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Pilot Study of the Use of Hybrid Multidimensional T2-Weighted Imaging–DWI for the Diagnosis of Prostate Cancer and Evaluation of Gleason Score

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Abstract

OBJECTIVE—The objective of our study was to evaluate the role of a hybrid T2-weighted imaging–DWI sequence for prostate cancer diagnosis and differentiation of aggressive prostate cancer from nonaggressive prostate cancer.

MATERIALS AND METHODS—Twenty-one patients with prostate cancer who underwent preoperative 3-T MRI and prostatectomy were included in this study. Patients underwent a hybrid T2-weighted imaging–DWI examination consisting of DW images acquired with TEs of 47, 75, and 100 ms and b values of 0 and 750 s/mm². The apparent diffusion coefficient (ADC) and T2 were calculated for cancer and normal prostate ROIs at each TE and b value. Changes in ADC and T2 as a function of increasing the TE and b value, respectively, were analyzed. A new metric termed “PQ4” was defined as the percentage of voxels within an ROI that has increasing T2 with increasing b value and has decreasing ADC with increasing TE.

RESULTS—ADC values were significantly higher in normal ROIs than in cancer ROIs at all TEs ($p < 0.0001$). With increasing TE, the mean ADC increased 3% in cancer ROIs and increased 12% in normal ROIs. T2 was significantly higher in normal ROIs than in cancer ROIs at both b values ($p = 0.0002$). The mean T2 decreased with increasing b value in cancer ROIs ($T2 = -17$ ms) and normal ROIs ($T2 = -52$ ms). PQ4 clearly differentiated normal ROIs from prostate cancer ROIs ($p = 0.0004$) and showed significant correlation with Gleason score ($\rho = 0.508$, $p < 0.0001$).

CONCLUSION—Hybrid MRI measures the response of ADC and T2 to changing TEs and b values, respectively. This approach shows promise for detecting prostate cancer and determining its aggressiveness noninvasively.

Keywords

apparent diffusion coefficient; DWI; MRI; prostate cancer; T2-weighted imaging

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Multiparametric MRI—a combination of T2-weighted imaging, DWI, and dynamic contrast-enhanced MRI (DCE-MRI)—is commonly used for the diagnosis, local staging, and detection of prostate cancer [1–7]. T2-weighted and DW images are the backbone of this protocol [8, 9]. According to a recent meta-analysis, the combination of these images provides a pooled sensitivity of 76% and specificity of 82% for the detection of prostate cancer [10]. Although these results are encouraging, higher sensitivity and higher specificity are needed for routine clinical applications of MRI.

In conventional multiparametric MRI, T2-weighted images and DW images are independently acquired, and T2 and ADC within a voxel are measured independently. T2 is calculated without taking into account the dependence of the T2 on the b value. Similarly, ADC is calculated without accounting for the dependence of the ADC on the TE. ADC and T2 are therefore implicitly assumed to be independent [8–10]. Previous studies have shown that T2 and ADC are frequently interdependent, and distinct populations of water molecules in each voxel with specific paired T2 and ADC values can be identified [11–15]. Does and Gore [15] used this approach, which they referred to as “hybrid DWI,” to study compartmentation in normal and ischemic rat brain. A pilot study showed that hybrid imaging may improve the accuracy of MRI in diagnosing biopsy-proven prostate cancer by exploiting the interdependence of ADC and T2 [16]. Hybrid imaging identifies subvoxel populations of water molecules within the prostate on the basis of changes in the measured T2 and ADC values in response to changes in the b value and TE, respectively. This approach has the potential to isolate a relatively small signal from cancerous foci within a voxel from a large background signal corresponding to normal glandular tissue. In the current study, we build on previous work with an expanded patient dataset and Gleason score information obtained from prostatectomy to evaluate cancer aggressiveness. Our purpose was to investigate the potential role of a novel hybrid T2-weighted imaging–DWI sequence in the diagnosis of prostate cancer and differentiation of aggressive prostate cancer from nonaggressive prostate cancer.

Materials and Methods

Patients

Twenty-one consecutive patients referred to the department of radiology at our institution between June 2012 and May 2013 for a diagnostic MRI examination of the prostate were recruited and consented to participate in this study. The study was approved by our institutional review board and was HIPAA-compliant. To be included in the study group, patients had to have undergone a transrectal ultrasound–guided biopsy that showed positive results for prostate cancer, a hybrid T2-weighted imaging–DWI examination performed at our institution after biopsy and before prostatectomy, and radical prostatectomy with the prostatectomy specimen showing positive results for prostate cancer. Twenty-one patients were recruited; in the study group of 21 patients, 40 cancerous regions were identified (Gleason score: range, 6–9; median, 7). MRI was performed on a 3-T scanner (Achieva TX, Philips Healthcare).

MRI Data Acquisition

Each patient underwent a multiparametric MRI examination that consisted of T2-weighted turbo spin-echo (TSE) sequences, a T1-weighted TSE sequence, T2 mapping, a DCE-MRI sequence, and a hybrid T2-weighted imaging–DWI sequence. All images were acquired while the patient was breathing freely. The hybrid sequence consisted of a series of pelvic prostate DWI pulse sequences that are standard protocol and consist of a spin-echo module with diffusion-sensitizing gradients placed symmetrically around the 180° pulse followed by single-shot echo-planar imaging for signal detection. This pulse sequence was used to acquire images with TEs of 47, 75, and 100 ms, and images at each TE were acquired with b values of 0 and 750 s/mm², which resulted in a 3 × 2 array of data associated with each image voxel. Hybrid images were acquired in the axial plane oriented perpendicular to the rectal wall as guided by sagittal images. Fat saturation was implemented using spectral attenuated inversion recovery (SPAIR). The scanning time was 7–9 minutes per sequence, and in-plane resolution was 2.5 × 2.5 mm. The hybrid sequence parameters are listed in Table 1. An endorectal coil (Medrad, prostate ecoil, Bayer HealthCare) and a 6-channel cardiac phased-array coil placed around the pelvis were used to detect signal. A dose of 1 mg of glucagon (Glucagon, Lilly) was injected intramuscularly immediately before scanning to limit peristalsis of the rectum.

Histology-MRI Correlation

After the MRI examination, histologically confirmed tumors were mapped onto the hybrid T2-weighted–DW images. The prostate cancer foci and regions of normal prostatic tissue were identified and defined through a correlative review of each prostatectomy specimen and the corresponding MR images by a genitourinary pathologist (9 years of experience in genitourinary pathology) and a radiologist (10 years of experience in prostate MRI). Each prostatectomy specimen was sectioned serially into 4-mm-thick slices from the apex to the base in transverse planes. Slices were halved or quartered and were fixed in 10% buffered formalin. The blocks were embedded in paraffin, and 4- to 5-μm microtome slices were extracted and stained with H and E.

The pathologist first identified all distinct tumor foci with a diameter larger than approximately 5 mm in all specimen block sections for each patient. The pathologist assigned a Gleason score to each cancer focus. Then, the radiologist and pathologist, in consensus, identified the MRI slice (i.e., T2-weighted image or ADC map) that matched the level of the pathology slice where the cancer focus was detected. The radiologist then manually delineated ROIs of cancer foci on the MR images that corresponded with the location of the cancer on histopathology. If the tumor focus was not apparent on the MR images, its location was determined from its spatial relationship relative to identifiable anatomic landmarks such as the urethra, a benign prostatic hyperplasia nodule with distinct characteristics, or the ejaculatory ducts. All tumors in both the peripheral zone and central gland that were identified on histology specimens were delineated on the MR images. Regions of prostate defined as normal tissue were also outlined unless no normal locations could be found in the prostate. A location was defined as normal by the pathologist if cancer or high-grade prostatic intraepithelial neoplasia, benign prostatic hyperplasia, prostatitis, or other benign abnormalities were not present. ROIs were delineated on either an ADC map or

a T2-weighted image depending on which image set showed better correlation with the histologic findings.

Transfer of ROIs

The ROIs were transferred to the hybrid image set semiautomatically using custom software written in Matlab (version R2013b, MathWorks). The software transferred the ROIs from the images on which they were delineated to the coordinate system of the hybrid scans based on the scanning geometry information. This procedure was based on the assumption that there was no patient motion between MRI sequences. After registration, the transferred ROIs were reviewed on the hybrid images by a radiologist for accuracy. If there was visually obvious misalignment, the ROI position was manually adjusted in 3D without changing the shape or size of the contour.

Quantitative Image Analysis

T2s and ADCs were estimated from the hybrid image set using the least squares regression. The ADC value (ADC) was calculated at each TE value (TE) using both b values (b) according to the following formula:

$$S(t) = A \exp(-b \times ADC(TE)),$$

where S is signal intensity detected at time $t = TE$, and A is a constant. T2 ($T2$) was calculated at each b value (b) using all TE values according to the following formula:

$$S(t) = A \exp\left(\frac{-TE}{T2(b)}\right),$$

where S is signal intensity detected at time $t = TE$, and A is a constant. Both ROI-based and voxel-based fits were performed. ROI-based fits were performed by averaging the signal intensities across all voxels within an ROI and performing a single fit to these averaged values. These fits yield a 3×2 imaging data grid with ADC at TEs of 47, 75, and 100 ms and T2 at b values of 0 and 750 s/mm². If signal intensity within a voxel increased with increasing the b value or the TE, data from that voxel were considered corrupted and were excluded from the analysis. One or more voxels were excluded in 17 of 59 ROIs.

The dependence of ADC on TE and the dependence of T2 on b value were evaluated by comparing ADCs at different TEs and T2s at different b values for normal and cancer ROIs. The linear discriminant analysis (LDA) was used to create a classifier to differentiate prostate cancer from normal tissue. The LDA was constructed from the three ADCs and the two T2s associated with each voxel. As a result, the LDA included not only the baseline ADC and baseline T2 but also the change in T2 and change in ADC when the b value and TE are increased. ROI-based ADC and T2 fits were used, and ADCs and T2s were normalized using minimum-maximum scaling to range from 0 to 1. The effectiveness of the LDA classifier was evaluated using the leave-one-out cross-validation and ROC analysis and was compared with the effectiveness of the baseline ADC ($TE = 47$ ms) alone.

An additional parameter, which we refer to as “PQ4,” was calculated to reflect the response of ADC to the changing TE value and the response of T2 to the changing b value. PQ4 was defined as the percentage of voxels within a single ROI that display an increase in T2 when the b value is increased from 0 to 750 s/mm² and a decrease in ADC when the TE is increased from 47 to 75 ms. These changes are the opposite of the observed changes in T2 and ADC with changing b value and TE in normal prostate. These voxels appear in quadrant 4 of plots of ADC [ADC (TE = 75 ms) – ADC (TE = 47 ms)] versus T2 [T2 (b = 0 s/mm²) – T2 (b = 750 s/mm²)] (Fig. 1); thus, the percentage of voxels with these characteristics is referred to as PQ4. The voxel-based ADCs and T2s were used for calculation of PQ4. The PQ4 value was compared for cancers versus normal tissues and for cancers of different Gleason scores. PQ4 was also compared with ROI-based ADC and T2 values at each TE and b value for all ROIs.

Statistical Analysis

The Mann-Whitney *U* test was used to compare ADC or T2 values for cancer and normal ROIs at each TE and b value, respectively. The Student *t* test for paired data was used to compare T2 values measured at each b value for cancer and normal ROIs. The Friedman rank sum test, a nonparametric rank-based test, was used to compare ADCs at different TE values for normal and cancer ROIs. The AUC was calculated for both the LDA classifier and the baseline ADC alone using the proper binormal model [17]. The Student *t* test was used to compare PQ4 values of cancer and normal ROIs, and the Spearman rank order correlation coefficient was calculated for PQ4 and Gleason score. All *p* values were two-sided and were calculated from ROI-based fits for ADC and T2, with the exception of PQ4, which was from voxel-based calculations. A Bonferroni correction was applied for 16 multiple comparisons and effectively set the alpha level for statistical significance at $\alpha = 0.0031$.

Results

The dependence of T2 on b value and the dependence of ADC on TE are shown in Table 2 for all cancer and normal ROIs. ADC was significantly higher in normal ROIs than in cancer ROIs at all TEs ($p < 0.0001$). T2 was significantly longer in normal ROIs than in cancer ROIs at both b values ($p = 0.0002$). The mean ADC in cancer ROIs increases by only 3% when TE was increased from 47 to 75 ms. In contrast, the mean ADC in normal ROIs increased by 12% (Fig. 2). This change results in a difference in mean ADC of cancer and normal ROIs at a TE of 75 ms of 0.70×10^{-3} mm²/s, or approximately 60%. This difference is highly significant ($p < 0.0001$). The mean T2 in both normal and cancer ROIs decreases with increasing b value. The decrease in mean T2 is larger in normal ROIs ($\Delta T2 = -52$ ms) than in cancer ROIs ($\Delta T2 = -17$ ms).

The AUC of the LDA classifier for differentiating cancer from normal tissue was 0.96, whereas the AUC of the baseline ADC alone was 0.91 (Fig. 3).

PQ4—that is, the percentage of voxels in each ROI for which T2 increased with increasing b value and that ADC decreased with increasing TE—differentiated cancer from normal tissue (Fig. 1). The mean PQ4 was $3\% \pm 6\%$ (SD) for normal ROIs ($n = 19$) and $19\% \pm 24\%$ for cancer ROIs ($n = 40$). This difference was statistically significant ($p = 0.0004$). PQ4 also

showed a significant correlation with Gleason score (Fig. 4). The mean value of PQ4 was 9.5% for cancers with a Gleason score of 6, 22.6% for cancers with a Gleason score of 7, and 30.0% for cancers with a Gleason score of 8 or 9. This trend is statistically significant with a Spearman rank order correlation coefficient of $\rho = 0.508$, indicating a significant linear trend, and $p < 0.0001$.

Discussion

Our results show that the mean ADC in normal prostate increases more than the mean ADC in cancerous prostate when TE is increased from 47 to 75 ms. The mean T2 of normal prostate tissue decreases more than the mean T2 of cancerous prostate tissue with increasing b value. These findings suggest that ADC at a TE value of 75 ms may be diagnostically more useful than ADC at a TE value of 47 ms, the current clinical standard (Fig. 5), and that the interdependence of T2 and ADC can be used to improve diagnosis of prostate cancer.

We hypothesize that the changes in ADC and T2 with increasing TE and b value, respectively, are related to the microanatomy of the tissue. Normal prostate tissue has a prominent glandular structure with a large volume of glandular lumen. The free fluid in the lumen has a long T2 and a high ADC [18]. The glandular lumen is surrounded by glandular epithelium and stromal tissue. Water in the epithelium and stromal environment has a relatively shorter T2 and a lower ADC than the lumen. As TE is increased, the contributions to ADC from the epithelium and stroma should be reduced, resulting in an increased ADC approaching that of the isolated lumen. Conversely, as b value is increased, signal from tissue with a high ADC (i.e., lumen) should be diminished. The measured T2 thus would approach the lower T2 of stroma. A large increase in ADC with increasing TE and a large decrease in T2 with an increase in b value suggest a large fractional luminal volume and therefore a decreased probability of cancer [19]. We hypothesize that hybrid imaging could provide quantitative estimates of luminal fraction by measuring these changes relative to the estimated ADC and T2 values of luminal fluid and stroma.

Prostate cancer is marked by a decreased percentage of glandular lumens and a dense cellular structure with a short T2 and a low ADC relative to the lumen. These changes are more prominent in aggressive cancers; as Gleason score increases, the luminal volume decreases [20]. Without a large luminal volume, the signal contributions should not change when b value is increased and T2 remains approximately constant.

In addition, our results suggest that a small but significant component of cancers is characterized by increasing T2 with increasing b value and by decreasing ADC with increasing TE. These findings suggest the presence of an environment in cancers in which diffusion is restricted (low ADC) and there is a long T2. This signal determines the value of the PQ4 parameter introduced here. A high PQ4 value may reflect the intracellular water signal from the cytoplasm or nuclei of cancer cells [21, 22] where diffusion of water is restricted and perhaps a larger fraction of mitotic cells in cancers are associated with increased T2 [23–26]. Virtually all of the pixels in quadrant 4 of Figure 1 are from cancers (hence, a high PQ4), whereas almost all voxels from normal prostate appear in quadrant 2 (a low PQ4). A high PQ4 value suggests a lower percentage of water in a luminal environment

and a higher percentage of water in a restricted environment with a long T2. Therefore, PQ4 shows promise in differentiating normal tissue from cancerous tissue with different glandular structures by encapsulating the dependence of T2 and ADC on b value and TE, respectively, and the underlying histologic changes consistent with cancer. Conventional approaches that measure T2 and ADC independently cannot detect these effects. PQ4 is fundamentally different from T2 and ADC and therefore may provide independent diagnostic information that increases diagnostic accuracy when used in combination with ADC and T2.

The LDA classifier improved prostate cancer detection relative to ADC at a TE value of 47 ms alone, although the increase in the AUC was not statistically significant. We hypothesize that limitations in the sample size and the lack of an independent testing database limit the statistical power. Nevertheless, these results suggest that the additional information included in the hybrid data matrix due to sampling using multiple combinations of TE and b values can increase diagnostic accuracy.

The heterogeneous nature of prostate cancer can make it difficult to detect when cancer foci are distributed within normal glandular tissues even when quantitative methods are used. Langer et al. [27] evaluated T2 and ADC in sparse and dense peripheral zone prostate cancer tumors that they defined as containing greater than or less than 50% primarily normal peripheral zone tissue, respectively. They reported no significant difference between ADC or T2 of sparse prostate tumors and normal peripheral zone tissue and concluded that MRI may be limited for prostate cancer detection and tumor volume assessment in sparse cancers [27]. Our hybrid imaging technique may be able to better assess these tumors when used in conjunction with ADC and T2 by isolating the cancerous component from the normal glands on the basis of the response of ADC to changing TEs and T2 to changing b values. This capability is particularly important in diagnosing low-grade tumors for which physicians and patients must choose treatment or active surveillance and for localization of tumors for targeted biopsy or focal therapies.

The small sample size ($n = 21$) of the patient cohort is a limitation of this study. In particular, only a small number of high-grade (Gleason score of 8 or 9) cancers ($n = 4$) satisfied the inclusion criteria. We plan to increase this number significantly in the future to more accurately assess the correlation of PQ4 and other hybrid parameters with Gleason score and to evaluate the morphologic features of high-grade cancers on hybrid images. Because of limitations on the time available for data acquisition, higher b values were not investigated in this study. We are developing accelerated hybrid methods that will allow sampling of more combinations of b and TE values with a realistic acquisition time. This study of patients who later underwent radical prostatectomy introduces a patient selection bias to the study. Histologic analysis of prostatectomy specimens is the reference standard for Gleason score assignment and cancer localization, so this bias is unavoidable. The method of correlating cancers on T2-weighted images or ADC maps with histologic results may introduce bias in the evaluation of parameters derived from ADC and T2 (e.g., PQ4). However, our primary goal was not to accurately measure sensitivity and specificity of hybrid parameters but rather to evaluate the characteristics of new hybrid parameters in regions that are identified as cancer on histology. The diagnostic performance of hybrid imaging in a blinded setting is

beyond the scope of this pilot study. Last, this study was confined to a single center, and all imaging examinations were performed at our institution.

In conclusion, hybrid T2-weighted imaging–DWI shows promise for the improved diagnosis of prostate cancer and for determining its aggressiveness. Hybrid imaging produces maps of the changes in ADC and T2 with changing TEs and b values. These changes in each voxel are likely determined by the histologic structure of the tissue. In the prostate, the structure of the tissue is heavily influenced by luminal volume, an important marker of cancer aggressiveness. In addition, hybrid MRI reveals a population of water molecules with restricted diffusion and a long T2, which are findings that are associated with cancer.

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Fig. 1.

Response of apparent diffusion coefficient (ADC) to increasing TEs and of T2 to increasing b values in voxels across all patients and ROIs. Each marker represents single voxel. Almost all normal voxels are in quadrant 2 (*upper left*). Quadrant 4 (*lower right*) contains increased number of voxels as Gleason score increases.

Fig. 2. Apparent diffusion coefficient (ADC) values ($\times 10^{-3} \text{ mm}^2/\text{s}$) of cancer (*red*) and normal (*green*) ROIs at TE of 75 ms versus at TE of 47 ms. Each point refers to one ROI. Histograms on *x*- and *y*-axes show collapsed data along respective axes. Overlapping regions of histograms are shown in brown. Difference in distributions of ADC values shows improved performance of ADC at TE of 75 ms compared with performance of ADC at TE of 47 ms in our dataset. Dotted line shows equivalence (45°) line.

Fig. 3. ROC curves

A and **B**, ROC curves for linear discriminant analysis-derived data classifier (**A**) versus baseline apparent diffusion coefficient (ADC) alone (**B**). AUCs were 0.96 and 0.91, respectively.

Fig. 4.

Boxplot shows PQ4—parameter describing percentage of voxels within quadrant 4 of Figure 1 (lower right of Fig. 1)—as function of Gleason score. This quadrant corresponds to increased T2 with increased b value and decreased ADC with increased TE. Gray lines represent median value of parameter, boxes extend to 25th and 75th quartiles, and plus signs (+) represent outliers. Black horizontal lines indicate median, and dashed lines extend to 1.5 times the interquartile range. Trend had Spearman rank order correlation coefficient (ρ) of 0.508, which indicates significant linear trend, and $p < 0.0001$.

Fig. 5. Apparent diffusion coefficient (ADC) and T2 maps of 66-year-old man with adenocarcinoma with Gleason score of 6

A–C, ADC map acquired with TE of 47 ms (**A**), ADC map acquired with TE of 75 ms (**B**), and subtraction image of these two ADC maps [i.e., $\text{ADC}(\text{TE} = 75 \text{ ms}) - \text{ADC}(\text{TE} = 47 \text{ ms})$] (**C**) show tumor (*arrows*). Subtraction image was generated to show effect of TE on ADC of prostate cancer focus compared with normal prostate.

D–F, T2 map generated with b value of 0 s/mm^2 (**D**), T2 map generated with b value of 750 s/mm^2 (**E**), and subtraction image of two T2 maps (i.e., $[\text{T2}(b = 0 \text{ s/mm}^2) - \text{T2}(b = 750 \text{ s/mm}^2)]$) (**F**) show tumor (*arrows*). Window and level settings were adjusted independently for each image.

TABLE 1**Hybrid T2-Weighted Imaging–DWI Sequence Parameters**

MRI Parameters	Value
TE (ms)	47, 75, 100
b Values (s/mm ²)	0, 750
TR (ms)	3000
No. of slices	20–25
Slice thickness (mm)	3
In-plane resolution (mm)	2.5 × 2.5
Matrix size	128 × 128
FOV (mm)	180 × 180
No. of signals acquired	4
SENSE factor	2
Received bandwidth (Hz)	3307.5
Scanning time per sequence (min)	7–9

Note—SENSE = sensitivity-encoding.

TABLE 2

Apparent Diffusion Coefficient (ADC) as a Function of TE and T2 as a Function of b Value in 21 Patients With Prostate Cancer

Value	Normal ROIs (<i>n</i> = 19 ROIs)	Cancer ROIs (<i>n</i> = 40 ROIs)	<i>p</i> ^{<i>a</i>}
ADC ($\times 10^{-3}$ mm ² /s), mean $\pm$ SD			
TE = 47 ms	1.61 $\pm$ 0.32	1.08 $\pm$ 0.28	< 0.0001
TE = 75 ms	1.81 $\pm$ 0.34	1.11 $\pm$ 0.26	< 0.0001
TE = 100 ms	1.85 $\pm$ 0.36	1.23 $\pm$ 0.33	< 0.0001
<i>p</i> ^{<i>b</i>}	< 0.0001	< 0.0001	
T2 (ms), mean $\pm$ SD			
b Value = 0 s/mm ²	146 $\pm$ 74	81 $\pm$ 54	< 0.0001
b Value = 750 s/mm ²	94 $\pm$ 41	64 $\pm$ 19	0.0002
<i>p</i> ^{<i>b</i>}	< 0.0001	< 0.0001	

Note—ADC and T2 values are from ROI-based fits.

^{*a*}These *p* values compare cancer ROIs versus normal ROIs (column) and were derived from the Mann-Whitney *U* test.

^{*b*}These *p* values compare ADCs at different TEs and T2s at different b values (rows) and were derived from the Friedman rank sum test and paired Student *t* test for paired data, respectively.