**Value of Diffusion Tensor Imaging of Prostate Cancer: Comparison with Systemic Prostate Biopsy**

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**Purpose:** This study was performed to evaluate the usefulness of diffusion tensor imaging (DTI) and to correlate systemic twelve biopsy in prostate cancer.

**Materials and Methods:** Thirty-one patients with suspected prostate cancer underwent MR imaging. DTI was performed prior to a prostate biopsy. We prospectively calculated the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) value in each corresponding biopsy site.

**Results:** Twenty-three of 31 patients had histopathologically proven adenocarcinoma. Among the 276 biopsy cores of 23 patients with prostate cancer, 109 cores showed positive results (39%). The ADC and FA value of positive cores were $1.31 \pm 0.34 \times 10^{-3}$ mm$^2$/s and 0.68 $\pm$ 0.07, and those of the negative cores were $1.74 \pm 0.45 \times 10^{-3}$ mm$^2$/s and 0.54 $\pm$ 0.09, respectively. Eight patients without carcinoma showed an ADC value of $1.83 \pm 0.26 \times 10^{-3}$ mm$^2$/s and an FA value of 0.47 $\pm$ 0.07. The ADC and FA value of positive cores were significantly lower and higher than those of negative cores and cancer-free patients, respectively ($p < 0.05$).

**Conclusion:** The ADC and FA values using DTI may provide useful diagnostic information in the differentiation of cancerous tissues, although there is overlap in some cases.

**Index words:** Prostate
Prostate Neoplasms
Magnetic Resonance Imaging
Diffusion Magnetic Resonance Imaging
Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) has been used primarily to demonstrate microstructure and identify abnormalities in the field of neurology, and has recently begun to be investigated for discriminating cancer (1, 2). DTI uses additional gradients to plot the relative degree of diffusion in multiple dimensions. The use of multiple diffusion gradient directions allows gradient summation, resulting in stronger applied gradients and shorter TE values. Several studies have recently reported the value of measuring the diffusion coefficient to correlate with histologic findings of disease extent in prostate cancer (3–8). These studies have reported the potential usefulness of diffusion weighted image (DWI) for detecting prostate cancer because it shows a lower apparent diffusion coef-
sufficient (ADC) than a normal peripheral zone (PZ). Prostate cancer could be detected more accurately by T2-weighted imaging (T2WI) with a diffusion weighted image as compared with T2WI. However, these studies obtained the DWI and ADC values with the diffusion gradients applied in only three different directions and correlated the ADC values with less than six histologic sites per patient. To our knowledge, few reports exist on the usefulness of ADC and FA values using DTI in correlation with histology for prostate cancer diagnosis. Our study obtained ADC and fractional anisotropy (FA) values using DTI with diffusion gradients applied in six different directions and correlated DTI values with 12 biopsy sites per patient.

The purpose of this study was to evaluate the usefulness of DTI and to correlate the systemic twelve biopsy in prostate cancer.

**Materials and Methods**

**Patients Population**

Our institutional review board approved this study, and the requirement for patient informed consent to participate in this study was waived. Informed consent had been obtained from all patients prior to the biopsy. Thirty-one patients with suspected prostate cancer were enrolled in our study. The mean patient age ranged from 47 to 72 years (mean, 56 years). Mean prostate volume was 49.7 gm (range, 21.0–78.9 gm) and the mean serum PSA level of the patients was 22.4 ng/mL (range, 4.1–96.0 ng/mL). Twelve patients had PSA levels below 10 ng/mL.

**MR Technique**

The patients underwent conventional MR imaging and DTI. MR examinations were performed with a 1.5T MR scanner (GE Signa Excite HD, General Electric, Milwaukee, WI, USA) along with an 8-channel phased array coil prior to transrectal ultrasound guided sys-

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**Fig. 1.** T2-weighted image (A) shows low signal intensity (arrow) of the left peripheral zone in accordance with a positive biopsy result. We obtained \( b = 500 \text{ s/mm}^2 \) image (B) and isotropic image (C) using diffusion tensor imaging. The ADC (D) and FA (E) value shows corresponding decrease and increase in the same regions.
temic 12-core biopsy. The parameters of conventional MR imaging were as follows: T2-weighted fast spin-echo images were obtained in three orthogonal planes (TR/TE, 4000 ms/109.7 ms; echo train length, 16; number of excitation, 2) with a $320 \times 224$ matrix, 4-mm slice thickness, 0.4-mm interslice gap, and an 18-cm field of view. T1-weighted spin-echo images were also obtained in the axial plane (TR/TE, 500 ms/14 ms; echo train length, 7; number of excitation, 1) with a $320 \times 224$ matrix, 4-mm slice thickness, 0.4-mm interslice gap, and a 21-cm field of view. We used a single-shot spin-echo echo-planar imaging (EPI) sequence using the following parameters: TR/TE, 4000 ms/6 ms; number of excitation, 4; $192 \times 192$ matrix; 5-mm slice thickness; no interslice gap; a 20-cm field of view; ASSET factor, 2. The acquisition time was 2 minutes and the b-factors were 0 and 500 s/mm$^2$ with the diffusion gradients applied in 6 different directions.

**Image Analysis and Prostate Biopsy**

A faculty radiologist with 10 years of experience in prostate MR imaging prospectively measured the ADC and FA value in each of the sites corresponding to the 12 systemic biopsy sites using an Advantage Windows workstation (Functool 2.6.6i, GE Medical Systems, Fremont, CA, USA). For each patient the radiologist drew 12 regions of interest (ROIs) in both PZs. The area of ROIs kept constant in each patient in order to reduce the standard error in measurement. These ROIs were manually set on images for EPI acquired with $b = 0$ s/mm$^2$ and accounting for the distortion of EPI on which structures could be easily identified, and then copied. Examples of ROI placement are shown in Fig. 1.

Transrectal ultrasound (TRUS) guided systemic biopsy of the prostate was performed on an ultrasound system (ACUSON Sequoia 512, Siemens, Mountain View, CA, USA). The patients were examined with gray scale imaging in the axial and sagittal planes with a 10 MHz transrectal probe. Local anesthetics were administered to patients before the prostate biopsy was performed. We obtained TRUS guided systemic 12 biopsy cores at sites including the lateral and medial regions of the apex, as well as the middle and base in both PZs (Fig. 2). A biopsy was not obtained in both transitional zones. The analysis of MR analysis and TRUS guided systemic biopsy were performed by the same radiologist. The radiologist made efforts to match the 12 biopsy sites to the ROIs. We classified biopsy cores into “positive” or “negative" for carcinoma.

**Statistical Analysis**

After confirming that the data was normally distributed, unpaired $t$-tests were used to determine whether there was a significant difference for the mean ADC and FA values between positive and negative cores, negative cores in cancer patients and negative cores in cancer-free patients. All of the tests were two-sided, and $p < 0.05$ was considered to be statistically significant.

The diagnostic power of the ADC and FA values in differentiating prostate cancer from noncancerous tissue was evaluated by the ROC curve analysis. Analysis was performed between positive cores in cancer patients and negative cores in cancer-free patients. To use the ADC and FA values as a diagnostic tool, we extracted the optimal cutoff value of ADC and FA from the ROC curve analysis. The sensitivity and specificity corresponding to the cutoff values were then calculated. A statistical analyses was then performed using SPSS 14.0 KO software for Windows (SPSS, Chicago, IL, USA).

**Results**

The ADC and FA values were successfully measured for all 31 patients. The time between the MR examination and systemic 12 biopsy was within one week. Twenty-three of 31 patients had histopathologically proven adenocarcinoma with a Gleason score of 6.2
Twelve of the 23 patients with prostate cancer underwent radical prostatectomy. Among the 276 biopsy cores taken from the 23 patients with prostate cancer, 109 showed positive results (39%). The mean ADC and FA values of the positive cores were $1.31 \pm 0.34 \times 10^{-3}$ mm$^2$/s (range, $0.6 \times 10^{-3} - 1.64 \times 10^{-3}$ mm$^2$/s) and $0.68 \pm 0.07$ (range, $0.53 - 0.87$), respectively. In contrast the negative cores had mean ADC and FA values of $1.74 \pm 0.45 \times 10^{-3}$ mm$^2$/s (range, $1.21 \times 10^{-3} - 2.73 \times 10^{-3}$ mm$^2$/s) and $0.54 \pm 0.09$ (range, $0.36 - 0.73$), respectively. Eight (96 biopsy cores) patients without carcinoma showed ADC and FA values of $1.83 \pm 0.26 \times 10^{-3}$ mm$^2$/s (range, $1.5 \times 10^{-3} - 2.51 \times 10^{-3}$ mm$^2$/s) and $0.47 \pm 0.07$ (range, $0.33 - 0.64$), respectively (Table 1). Only a slight overlap was observed between the positive and negative cores. The ADC and FA values of the positive cores were significantly lower and higher than those of negative cores and cancer-free patients ($p < 0.05$), respectively. However, there were no significant differences between the negative cores of cancer patients and the negative cores of cancer-free patients for both the ADC and FA values ($p > 0.05$).

The ROC curves calculated to determine the diagnostic performance of the ADC and FA values for differentiating prostate cancer from non-cancerous tissue are demonstrated in Fig. 3 and Fig. 4. The area under the ROC curve (Az) of the ADC was 0.914 (95% confidence interval [CI], 0.879–0.950, $p < 0.01$). In comparison, the Az of the FA was 0.983 (95% CI, 0.970–0.997, $p < 0.01$). The optimal cutoff value of the ADC from the ROC analysis was $1.65 \times 10^{-3}$ mm$^2$/s with 87.2% sensitivity and 71.9% specificity. The optimal cutoff value of the FA was 0.55 with a 99.1% sensitivity and 88.5% specificity. The ROC analyses showed that the ADC and FA values provided good diagnostic performance for differentiating cancer and noncancerous tissue.

### Discussion

DTI is an emerging MR imaging method for gaining insight into tissue microstructure through the monitoring of random movement of water molecules, which is usually restricted in anisotropic tissues. Tissues that have a regularly ordered microstructure reflect a marked anisotropy in their diffusion properties. DTI to map anisotropy and fiber orientation has primarily been performed in vivo in the human brain. However, the advent of EPI has enabled the use of diffusion imaging in other organ systems. Diffusion in the prostate is also direction-dependant (9). Prostate anisotropy measurements can provide useful indices for lesion characterization. Several studies have recently reported the values of measuring diffusion anisotropy to correlate with histologic findings of disease extent in prostate cancer (3–8). However, these studies obtained DWI in three ortho-

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**Table 1. Comparison of the Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) Value in Prostate Cancer Tissue and Noncancerous Tissue**

<table>
<thead>
<tr>
<th>Results of Biopsy Core</th>
<th>ADC ($\times 10^{-3}$ mm$^2$/s)</th>
<th>FA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Cancer ($n = 23$)</td>
<td>Positive</td>
<td>$1.31 \pm 0.34^*$</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>$1.74 \pm 0.45$</td>
</tr>
<tr>
<td>Patients without Cancer ($n = 8$)</td>
<td>Negative</td>
<td>$1.83 \pm 0.26$</td>
</tr>
</tbody>
</table>

Note. * $p < 0.05$
nal planes (not six orthogonal planes) and correlated them with less than six histologic sites per patient.

We measured the ADC and FA values using diffusion gradients along the six directions of the motion-probing gradients. To our knowledge, there are few studies on the use of ADC and FA values in the correlation with histology for prostate cancer diagnosis. Also, we correlated DTI values with 12 biopsy sites in the peripheral zone of a given patient. Several indices have been introduced to characterize diffusion anisotropy. Initially, simple scalar indices calculated from DWI or ADCs obtained in perpendicular directions were used. However, these indices are not really quantitative, as they do not correspond to a single meaningful physical parameter and, more importantly, are clearly dependent on the choice of directions made for the measurements. The degree of anisotropy would then vary according to the respective orientation of the gradient hardware as well as the tissue frames of reference and would generally be underestimated. Thus, invariant indices have been made of the combination of the terms of the diagonalized diffusion tensor, [i.e., the eigenvalues $\lambda_1$, $\lambda_2$, and $\lambda_3$]. The most commonly used invariant indices are the relative anisotropy, the FA, and the volume ratio indices [10]. These DTI indices can be used for determining quantitative diffusion metrics. The ADC value reflects molecular diffusivity under motion restriction. Moreover, the FA index is used to characterize directional variability in diffusion. FA is obtained by using at least 6 different directions which provide directional data pertaining to diffusion anisotropy. A tissue is considered to be fully isotropic when its anisotropy is equal to 0, and fully anisotropic when its anisotropy is equal to 1 [10].

Previous studies have indicated that DWI can distinguish prostate cancer from normal tissue with the ADC value [3–8]. Our results indicated a significant low ADC value in cancerous tissue compared to normal tissue. The mean ADC value of cancer was $1.31 \pm 0.34 \times 10^{-3}$ mm$^2$/s, which compared to $1.74 \pm 0.45 \times 10^{-3}$ mm$^2$/s in negative cores. These findings were consistent with the $1.08 \pm 0.39$ and $1.8 \pm 0.41 \times 10^{-3}$ mm$^2$/s reported by Sato et al. [3] and reported $0.99 \pm 0.21$ and $1.5 \pm 0.18 \times 10^{-3}$ mm$^2$/s reported by Kim et al. [8]. However, the b-value in our study was different from those reports. Also, our results indicated a significant higher FA value in cancerous tissue than normal tissue. To our knowledge, there few reports deal with the FA value in prostate cancer. Only the FA value of normal tissue for the PZ was reported by Sinha et al. [9]. Our FA value, $0.42 \pm 0.07$ for normal PZ was similar to a previous report $0.46 \pm 0.04$ [9].

With the relatively low b-value employed in our study, the measured ADC primarily reflects the diffusion coefficient of extracellular water [11]. Applied b-factor was 500 s/mm$^2$ in this work. However, there is no consensus about the optimal b-value for prostate cancer. Although a DTI with a high b-value can allow the decrease in signal-to-noise ratio (SNR) loss in a high-Tesla MR system, further studies should be performed for the benefit of high b-value in the prostatic tissues. The normal prostate gland consists of a network of water-rich ducts and acini supported by stroma. The stroma is much looser in the PZ than in the central gland (CG), resulting in a larger extracellular space. These differences in histology can then account for higher ADC values in the more glandular PZ compared to the CG. In cases of prostate cancer, loose stroma is replaced by densely packed malignant epithelial cells, resulting in a significant decrease in extracellular space and thus a lower ADC value [4]. The anisotropy values (FA) of PZ and CG are close, with a slightly higher value for the PZ compared to CG. This is given that the greater structural organization of CG may be expected to yield higher anisotropy values [9]. We suggest that densely packed malignant epithelial cells may yield the greater structural organization compared to a normal looser structure in the PZ. Our study showed that cancerous lesions had the lower ADC and higher FA values than normal prostate tissue. These findings suggest that the measurement of the ADC and FA values may be additional useful information for the differentiation of cancerous tissues.

The ADC and FA values slightly overlap between cancer and noncancerous tissue. The indices reflect various physical and physiological characteristics of tissue but are not specific for cancer itself. Variable abnormal and different conditions, such as prostatitis, ischemia, benign prostatic hyperplasia, intratumoral hemorrhage, age, body temperature, regional gradient, tissue pressure, perfusion rate, or magnetic environment of an individual subject, alter the DTI indices [8, 12, 13]. Many different MR acquisition protocols and MR devices also make it difficult to determine the cut-off value for differentiating cancer from non-cancerous tissue.

There are limitations to our study. Despite our best efforts to match the 12 biopsy sites to the ROIs in the PZ, the biopsy sites may be actually different from the ROIs.
because of the transrectal ultrasound angle. The biopsy result may not represent the histologic feature in the ROI. Hence, a histopathologic analyses would need to be performed using a total histologic specimen from radical prostatectomy.

In conclusion, the ADC and FA values using DTI may provide useful diagnostic information in the differentiation of cancerous tissues, although there is overlap in some cases.

References