Diffusion-weighted MRI and PSA Correlations in Patients with Prostate Cancer Treated with Radiation and Hormonal Therapy

YUKO IRAHA¹, SADAYUKI MURAYAMA¹, AYANO KAMIYA¹, SHIRO IRAHA² and KAZUHIKO OGAWA³

¹Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, Okinawa, Japan;
²Department of Radiology, Okinawa South Medical Center, Okinawa, Japan;
³Department of Radiation Oncology, Osaka University Graduate School of Medicine, Osaka, Japan

Abstract. Aim: To investigate the correlation between signal intensity (SI) on diffusion-weighted imaging (DWI) and the levels of prostate-specific antigen (PSA) in patients with prostate cancer treated with radiation and hormonal therapy.

Patients and Methods: Forty-four patients with prostate cancer treated with hormonal therapy and radiation therapy were evaluated. Areas with high SI on DWI were detected and the apparent diffusion co-efficient (ADC) values were measured. The ADC values and PSA levels were compared between patients with high-DWI SI and patients with a normal DWI signal. Results: Fourteen patients had high SI on DWI. The mean ADC value in these cancerous lesions was lower than in non-cancerous tissues. The mean PSA level in patients with high-DWI SI was significantly higher than in patients with a normal signal. Conclusion: The present results suggest that SI on DWI appears to correlate with PSA levels in patients with prostate cancer treated with radiation and hormonal therapy.

Prostate-specific antigen (PSA) is widely used for screening, diagnosis, determination of prognosis, selection of appropriate treatment, and for predicting disease status after treatment of prostate cancer in men (1).

Magnetic resonance imaging (MRI) is now a major imaging modality for prostate cancer detection and localization. MRI techniques have recently progressed, and can provide good quality diffusion-weighted images (DWI), especially with the use of parallel imaging techniques. DWI can be used to detect malignant tumours. Several investigators have reported on the potential usefulness of DWI for detecting prostate cancer that is in part due to the lower apparent diffusion co-efficient (ADC) values of tumor compared to the non-cancerous regions of the prostate (2-6). DWI may also provide qualitative and quantitative information for measuring therapeutic response in patients with prostate cancer during and after radiotherapy. On the contrary, imaging methods have not been widely used in daily practice to assess the effect of hormonal therapy or disease status after hormonal therapy in patients with prostate cancer. Furthermore, few investigations have reported on the usefulness of DWI for assessment of the radiation and hormonal therapy response for prostate cancer (7-10).

In the present study, the performance of DWI for visualizing prostate cancer treated with radiation and hormonal therapy was investigated, and the correlation between the signal intensity (SI) on DWI and the PSA levels was examined.

Patients and Methods

Patients. This study was approved by our Institutional Review Board. Written informed consent was waived because of the retrospective nature of the analysis. Between May 2007 and April 2010, 44 patients with biopsy-proven prostate cancer underwent hormonal therapy prior to radiation therapy, and underwent MRI examinations before and after radiation therapy. The median patient age was 72 years (range=55-81 years). The mean PSA level before all therapy was 31.4 ng/ml (range=5-270 ng/ml). Nineteen of the men were at high risk, 17 were at intermediate risk, and eight were at low risk according to the classification by D’Amico et al. (11).

The mean PSA level after the start of hormonal therapy and before radiation therapy was 0.66 ng/ml (range=0.01-10.31 ng/ml). Nineteen of the men were at high risk, 17 were at intermediate risk, and eight were at low risk according to the classification by D’Amico et al. (11). The mean PSA level after the start of hormonal therapy and before radiation therapy was 0.66 ng/ml (range=0.01-10.31 ng/ml). Table I presents the patients’ characteristics. The median interval from prostate biopsy to MRI examination was 7.5 months (range=0.5-96.1 months). The mean PSA level after the start of hormonal therapy was 3.14 ng/ml (range=5-270 ng/ml). The mean PSA level after the start of hormonal therapy was 0.66 ng/ml (range=0.01-10.31 ng/ml). All MRI were carried out before radiation therapy and 3 to 4 months after the completion of therapy.
All patients received hormonal therapy with a luteinizing hormone releasing-hormone analog and an anti-androgen. Radiation therapy was administered at 2 Gy/fraction to a total dose of 72-76 Gy (mean dose=75.4 Gy) with the use of 10-MV modulated radiation therapy.

**MRI techniques.** All images were collected using a 1.5-T MRI system (Intera Achieva; Philips Healthcare, Best, the Netherlands), equipped with a five-channel phased-array coil. All patients underwent DWI in addition to imaging studies using a routine prostate MRI protocol. Axial T1- and T2-weighted images and coronal T2-weighted images with spectral pre-saturation with inversion recovery (SPIR) were acquired.

Imaging parameters for T1-weighted imaging were as follows: repetition time/echo time (TR/TE)=497/12 ms, echo-train length (ETL)=5, bandwidth (BW)=217.7 kHz, field of view (FOV)=22 cm, slice thickness/gap=4/1 mm, number of excitations (NEX)=4, matrix size=288×288, and sensitivity-encoding (SENSE) factor=2. The time required to acquire the T1-weighted image set was 2 minutes and 47 seconds.

Imaging parameters for turbo spin-echo T2-weighted imaging were as follows: TR/TE=4700/120 ms, ETL=11, BW=145.9 kHz, FOV=22 cm, slice thickness/gap=4/1 mm, NEX=4, matrix size=288×288, and SENSE factor=2. The time required to acquire the T2-weighted image set was 2 minutes and 44 seconds.

Axial echo-planar DWI with STIR was performed using slice locations similar to those used for T1- and T2-weighted image sequences, respectively, using the following parameters: b values=0, 800 and 2,000 s/mm², TR/TE=6000/80 ms, Ti=160-170 ms, BW=41.4 kHz, FOV=25 cm, slice thickness/gap=4/0.6 mm, NEX=3, matrix size=80×80, and SENSE factor=2. Motion-probing gradients were applied in three orthogonal orientations. ADC maps were automatically constructed on a pixel-by-pixel basis (0, 800 and 2,000 s/mm²). The time required to acquire the DWI set was 5 minutes and 6 seconds.

**Image analysis.** All images were retrospectively analyzed by consensus by two radiologists, each with 16 years of experience, who were unaware of the clinical findings. The two readers did know that all patients in the study had biopsy-proven prostate cancer.

The readers first reviewed the axial DWI images obtained for each case using a b-value of 2000 s/mm², in order to identify areas suspicious for cancer. An area with focal high-SI relative to that of the surrounding prostate tissue was regarded as a cancerous lesion by consensus of the two readers. These images were reviewed in conjunction with the axial T1-weighted images and axial and coronal T2-weighted images to localize hemorrhage. An area with normal SI on DWI was regarded as non-cancerous prostate tissue. An area with diffuse high-SI in the peripheral zone on DWI was also regarded as non-cancerous tissue, since that area might be affected by hormonal therapy. The ADC values of the cancerous lesions and non-cancerous prostate tissue were measured by placement of regions of interest (ROIs). When the ROIs were drawn, great care was taken to exclude both the neurovascular bundle and the urethra. ROIs of cancerous lesions were drawn on ADC maps to include as much of the lesions as possible with the use of T2-weighted images to assist in the identification of the detailed anatomy of the prostate. ADC values of the lesions were assessed twice in the same site, and the average ADC value was calculated. For non-cancerous prostate tissue of the peripheral zone and transition zone, ROI circles were drawn in three different areas, and the ADC values were averaged.

**Results**

In 14 out of 44 patients, an area with high SI on DWI was detected (Figure 1). In these 14 patients, ten were at high risk and four were at intermediate risk for prostate cancer. The cancerous lesion was mainly detected within the peripheral zone in nine patients and in the transitional zone in five. The mean ADC value of cancerous lesions was 0.76×10⁻³ mm²/s, significantly smaller than that in non-cancerous prostate tissue (1.07×10⁻³ mm²/s) (p<0.001) (Figure 2a).

The mean PSA level in patients with high SI on DWI before radiation therapy was 1.88 ng/ml, significantly higher than that (0.08 ng/ml) in patients with normal SI on DWI (p<0.001) (Figure 2b).

The time from start of hormonal therapy to radiation therapy was within six months in 19 patients, six months to two years in 18, and more than two years in 7 patients. Mean PSA levels in the stratified patients were 1.07, 0.18 and 0.76 ng/ml respectively, and statistically significant differences were found (p=0.001).

**Table I. Characteristics of included patients.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>Prostate-specific antigen level (ng/ml)**</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>Gleason score</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

**Note:** Unless otherwise indicated, data represent the number of patients. **Before radiation therapy.
After radiation therapy, the mean ADC value of cancerous lesions increased significantly (1.02×10⁻³ mm²/s) \((p=0.001)\) (Figure 3) and high-DWI SI disappeared. However, significant differences in the ADC values between cancerous lesions and non-cancerous tissue (1.14×10⁻³ mm²/s) remained. The mean ADC value of non-cancerous prostate tissue was statistically higher after radiation therapy \((p<0.001)\), but the increase in the ratio was lower than in cancerous lesions.

After radiation therapy, the mean PSA level in patients with a high SI on DWI decreased significantly (0.2 ng/ml, \(p=0.002\)). The mean PSA level in patients with normal DWI signal did not change.

No correlation in the degree of changes between the PSA levels and ADC values was found \((p>0.05)\).

**Discussion**

Several studies have shown that the ADC values of prostate cancer are lower than those of benign non-cancerous tissue \((2-6)\), and, following treatment, tumor ADC values increase \((7-10)\). This reflects increased water mobility through the loss of membrane integrity or an increase in the proportion of total extracellular fluid due to a decrease in cell size or number \((12, 13)\).
The treatment effect of hormonal therapy for prostate cancer is usually evaluated with serum PSA. Imaging methods including MRI are not commonly used to monitor the treatment response in patients with prostate cancer because the measurement of PSA kinetics is simpler and more convenient. Nemoto et al. (10) reported that ADC values of prostate cancer increase after hormonal therapy.

In the present study, more than a quarter of the patients had areas with high SI on DWI that were regarded as cancerous lesions, despite hormonal therapy. In these patients, serum PSA levels were significantly higher than in patients with a normal DWI signal. This suggests that cancer viability remained in patients with high SI on DWI. ADC values increased significantly after radiation therapy in these patients, as has been seen in previous reports (7, 8). Thus, DWI could be used as an imaging biomarker to assess the therapeutic effect in patients with prostate cancer treated with hormonal and radiation therapy. Furthermore, as has been shown in previous reports (14-16), DWI might be used for predicting locally-recurrent prostate cancer after therapy.

The present results showed that the ADC values of non-cancerous prostate tissue also statistically increased after radiation therapy. As all patients received hormonal therapy prior to radiation therapy in the present study, the effect of hormonal therapy might remain during radiation therapy. These changes in ADC values might reflect the weakened hormonal therapy effect, especially in the peripheral zone. Several patients had an area with diffuse high-SI in the peripheral zone with relatively decreased volume and SI on T2-weighted images. These areas were excluded as cancerous lesions in order to avoid the hormonal therapy effect on normal tissue. In previous reports (17-19), histological findings in the prostate gland after hormonal therapy revealed marked glandular shrinkage, glandular atrophy, and fibrosis. These changes would be expected to result in a smaller, darker prostate gland with relatively decreased ADC values before radiation therapy. Further investigation is needed for evaluating such ADC changes.

In the present study, all patients were treated with the same hormonal therapy but the different time from starting hormonal therapy to radiation therapy. The mean PSA levels were significantly higher in patients treated with hormonal therapy within six months or more than two years before radiotherapy. Possible reasons for this phenomenon include the following: the therapeutic effect of hormonal therapy may be inadequate when treated within six months, and PSA failure may arise when patients are treated for more than two years.

There are several limitations to this study. Firstly, no histopathological confirmation was obtained. Second, a b value of 2,000 s/mm² was used for DWI in spite of the fact that most previous reports have used a b value of 1,000 s/mm² for DWI, as is commonly used for other organs. Therefore, ADC values in the present study were relatively low compared with these of other studies; however, recent studies (20, 21) have shown that using a high b value of 2,000 s/mm² can

Figure 3. Apparent diffusion co-efficient values of cancerous lesions and non-cancerous tissue before and after radiation therapy. ADC values of both cancerous lesions and non-cancerous tissue increased after radiation therapy, but the increase in the ratio of non-cancerous tissue was lower than that of cancerous lesions. PZ, Peripheral zone; TZ, transitional zone.
improve diagnostic performance in prostate cancer detection.
In conclusion, the present results suggest that SI on DWI appears to correlate with PSA levels for prostate cancer treated with radiation and hormonal therapy. ADC values appear to be useful for monitoring the therapeutic response of prostate cancer.

References