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The value of diffusion-weighted MRI for prostate cancer detection and localization

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PURPOSE
The aim of this study was to evaluate the role of prebiopsy T2-weighted imaging (T2WI), quantitative diffusion-weighted imaging (DWI), and the combination of these magnetic resonance (MR) techniques (T2WI+DWI) in the detection and localization of peripheral zone prostate cancer.

MATERIALS AND METHODS
T2WI and DWI (b value = 800 s/mm^2) with an endorectal coil at 1.5 T were performed prospectively in 43 consecutive male patients with suspicion of prostate cancer before a systematic 12-core prostate biopsy. The peripheral zone of the prostate was evaluated after dividing it into sextants (n = 258). Minimum apparent diffusion coefficient (ADC) values of each sextant in the peripheral zone were measured. Two core biopsies were obtained from each sextant under transrectal ultrasound guidance.

RESULTS
The mean minimum ADC values of the malignant sextants were significantly lower than that of noncancerous tissue, with a significant negative correlation between the ADC value and the Gleason score. The sensitivity, specificity, and area under the receiver operating characteristic curve for the detection and localization of prostate cancer within the peripheral zone were 71%, 77%, and 0.741 for T2WI alone; 84%, 82%, and 0.830 for quantitative DWI alone; and 81%, 92%, and 0.863 for T2WI+DWI, respectively. The use of quantitative DWI, alone or combined with T2WI, improved diagnostic performance in prostate cancer detection and localization compared with T2WI alone (P = 0.020 and P = 0.001, respectively).

CONCLUSION
Prebiopsy DWI is valuable in detecting, localizing, and grading prostate cancer within the peripheral zone, and the lowest ADC values can indicate the regions to be biopsied.

Key words: • *prostatic neoplasms* • *magnetic resonance imaging* • *diffusion magnetic resonance imaging*

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The diagnosis and localization of prostate cancer are based on a digital rectal examination (DRE) and assessment of serum prostate-specific antigen (PSA) followed by transrectal ultrasound (TRUS)-guided biopsy, with a positive biopsy rate of 36.8% (1). However, the false-negative rate of standard sextant biopsy has been reported to be as high as 15% to 31%, and several studies have shown that additional biopsy cores would increase the detection of prostate cancer at the expense of an increased number of unnecessary biopsies (2). The accurate detection and localization of prostate cancer before a biopsy would likely decrease the excessive biopsy rate. Conventional imaging techniques have a limited role in the precise detection of localized prostate cancer. Because of the low specificity of morphologic examinations, pre-biopsy magnetic resonance imaging (MRI) is not recommended as a first-line imaging approach to discriminate between cancer and benign processes. However, recent advancements in anatomical and functional MR techniques, such as diffusion-weighted imaging (DWI), MR spectroscopy, and dynamic contrast-enhancement studies that provide relatively superior conspicuity of the lesions, have improved the imaging evaluation of localized prostate cancer (3, 4). Based on these data, we questioned whether DWI could be used as an accurate screening and guiding tool before a biopsy in patients with suspicion of prostate cancer.

In this study, we investigated quantitative DWI characteristics of prostate cancer in the peripheral zone and evaluated the diagnostic performances of T2-weighted imaging (T2WI) alone, quantitative DWI alone, and T2WI combined with quantitative DWI (T2WI+DWI) in the detection and localization of prostate cancer before an initial systematic 12-core biopsy. We also evaluated the relationship between the histological grade of prostate cancer and the minimum apparent diffusion coefficient (ADC) values in the peripheral zone.

Materials and methods

This was a prospective and retrospective study at a single institution. The local institutional review board approved the study, and informed consent was obtained from each subject before participation. Between September 2007 and March 2009, 43 consecutive male patients (mean age, 66 years; range 49–79) with serum PSA levels of >2.5 ng/mL or positive DRE were evaluated by MRI before a 12-core systematic transrectal prostate biopsy. None of the patients had a history of previous prostate biopsy. In our study population, total PSA levels ranged from 1.4 to 120 ng/mL (median, 9.1 ng/mL), and 22 patients had a positive DRE. MRI was performed with a 1.5-T unit (Signa Excite HD; GE Healthcare, Milwaukee, Wisconsin, USA), with a maximum gradient amplitude of 33 mT/m and maximum slew rate of 120 mT/m/sec, using a flexible endorectal coil (eCoil; Medrad, Pittsburgh, USA) combined with a pelvic

phased-array coil. The balloon-covered expandable endorectal coils were filled with 45–50 mL of air according to patient tolerance. After routine MRI (axial, coronal and sagittal T2-weighted images and axial T1-weighted images), axial diffusion-weighted images were obtained. The imaging parameters for the fast spin-echo T2-weighted images were TR/TE, 4500/116 ms; echo-train length, 19; bandwidth, 31.25 kHz; field of view, 14 cm; slice thickness, 3 mm; gap, 0.5 mm; number of excitations, 3; phase-encoding direction, right to left; and matrix, 288 × 224. Axial echo-planar DWI was performed using slice locations similar to those used for the T2-weighted sequence using the following parameters: b value, 800 s/mm^2; TR/TE, 4850/97.5; bandwidth, 250 kHz; field of view, 24 cm; slice thickness, 4 mm; number of excitations, 8; matrix, 128 × 128. The time required to acquire the DWI image set was 2 minutes and 35 seconds.

All images were reviewed by a single radiologist with 4 years of experience in interpreting prostate MRI, using an Advantage Workstation 4.3 (GE Healthcare). The peripheral zone of the prostate was divided into six regions: base, middle, and apex and left and right halves. The base was defined as the upper third of the prostate, which extended from the vesical margin of the prostate; the midregion was defined as the central third; the apex was defined as the remaining inferior third. For all patients, T2WI alone was reviewed first. On the T2WI, sextants with areas of any nodular low signal intensity in the peripheral zone were assigned as malignant, whereas mild low signals with linear or feathered appearances were accepted as benign. For DWI alone, the ADC maps were constructed on the workstation. The ADC values of each region in the peripheral zone were measured by placement of the region of interest (ROI) circles (area, 14 mm^2) on hypointense areas of the ADC map images. The lowest ADC values of at least four ROI measurements were recorded for each sextant. After a minimum interval of 4 weeks, T2-weighted images were reviewed in conjunction with the ADC maps, without knowledge of the biopsy results. For T2WI+DWI, any low T2 intensity with abnormal ADC values or a mass-like appearance on T2WI with borderline ADC values was assigned as malignant, whereas mild low signals in a linear or feathered appearance with borderline ADC values were accepted as benign.

Systematic 12-core prostate biopsies were performed in all the patients within 7 days after MRI examination by a single radiologist without knowledge of the MRI findings. Two core biopsies using an 18-G needle were obtained from the mid-lobar peripheral zone (the area of the standard sextant pattern) plus the lateral peripheral zone of each sextant under TRUS guidance. For all cases, the same pathologist, who was highly experienced in prostate cancer diagnosis, assessed the biopsied samples without knowledge of the radiologic findings and constructed a pathologic map of the prostate peripheral gland for use as the reference standard. Gleason scoring was performed for patients with carcinoma of the prostate.

The results are expressed as the mean ± standard deviation. Student's *t* test was used to determine significant differences in the mean ADC value between benign and malignant sextants in the peripheral gland. For each patient with prostate cancer, the mean of the minimum ADC values of malignant sextants was calculated. Relationships between mean ADC values in cancerous sextants and total Gleason scores were assessed using Spearman's ρ correlation test. For DWI, the cut-off ADC value distinguishing between benign and malignant lesions and "gray zone" (borderline) ADC values were defined using receiver operating characteristic (ROC) curve analysis. Sensitivities, specificities, positive predictive values, negative predictive values, and accuracies of detecting prostate cancer were calculated for each MRI protocol. The area under the ROC curve (A_z) was used to evaluate the overall diagnostic performance of T2WI alone, DWI alone, and T2WI+DWI. The 95% confidence intervals (CI) for the A_z values were calculated. The *Z* test was used to compare the A_z values. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Prostate cancer was pathologically detected in 21 (48.8%) of the 43 patients and in 69 (26.7%) of 258 sextants. The median Gleason score was 7 (4+3), with a range of 6 to 10. The mean minimum ADC values were 0.94 ± 0.32 x10^{-3} mm^2/s for the malignant sextants and 1.58 ± 0.36 x10^{-3} mm^2/s for the noncancerous peripheral zone tissue. The *t* test revealed that the difference between cancerous and benign sextants was significant ($P < 0.001$). In addition, in the patients with prostate cancer, a significant negative correlation was found between the mean minimum ADC value of malignant sextants and the total Gleason score ($\rho = -0.454$, $P = 0.039$) (Table 1). The ROC curve analysis revealed an optimal cut-off ADC value of ≤1.2x10^{-3} mm^2/s for the prediction of prostate cancer for DWI alone and a gray zone between ≥1.0x10^{-3} and ≤1.4x10^{-3} mm^2/s for T2WI+DWI, with an A_z value of 0.907 (95% CI, 0.865–0.940). Table 2 shows the sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and A_z value for the detection and localization of prostate cancer within the peripheral zone for T2WI alone, DWI alone, and T2WI+DWI. The *Z* test revealed that the A_z values for DWI alone and T2WI+DWI were significantly higher than that of T2WI alone ($P = 0.020$ and $P = 0.001$, respectively), but the difference between DWI alone and T2WI+DWI was not significant ($P = 0.277$).

Discussion

Currently, prostate MRI with an endorectal surface coil is recommended if cancer is suspected despite negative biopsy findings and for local staging of the cancer (5). However, a prebiopsy MRI has not been indicated for the detection and localization of cancer as a screening imaging modality in patients with suspected prostate cancer. DWI has recently received more attention; however, clinical experience with DWI in localized prostate cancer remains relatively limited. Our results showed that DWI, alone or in conjunction with T2WI, improved the diagnostic performance of endorectal prostate MRI in the detection and sextant-based localization of prostate cancer in the peripheral zone, before an initial biopsy. Moreover, we found a significant negative correlation between the ADC value and the Gleason score in patients with prostate cancer.

T2WI is the most widely used sequence to localize prostate cancer. Most prostate cancers arise in the peripheral zone as round or ill-defined low-signal-

intensity foci on T2-weighted images. However, T2 hypointensity within the high intensity of the normal peripheral zone can also be related to other benign conditions, such as nonspecific inflammation, post–radiation therapy fibrosis, biopsy-related hemorrhage, and changes after hormone deprivation therapy (3). Wide ranges of sensitivity and specificity rates have been reported (between 22–85% and 50–99%, respectively) for prostate cancer detection with T2-weighted MRI (6).

DWI assesses the Brownian motion of free water in tissue. In tumors, the motion of water is restricted, probably due to their higher cellular density and increased nucleocytoplasmic ratio, and it can be depicted on ADC maps, permitting a quantitative evaluation (7). Numerous authors have demonstrated that malignant lesions (range, 0.49 ± 0.13–1.66 ± 0.32x10^{-3} mm^2/s) have approximately 20 to 60% lower ADC values than noncancerous tissue (range, 1.26 ± 0.27–2.19 ± 0.24x10^{-3} mm^2/s) in the peripheral zone of the prostate, depending on patient population characteristics and technical issues (8–20). Recently, ADC values have also been correlated with the degree of tumor cellularity in prostate cancer (14–16). In previous studies conducting lesion-based analysis on 1.5 T field–strength MRI scanners, increased diagnostic rates in prostate cancer detection were shown when DWI was used in conjunction with T2WI (sensitivity, 53–74% vs. 71–88%; specificity, 54–91% vs. 61–89%; and A_z, 0.71–0.80 vs. 0.87–0.91, for T2WI vs. T2WI+DWI, respectively) (20–22). In this study, T2WI alone, quantitative DWI alone and T2WI combined with DWI were evaluated individually. Our results suggest that quantitative DWI alone (sensitivity, 84%; specificity, 82%; and A_z, 0.830) and T2WI+DWI (sensitivity, 81%; specificity, 92%; and A_z, 0.863) both have higher diagnostic performances than T2WI alone (sensitivity, 71%; specificity, 77%; and A_z, 0.741) for peripheral zone cancer detection and localization. Using quantitative DWI in conjunction with T2WI provided a marked increase in specificity (82% vs. 92%) and a positive predictive value (63% vs. 78%) but an insignificant increase in overall diagnostic performance, as compared to DWI alone. The ADC map appeared to demonstrate greater contrast between the cancer lesion and the prostate tissue than did T2WI (Figure), which indicates that better detection and localization of prostate cancer might be achieved with quantitative DWI as compared to T2WI. In the literature, DWI alone has a sensitivity and specificity of 81–94% and 72.2–91%, respectively, with a cut-off ADC value of 1.45–1.67 x10^{-3} mm^2/s for tumor detection, at 1.5 or 3.0 T (17–19). Our results indicate that the mean minimum ADC value of the cancerous sextants was significantly lower than that of the nonmalignant tissue, and using a cut-off ADC value

Table 1. Relationship between sextant-based prostate biopsy results and mean minimum ADC values

Systematic 12-core biopsy results	Number of patients	Number of sextants	Mean ADC value of the sextants[a]
Benign	*22*	189	1.58 ± 0.36x10^{-3} mm^2/s[b]
Malignant	*21*	69	0.94 ± 0.32x10^{-3} mm^2/s[b]
Gleason score = 6	*6*	8	1.18 ± 0.44x10^{-3} mm^2/s[c]
Gleason score = 7	*6*	23	1.05 ± 0.15x10^{-3} mm^2/s[c]
Gleason score ≥ 8	9	38	0.84 ± 0.16x10^{-3} mm^2/s[c]

ADC, apparent diffusion coefficient
[a]Values indicate the mean ± standard deviation
[b]$P < 0.001$, benign vs. malignant sextants
[c]$\rho = -0.454$, $P = 0.039$, correlation between mean ADC values and Gleason scores

Table 2. Diagnostic performance of endorectal MRI in the detection and sextant-based localization of prostate cancer in the peripheral zone (n = 258 sextants)

Performance measure	T2-weighted imaging alone	Quantitative ADC alone[a]	T2-weighted plus quantitative ADC
Sensitivity	71%	84%	81%
Specificity	77%	82%	92%
Positive predictive value	53%	63%	78%
Negative predictive value	88%	93%	93%
Accuracy	76%	83%	89%
Area under ROC curve (95% confidence interval)	0.741 (0.683–0.794)	0.830[b] (0.779–0.874)	0.863[c, d] (0.815–0.903)

ADC, apparent diffusion coefficient; ROC, receiver operating characteristic
[a]Cut-off ADC value = 1.2x10^{-3} mm²/s
[b]$P = 0.020$, compared with T2-weighted imaging alone
[c]$P = 0.001$, compared with T2-weighted imaging alone
[d]$P = 0.277$, compared with quantitative ADC alone

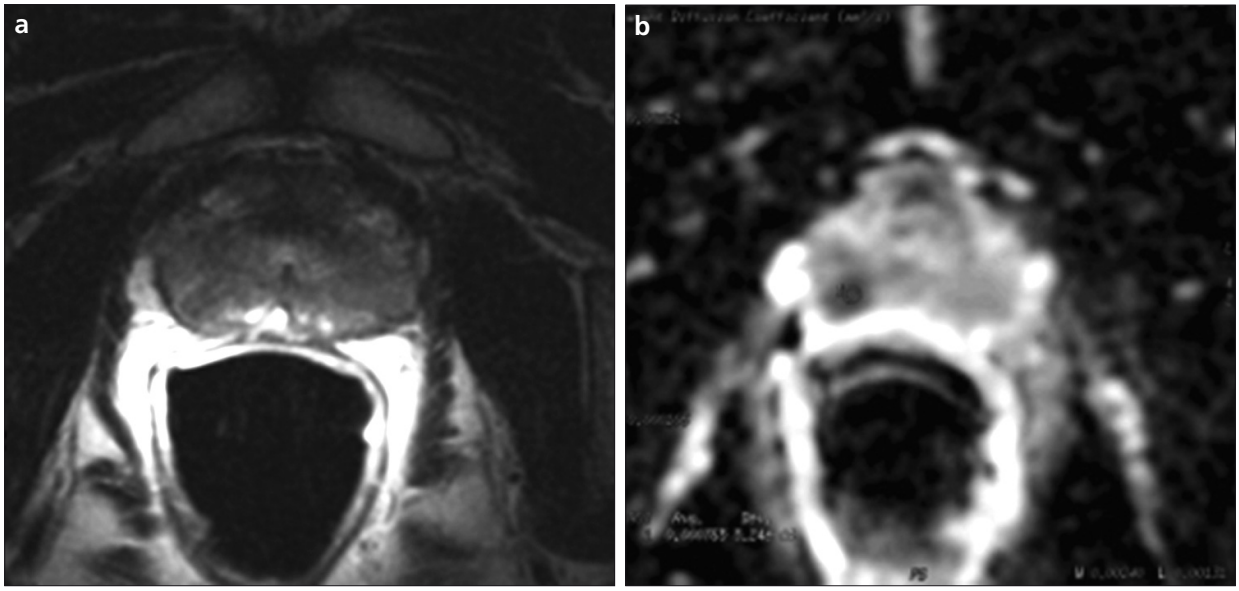

Figure. a, b. A 71-year-old man with prostate cancer in the right peripheral zone. Prostate-specific antigen was 4.0 ng/mL, and Gleason score was 7. Endorectal T2-weighted transverse MR image **(a)** showing a generalized low signal intensity in the peripheral zone bilaterally and no focal lesion. However, the apparent diffusion coefficient (ADC) map **(b)** shows a clear focal lesion with low signal intensity in the right peripheral zone, within the sextant that was biopsy-positive for tumor. A circular region of interest of 14 mm² superimposed on the lesion reveals a minimum ADC value of 0.765×10^{-3} mm²/s.

of $\leq 1.2 \times 10^{-3}$ mm²/s achieved 84% sensitivity and 82% specificity for the differentiation of cancerous tissues from benign prostatic sextants. The significant decrease in the ADC values of prostate cancer is thought to reflect the tissue architecture, such as the tightly packed glandular elements with increased cellularity and the diminished extracellular spaces that replace the fluid-containing peripheral zone ducts (4, 6, 7, 14, 15). Moreover, we showed a significant negative correlation between the mean minimum ADC value in malignant sextants and the Gleason score (which represents the degree of prostate tumor differentiation). Tamada et al. (23) have also reported a significant negative correlation between the ADC value in the cancerous peripheral zone and the tumor Gleason score. Yoshimitsu et al. (24) have found a significant difference between the ADC values for well- and poorly-differentiated prostate cancer and a subtle but significant correlation between the ADC value and the histological grade of prostate cancer. DeSouza et al. (25) have shown a significant difference between tumor ADC values in patients with low-risk localized disease (Stage ≤T2a and Gleason score <7 and PSA <10 ng/ml) and those with intermediate- or high-risk disease (Stage ≥T2b and/or Gleason score ≥7 and/or PSA >10 ng/ml). The correlation between the ADC value and the pathologic result suggests that the ADC value may be a marker for the degree of tumor differentiation in prostate cancer and may serve as a prognostic indicator. The lowest ADC value can indicate the region of greatest cellularity and may be helpful in selecting biopsy targets.

On the other hand, quantitative ADC analysis has an advantage that allows the radiologist to choose an adequate cut-off value to achieve a higher sensitivity or specificity, according to the actual diagnostic purposes. To use MRI as a screening and guiding tool, it should have a high sensitivity and a negative predictive value. For this use in the present study, if biopsies were obtained only from sextants with ADC values $\leq 1.4 \times 10^{-3}$ mm²/s (sensitivity 94%, specificity 60%, and negative predictive value 97%), the number of patients with prostate cancer would have remained unchanged, but the number of patients who underwent biopsy and the total number of sextants biopsied would have been reduced 9% and 46%, respectively. Further studies are needed to determine the significance of this potential utility of MRI with DWI.

Our study had a number of limitations. Histopathological analysis of core needle biopsy specimens was used as the reference standard. Matching sextant maps of MRI and histopathological data of biopsy samples can be challenging. Because the detection of prostate cancer depends on the size of the tumor, some small tumors may not be biopsied, some of the sampled tissues may not be from the same lesions observed in the MR images in a sextant, or some tumors may be undergraded. To minimize errors in the histopathologic and imaging data correlations, we performed a systematic TRUS-guided prostate biopsy protocol with an optimal number of 12 cores as an initial biopsy procedure; thus, there were two cores from each sextant. We analyzed cancer in only the peripheral zone, where most cancers occur. The lack of an analysis of the central part of the gland was a limitation of this study. Another limitation was that interobserver variability was not assessed. However, our standard T2WI interpretation results are consistent with those of prior studies, and we used quantitative ADC values for an objective interpretation with DWI. Finally, DWI itself also has some limitations. This sequence is affected by magnetic susceptibility, resulting in spatial distortion and signal loss. Moreover, there is no consensus on the optimal b-value for DWI of the prostate. The use of higher field

strengths and higher b-values can improve lesion detection.

In conclusion, DWI with ADC measurement is useful to distinguish between benign and malignant lesions, with a correlation between ADC values and the degree of prostate tumor differentiation. Compared with T2WI, the addition of an ADC map improves the diagnostic performance of MRI in prostate cancer detection and localization. Our results suggest a role for quantitative DWI in detecting, localizing, and grading prostate cancer within the peripheral zone. The selection of biopsy targets from the regions with the lowest ADC values can potentially reduce false-negative biopsy rates and unnecessary biopsies.

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