the ADC maps. Figure 2 depicts the image analysis workflow. The lesion ROI sizes ranged from 6 to 442 mm² (median, 55 mm²). For each targeted lesion and NPZ, the mean T1, T2, and ADC were recorded. Based on targeted core biopsy reports, final

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### TABLE 1. Imaging Parameters for Diagnostic MRI

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR/TE, ms</th>
<th>Field of View, mm</th>
<th>Resolution, mm</th>
<th>Matrix</th>
<th>Flip Angle, Degrees</th>
<th>Slice Thickness, mm</th>
<th>b Value, s/mm²</th>
<th>Sequence Duration, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localizer, 3 planes</td>
<td>2000/95</td>
<td>305 × 285</td>
<td>1.2 × 1.2</td>
<td>320 × 240</td>
<td>150</td>
<td>5</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Three-plane, single-shot fast spin-echo</td>
<td>2000/92</td>
<td>305 × 244</td>
<td>1.2 × 1.2</td>
<td>384 × 308</td>
<td>150</td>
<td>5</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Transverse turbo spin-echo T2-weighted</td>
<td>8600/103</td>
<td>160 × 160</td>
<td>0.6 × 0.6</td>
<td>320 × 320</td>
<td>150</td>
<td>3</td>
<td>3:30</td>
<td></td>
</tr>
<tr>
<td>Diffusion-weighted imaging</td>
<td>7900/88</td>
<td>240 × 240</td>
<td>1.2 × 1.2</td>
<td>198 × 198</td>
<td>50, 600, 1000, 1400</td>
<td>4:46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRF</td>
<td>13–15</td>
<td>400 × 400</td>
<td>1 × 1</td>
<td>400 × 400</td>
<td>5–75</td>
<td>0.39 per slice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast T1-weighted imaging with DCE perfusion*</td>
<td>3.34/1/02</td>
<td>240 × 240</td>
<td>1.9 × 1.9</td>
<td>128 × 128</td>
<td>15</td>
<td>3</td>
<td>4:31</td>
<td></td>
</tr>
<tr>
<td>Postcontrast T1-weighted*</td>
<td>3.63/1.33</td>
<td>240 × 240</td>
<td>1.0 × 1.0</td>
<td>128 × 128</td>
<td>9</td>
<td>2</td>
<td>0.23</td>
<td></td>
</tr>
</tbody>
</table>

*The patients in cognitive biopsy group underwent a noncontrast MRI protocol.

MRI indicates magnetic resonance imaging; TR, time of repetition; TE, time of echo; MRF, magnetic resonance fingerprinting; DCE, dynamic contrast enhanced.
FIGURE 1. Flow diagram of patient and lesion selection. PZ indicates peripheral zone; HGPIN, high-grade intraepithelial neoplasia; ASAP, atypical small acinar proliferation; ROI, region of interest.

FIGURE 2. Regions of interest (ROIs) analysis. Cancer-suspicious lesions (solid arrow) were identified based on axial T2-weighted slice (A) and ADC map (B). The anatomically corresponding MRF slices (C and D) were aligned with T2-weighted slice, and lesions ROIs were drawn on MRF map (black oval). As MRF maps were coregistered, both T1 and T2 values were simultaneously obtained from single MRF ROI. Independent ROIs were drawn on ADC map (red oval) coregistered to the T2-weighted slice. Regions of interest were also drawn on the visually normal peripheral zone (NPZ) covering whole contralateral NPZ.
pathologic diagnosis for each targeted lesion was recorded. For cancers, Gleason scores were recorded. For targeted lesions for which more than one Gleason score was given, the highest score was recorded as the final pathologic diagnosis.

Statistical Analysis
Lesions diagnosed as cancer, prostatitis, and negative on biopsy were included for analysis. Mean T1, T2, and ADC were compared between individual biopsy groups and with NPZ using linear mixed models. Generalized estimating equations logistic regression analysis was used to assess the utility of MRF-derived T1, T2, and ADC in the differentiation of (1) all prostate cancers from (a) prostatitis, (b) negative biopsies, and (c) all noncancers (prostatitis + negative biopsies), and (2) clinically significant cancers from (a) low-grade cancers, (b) all noncancers (prostatitis + negative biopsies), and (c) all clinically insignificant lesions (low-grade cancers + prostatitis + negative biopsies).

Low-grade cancer was defined as Gleason score \( 3 + 3 = 6 \), clinically significant cancer was defined as Gleason score \( \geq 7 \), as Gleason 6 cancers are considered for active surveillance at our institution. Low-grade cancers were grouped with noncancers and compared with them with clinically significant cancers to see if quantitative mapping could be used to differentiate lesions that do not need intervention (low-grade cancers, prostatitis, benign prostatic tissue) versus lesions that are clinically significant.

Receiver operating characteristic curves and areas under the receiver operating characteristic curve (AUCs; C-statistics) were obtained from logistic regressions by using the linear predictors obtained from the generalized estimating equations regressions. For significant univariate performances for separation (Table 3). AUC\(_{T2} = 0.71\), whereas AUC\(_{ADC} = 0.79\) with no significant difference between the 2 AUCs (\( P = 0.37\)).

All Prostate Cancers Versus Noncancers
Prostate Cancer Versus Prostatitis
Means of T1, T2, and ADC differed significantly between prostate cancer and prostatitis (\( P = 0.039 \) for T1, \( P = 0.015 \) for T2, \( P < 0.0001 \) for ADC)). Both T2 and ADC were significant predictors in logistic regression models with both having moderate diagnostic performance for separation (Table 3). AUC\(_{T2} = 0.71\), whereas AUC\(_{ADC} = 0.79\) with no significant difference between the 2 AUCs (\( P = 0.37\)).

Prostate Cancer Versus Negative Biopsies
Means of T1, T2, and ADC differed significantly between prostate cancer and negative biopsies (\( P = 0.0029 \) for T1, \( P = 0.0058 \) for T2, \( P < 0.0001 \) for ADC)). The best separation was provided by T1 + ADC (AUC\(_{T1 + ADC} = 0.83\) and was significantly higher than AUC\(_{ADC} = 0.028\); Table 3).

Prostate Cancer Versus Noncancers (Prostatitis and Negative Biopsies)
Means of T1, T2, and ADC differed significantly between prostate cancer and all noncancers (\( P = 0.0009 \) for T1, \( P = 0.0004 \) for T2, \( P < 0.0001 \) for ADC)). Both ADC and T1 + ADC had comparable diagnostic performances for separation (AUC\(_{ADC} = 0.797\), AUC\(_{ADC + T1} = 0.801\); Table 3; Fig. 4B).

Clinically Significant Prostate Cancers Versus Low-Grade Cancers and Noncancers
Clinically Significant Cancer Versus Low-Grade Cancers
Means of T2 and ADC differed between low-grade and high-/intermediate-grade cancers (\( P < 0.0031 \) for T2 and \( P < 0.0001 \) for ADC), and both were significant univariable predictors with similar diagnostic performances for differentiating cancer grades (AUC\(_{T2} = 0.77\), AUC\(_{ADC} = 0.84\), difference between 2 AUCs not significant, \( P = 0.48\)). The best separation was obtained with T2 + ADC (AUC\(_{T2 + ADC} = 0.91\); Table 3).

Clinically Significant Cancer Versus All Noncancers (Prostatitis and Negative Biopsies)
Means of T1, T2, and ADC differed between clinically significant prostate cancer and all noncancers (\( P = 0.0003 \) for T1, \( P = 0.0004 \) for T2, \( P < 0.0001 \) for ADC). The best separation was provided by T2 + ADC (AUC\(_{T2 + ADC} = 0.86\) and was significantly higher than AUC\(_{ADC} = 0.04\); Table 3).

### RESULTS
In 89 patients with PZ lesions, 111 lesions were targeted (80 cognizant sampling, 31 in-gantry sampling). Sixty-three lesions were prostate cancer (10 low grade [Gleason score 6], 38 intermediate grade [Gleason score 7], 15 high grade [Gleason score ≥8]), 15 were prostatitis, 26 were negative with biopsy showing normal prostatic tissue, and 7 had another diagnosis (5 high-grade prostatic intraepithelial neoplasia and 2 atypical small acinar proliferation). These 7 lesions (4 patients) were excluded, and the remaining 104 lesions (85 patients) were analyzed (Fig. 1). T1 and T2 numbers were available for all 104 targeted lesions included in final analysis, and ADC measurement was not available for one lesion due to distorted ADC map. Normal peripheral zone ROIs for T1 and T2 measurements were available for 82 patients for comparison with the measurements in the different histologic groups and were not drawn for 3 patients due to lack of visually NPZ on T2-weighted images.

Mean T1, T2, and ADC for NPZ, histologically proven prostate cancer including low-grade cancer, and clinically significant cancers, prostatitis, and negative biopsies are summarized in Table 2, and the distributions depicted as box-and-whisker plots in Figure 3. Table 3 summarizes the AUCs for regression models. The best diagnostic performance cutoff points are summarized in Table 4.

### Table 2. Summary of Means of T1, T2, and ADC of Normal Peripheral Zone and Different Histopathologic Groups

<table>
<thead>
<tr>
<th>Group (No. Samples)</th>
<th>T1, Mean ± SD, ms</th>
<th>T2, Mean ± SD, ms</th>
<th>ADC, Mean ± SD, ( \times 10^{-3} ) mm(^2)/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal peripheral zone (n = 82)</td>
<td>2240 ± 360</td>
<td>146 ± 61</td>
<td>1.68 ± 0.31</td>
</tr>
<tr>
<td>Prostate cancer (n = 63)</td>
<td>1660 ± 270</td>
<td>56 ± 20</td>
<td>0.70 ± 0.24</td>
</tr>
<tr>
<td>Prostatitis (n = 15)</td>
<td>1760 ± 350</td>
<td>77 ± 36</td>
<td>1.00 ± 0.30</td>
</tr>
<tr>
<td>Biopsy-proven benign prostatic tissue (n = 26)</td>
<td>1810 ± 250</td>
<td>71 ± 37</td>
<td>1.00 ± 0.33</td>
</tr>
<tr>
<td>Low-grade cancer/Gleason score = 6 (n = 10)</td>
<td>1690 ± 400</td>
<td>75 ± 29</td>
<td>0.96 ± 0.34</td>
</tr>
<tr>
<td>Clinically significant cancers/Gleason score ≥7 (n = 53)</td>
<td>1650 ± 240</td>
<td>52 ± 16</td>
<td>0.65 ± 0.18</td>
</tr>
<tr>
<td>Noncancers (prostatitis + benign prostatic tissue) (n = 41)</td>
<td>1790 ± 290</td>
<td>73 ± 37</td>
<td>1.00 ± 0.32</td>
</tr>
</tbody>
</table>

ADC indicates apparent diffusion coefficient.
Clinical Significance of Cancer Versus Clinically Insignificant Lesions (Low-Grade Cancers and Noncancers)

Mean T1, T2, and ADC differed between clinically significant prostate cancer and low-grade cancers + noncancers ($P = 0.0027$ for T1, $P = 0.0003$ for T2, $P = 0.0001$ for ADC). The best separation was provided by T2 + ADC (AUC$_{T2+ADC} = 0.86$) and was significantly higher than AUC$_{ADC}$ ($P = 0.005$) (Table 3).

Figure 5 shows representative cases from our dataset.

**DISCUSSION**

This study provides targeted biopsy validation of MRF-based relaxometry and ADC mapping for prostate imaging and adds to previous work on the demonstration of a combined quantitative examination using MRF and ADC mapping. Using targeted biopsy as a pathology reference allowed better exploration of the differences in relaxation times and ADC between grades of prostate cancer, prostatitis, and negative biopsies and quantitative comparison of these histologic groups with visually NPZ. As reported previously and expected due to the choice of ROIs, mean T1, T2, and ADC in visually NPZ were higher than prostate cancer and prostatitis (Table 2). Histologically, the long T2 and high ADC in NPZ have been attributed to the larger volume of glandular lumen that has “water-like” T2 relaxation times and shows increased diffusivity within the lumen. The longer T1 in NPZ may relate to the proteinaceous contents of the glandular sections within the lumen. The destruction of glandular architecture in cancers is also associated with decreased secretory function, which may potentially account for the difference in T1 relaxation times between NPZ and cancer. More

**TABLE 3. Differentiation of Various Groups With T1, T2, and ADC and Their Combinations**

<table>
<thead>
<tr>
<th>Groups Compared</th>
<th>T1 AUC</th>
<th>T1+ T2 AUC</th>
<th>T1+ T2+ ADC AUC</th>
<th>T1+ ADC AUC</th>
<th>T2+ ADC AUC</th>
<th>T1+ T2+ ADC AUC</th>
<th>Highest AUC†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All prostate cancers vs noncancers</td>
<td>0.60</td>
<td>0.79*</td>
<td>0.79*</td>
<td>0.76</td>
<td>0.79</td>
<td>0.79</td>
<td>ADC (0.79)</td>
</tr>
<tr>
<td>Prostate cancer (n = 63) vs prostatitis (n = 15)</td>
<td>0.41-0.78</td>
<td>0.55-0.88</td>
<td>0.65-0.93</td>
<td>0.54-0.88</td>
<td>0.59-0.92</td>
<td>0.64-0.94</td>
<td>0.65-0.95</td>
</tr>
<tr>
<td>Prostate cancer (n = 63) vs negative biopsies (n = 26)</td>
<td>0.67*</td>
<td>0.62</td>
<td>0.80*</td>
<td>0.67</td>
<td>0.83*</td>
<td>0.80</td>
<td>0.83</td>
</tr>
<tr>
<td>Prostate cancer (n = 63) vs noncancers (n = 41)</td>
<td>0.64*</td>
<td>0.66*</td>
<td>0.80*</td>
<td>0.68</td>
<td>0.80*</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>CS cancers vs other histologic groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS cancer (n = 53) vs low-grade cancers (n = 10)</td>
<td>0.48</td>
<td>0.77*</td>
<td>0.84*</td>
<td>0.76</td>
<td>0.85</td>
<td>0.91*</td>
<td>0.90</td>
</tr>
<tr>
<td>CS cancer (n = 53) vs noncancers (n = 41)</td>
<td>0.64*</td>
<td>0.70*</td>
<td>0.84*</td>
<td>0.70</td>
<td>0.85</td>
<td>0.86*</td>
<td>0.86</td>
</tr>
<tr>
<td>CS cancer (n = 53) vs noncancers + low-grade cancers (n = 51)</td>
<td>0.61</td>
<td>0.71*</td>
<td>0.84*</td>
<td>0.70</td>
<td>0.85</td>
<td>0.86*</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Clinically significant cancers included all cancers with Gleason score ≥7, whereas low-grade cancers was denoted by cancers with Gleason score = 6.

Negative biopsy = targeted lesions with biopsy report of benign prostatic tissue.

*Models with significant variables ($P < 0.05$) obtained from generalized estimating equation logistic regression analysis. The numbers in parenthesis indicate 95% confidence intervals, and numbers in brackets indicate $P$ value for the variables in the univariate models.

†The highest AUC represents model(s) with significant variables after generalized estimating equation logistic regression analysis.

ADC indicates apparent diffusion coefficient; AUC, area under curve; CS, clinically significant.
TABLE 4. The Best Performance Cutoff Values for T1, T2, and ADC Based on Regression Models

<table>
<thead>
<tr>
<th>Groups Compared</th>
<th>T1 (Sensitivity/Specificity)</th>
<th>T2 (Sensitivity/Specificity)</th>
<th>ADC (Sensitivity/Specificity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All prostate cancers vs noncancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer (n = 63) vs prostatitis</td>
<td>Regression model not significant</td>
<td>68 ms (79%/67%)</td>
<td>1.04 × 10⁻³ mm²/s (98%/53%)</td>
</tr>
<tr>
<td>prostate biopsies (n = 26)</td>
<td>1720 ms (68%/62%)</td>
<td>Regression model not significant</td>
<td>0.75 × 10⁻³ mm²/s (62%/92%)</td>
</tr>
<tr>
<td>Prostate cancer (n = 63) vs noncancers</td>
<td>1720 ms (67%/59%)</td>
<td>67 ms (79%/46%)</td>
<td>0.75 × 10⁻³ mm²/s (62%/87.5%)</td>
</tr>
<tr>
<td>CS cancers vs other histologic groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS cancer (n = 53) vs low-grade cancers</td>
<td>Regression model not significant</td>
<td>52 ms (62%/90%)</td>
<td>0.78 × 10⁻³ mm²/s (73.5%/80%)</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>1720 ms (68%/58%/5%)</td>
<td>52 ms (62%/71%)</td>
<td>0.75 × 10⁻³ mm²/s (70%/87.5%)</td>
</tr>
<tr>
<td>CS cancer (n = 53) vs noncancers (n = 41)</td>
<td>1730 ms (68%/55%)</td>
<td>60 ms (62%/74.5%)</td>
<td>0.75 × 10⁻³ mm²/s (70%/86%)</td>
</tr>
<tr>
<td>CS cancer (n = 53) vs clinically insigni-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ficant lesions (noncancers + low-grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cancers) (n = 51)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For multivariate regression models, the individual cutoff values contributed independently to overall performance. The numbers in parenthesis indicate sensitivity and specificity for respective cutoff values.

ADC indicates apparent diffusion coefficient; CS, clinically significant.

Interestingly, targeted lesions diagnosed as normal prostatic tissue on biopsy, despite confirmed intraskeletal needle positions, had T1, T2, and ADC lower than visually NPZ, but higher than prostate cancer (Table 2). Although the exact histological basis for these changes in negative biopsies is not known, these may represent nonspecific changes in PZ as prior ischemic/biopsy/inflammatory sequela or may be attributed to the proposed existence of two populations of water protons in normal prostate tissue, one with characteristic long T2 and ADC within the glandular lumen and the other with shorter T2 and ADC due to increased stromal content.12,38,39

There were significant differences in T1 and T2 between prostate cancer and noncancers (prostatitis and negative biopsies), which have not been reported previously.20,21,41 T1 and T2 were found to be complementary to ADC for differentiating prostate cancers from negative biopsies and prostatitis, respectively (Table 3). Previous studies have shown an overlap in ADC values between prostatitis, negative biopsies, and prostate cancer. The ADC values are dependent on the b-values used and the MR system gradient performance; thus no absolute ADC cutoff value can be recommended for diagnosis.20,21,32 In practice, ADC values between 0.75 and 0.95 × 10⁻³ mm²/s are the usual recommended thresholds for diagnosing malignancy.1 In this study too, an ADC value of less than 0.75 × 10⁻³ mm²/s was specific for separating prostate cancers from noncancers and (b) clinically significant cancers from both noncancers and low-grade cancers, but missed cancers with higher ADC values (Table 4, Fig. 4). Vice-versa, a higher ADC cutoff of 1.04 × 10⁻³ mm²/s was sensitive for separating prostate cancer from prostatitis but had lower specificity due to a considerable overlap in ADC values between low-grade cancers, clinically significant cancers, and prostatitis (Table 4, Fig. 4).

For separation of cancers and noncancers, AUC T2 and AUC ADC were higher than the previously reported AUC T2 of 0.52 to 0.74 and AUC ADC of 0.66 to 0.69,7,32 which may be due to better pathologic...
FIGURE 5. Comparison of ADC, T1, and T2 values for targeted biopsy-proven prostate cancer (A–D), prostatitis (E–H), and benign prostatic tissue (I–L). Prostate cancer: T2-weighted image (A) shows focal dark lesion against diffuse dark background signal in right peripheral zone (arrow, A) with ADC of $0.87 \times 10^{-3}$ mm$^2$/s (B). T1 and T2 values were 1560 milliseconds and 42 milliseconds, respectively. Prostatitis: T2-weighted (E) shows a wedge-shaped mildly dark lesion in left peripheral zone (arrow, E) with ADC of $0.87 \times 10^{-3}$ mm$^2$/s (F). T1 and T2 values were higher than cancer at 1770 milliseconds and 83 milliseconds, respectively. Benign prostatic tissue: T2-weighted (I) shows a focal lesion in right apical peripheral zone (arrow, I) with ADC of $0.82 \times 10^{-3}$ mm$^2$/s. Based on suspicious morphology on clinical MRI, biopsy was performed which revealed benign prostatic tissue. T1 and T2 values were higher than cancer at 2310 milliseconds and 73 milliseconds, respectively.

FIGURE 6. MRF with susceptibility artifacts on ADC mapping in a biopsy-proven case of $4+3=7$ cancer. T2-weighted image (A) shows ill-defined dark lesion in right apical peripheral zone (arrow) with low ADC value of $0.60 \times 10^{-3}$ mm$^2$/s (B). However, due to gas in rectum (asterisk), there is susceptibility artifact on ADC map with anteroposterior deformation of the gland. MRF T1 (A) and T2 (B) color maps are relatively unaffected by rectal gas and corresponding lesion T1 and T2 values were 1600 milliseconds and 52 milliseconds, respectively.
correlation provided by targeted biopsy, whereas the T1 differences between prostate cancers and noncancers is an additional finding in this study. The MRF-T2 values for different histopathologic groups are lower compared with values previously reported elsewhere and may relate to differences from multiple spin-echo mapping, such as noise floor effects at long echo times.

Both T2 and ADC had comparable performance for differentiating low-grade from clinically significant cancers, with the combination of T2 and ADC being additive (Table 3). Again, the AUC T2 from targeted biopsy validation is higher than the AUC T2 of 0.67 to 0.77 reported previously using TRUS biopsy whereas the AUC ADC for differentiating grades of cancers is comparable to the AUC ADC of 0.70 to 0.82 reported previously. At the microstructural level, higher Gleason grades are correlated with increased nuclear count and area, increased epithelial, and decreased luminal and stromal volume fractions. Although ADC was previously shown to correlate better with tissue composition changes and increased cellularity metrics as compared with T2, both tissue properties had similar performance for predicting cancer aggressiveness in this study. Due to the FISP acquisition scheme used, MRF as implemented is less adversely affected by rectal gas than EPI-based diffusion acquisitions (Fig. 6). Subject to future validation, relaxation time mapping obtained in this manner could potentially have quantitative utility as an alternative to ADC mapping in situations when diffusion-weighted imaging is distorted due to susceptibility artifacts. Mean T2 and ADC for low-grade cancers were similar to those of prostatitis and benign biopsies (Table 2). This is concordant with previous reports and the knowledge that low-grade cancers often have a low fraction of tumor cells intermixed with normal prostatic tissue and have lower epithelial and higher luminal fraction compared with higher-grade cancers.

This study had several limitations. First, only PZ lesions were analyzed in this study. This is because both peripheral and transition zones have different histological characteristics and are evaluated differently on conventional MRI, with ADC being the primary sequence for PZ lesions and T2-weighted imaging being the primary sequence for transition zone lesions. Separate analysis evaluating transition zone lesions will add further insight on the utility of this approach in prostate imaging. Second, the utilities of relaxometry and ADC mapping were used for lesion characterization and not for detection. Third, since the resolution of the technique is not comparable yet to T2-weighted imaging, volumetric analysis was not performed, and this remains a limitation of the work at this time. Efforts are underway at multiple institutions to develop and implement MRF examinations with higher spatial resolutions that would be better suited for detection and volumetric analysis in the future. Fourth, as targeted biopsy correlation was used instead of whole-mount prostatectomy specimens for a more practical and clinically feasible histologic validation, our dataset contained a larger number of clinically significant cancers versus low-grade cancers and prostatitis. This introduces a potential selection bias because targeted biopsy is known to detect a higher number of clinically significant cancers compared with TRUS biopsy or prostatectomy. In the future, a prospective analysis accompanied by prostatectomy correlations may also allow analysis of larger subject/lesion populations. Fifth, cognitive biopsy was the predominant biopsy method in our study because, in our institution, intra-gantry biopsy was performed more often for anterior transition zone lesions and in patients with prior negative biopsies, and this may have introduced an element of sampling bias. Finally, this was a single-center retrospective study with a single-reader analysis. Thus, the findings described need future prospective validation with larger datasets obtained from multi-institutional studies.

CONCLUSIONS
This work shows that the combination of T1 and T2 relaxometry can be complementary to ADC in predicting prostate cancer aggressiveness and may help in additional separation of cancers from prostatitis and negative biopsies for lesions on T2-weighted images in the PZ.

REFERENCES