Determination of the cut-off level of apparent diffusion coefficient values in the detection of prostate cancer

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Authors: M. Nagayama, Y. Watanabe, A. Terai, T. Araki, K. Notohara, S. Nakashita; Kurashiki, Okayama/JP
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Purpose

Magnetic resonance imaging (MRI) of the prostate has been used for the localization and staging of prostate cancer to determine the treatment plan. Previous studies have reported the usefulness with MRI including T2-weighted images (T2WI), dynamic contrast-enhanced images and MR spectroscopy for detection of prostate cancer with some limitations. Prostate cancer in the peripheral zone (PZ) usually appears as a hypointensity area relative to normal area on T2WI. However, other pathological conditions, including inflammation, hyperplasia, fibrosis, and hemorrhage, can also show low signal intensity on T2WI. Detection of a transition zone (TZ) cancer could be much more difficult because the TZ is a common site of origin of benign hyperplasia, whose signal intensity can be similar to that of cancer on T2WI. Although dynamic contrast-enhanced MRI can detect prostate cancer as an enhanced area, some overlap in the enhancement patterns between tumors and hyperplastic nodule has been reported. MR spectroscopy has been shown to provide the metabolic information for the localization of prostate cancer. However, it requires additional software, a long imaging time, and training of radiological technologists.

Recent studies have reported the usefulness of apparent diffusion coefficient (ADC) maps based on diffusion weighted imaging (DWI) for detecting prostate cancer. MRI can be made sensitive to diffusion using strong bipolar motion probing gradient (MPG) pulses with high b values inserted into a pulse sequence. Tissues with restricted diffusion appear as a relatively hyperintensity area on DWI scans and a hypointensity area on reconstructed ADC maps. Application of DWI to the body has been difficult because this type of imaging is extremely sensitive to physiological motion and susceptibility. However, recent advances in MRI technologies, such as high-performance gradient coils and parallel imaging techniques, have improved image quality of the prostatic DWI scans by shortening the effective time of echo (TE), increasing signal-to-noise ratio, and reducing susceptibility artifacts. Some preliminary studies reported that ADC values of prostate cancer were significantly lower than those of noncancer tissues. Some studies used visual assessment of ADC map for the detection of prostate cancer and correlated the MRI result with histopathologic findings in biopsy specimens. We postulated that determinating the cutoff ADC value could provide objective assessment of ADC maps in the detection of cancer and in the differentiation between malignant and nonmalignant lesions.

The purpose of this study was to determine the cutoff level of ADC value for detecting cancer lesions by comparing the ADC values of cancer lesions with those of noncancer areas with reference to histological specimens obtained from radical prostatectomies.
Methods and Materials

Patient population

A total of 45 consecutive patients (age range 53-74 years, mean 67 years) with biopsy-proven prostate cancer who underwent radical prostatectomy were included in this study between January 2004 and March 2006. All the subjects, who were suspected to have prostate cancer because of high prostate-specific antigen (PSA) values (range 4.1-22.8 ng/ml, mean 8.7 ng/ml), underwent MRI of the prostate followed by systematic prostate biopsy prior to radical prostatectomy. The median time interval between MRI and radical prostatectomy was 59 days (range 24-130 days). None of the patients received preoperative hormonal or radiation therapy. The pathological T stage of the prostate cancer in these patients was pT2a \((n = 3)\), pT2b \((n = 33)\), and pT3a \((n = 9)\). All of the patients provided written informed consent to participate in this study, which was approved by the institutional review board.

MRI examinations

All MRI studies were performed on 1.5-T superconductive units (Gyroscan ACS-Intera; Philips Medical systems, Best, The Netherlands) with a commercially available five-channel cardiac phased array coil, which was placed on the patient's lower pelvis over the prostate. The routine MRI protocol included DWI, T2WI \((\text{TR/TE } 3500/300)\), and dynamic contrast-enhanced turbo spin echo MRI \((\text{TR/TE/echo train length } 514/16/3)\) for the entire prostate gland and seminal vesicle. It also included T1WI \((\text{TR/TE } 450/15)\) and fat-suppressed T2WI \((\text{TR/TE } 1800/100)\) through the whole pelvis for the purpose of evaluating pelvic lymph nodes and bone metastases. The total examination time was 40 min, including patient positioning and coil placement.

Diffusion-weighted images of the entire prostate gland in the transaxial direction were obtained using the single-shot spin echo echoplanar imaging (EPI) sequence with the following parameters: TR 3500 ms; TE 74 ms; b-factor 0 and 800 s/mm\(^2\); field of view (FOV) of 270 mm; matrix 144 x 256; section thickness of 4-5 mm; intersection gap of 0.5 mm; number of signal averages (NSA) 8; scan time of 3 min 30 s; sensirivity-encoding (SENSE) reduction factor 2. Parallel imaging was used to reduce the number of phase-encoding steps and reduce readout time, which can make the TE as short as possible and reduce image blurring and susceptibility artifacts. Spectral presaturation with inversion recovery was used for fat suppression. MPG pulses were applied in three directions. Isotropic images were synthesized from the DWI scans obtained in the three directions, and ADC maps were reconstructed from \(b = 0\) images and isotropic DWI scans.
Histological evaluation of surgical specimen

A radical prostatectomy specimen was fixed with formalin. It was then divided into 10-mm transverse contiguous slices, processed, and embedded in paraffin. The slices were then subjected to hematoxylin-eosin (H&E) staging. A pathologist examined the histological slices microscopically. When necessary, the 10 mm thick slices were cut into 2-mm contiguous slices for detailed histological examination. When prostate cancer was histologically diagnosed, the following details were also reported; location, size, and differentiation type of cancer. A histological map of the prostate cancer was then made by recording open circles on the photocoy of each section of the radical prostatectomy specimens.

Assessment of ADC value

The MRI sections and histological slices were matched using the urethra as a landmark in the longitudinal orientation and the shape of the transition and peripheral zone for the corresponding cross-sectional orientation. The correlation between the ADC map and histological map was made retrospectively section by section. T2WI and dynamic contrast-enhanced MRI scans were also compared with the corresponding histologic slices. The cancer lesions and surrounding noncancer areas were identified on the ADC map by two readers, with consensus.

Cancer lesions with a short diameter of # 8 mm were included in the evaluation. The diameter of 8 mm was double the slice thickness of 4 mm, which allowed reliable statistical comparison of the lesion according to the RECIST criteria.\textsuperscript{30}

The ADC values for the cancer lesions and the surrounding noncancer areas were measured with multiangular operator-defined regions of interest (ROIs) drawn over them. The ROI was as large as possible to minimize noise, with care to avert a partial-volume effect. According to this criterion, the area of the ROI was about 75%-90% of the area of the cancer lesions and the surrounding noncancer areas. When a cancer lesion more or less occupied both the peripheral and transition zones, ADC values of the surrounding noncancer areas were measured for both zones. When a cancer lesion made it difficult to measure surrounding noncancer areas by a single operator-defined ROI, two operator-defined ROIs were used to cover the corresponding zone entirely.

From the data obtained, the cutoff level for the ADC value for the diagnosing prostate cancer was proposed using the mean plus multiplied standard deviation of ADC values obtained from all the cancer lesions.\textsuperscript{31} The multiplicity of the standard deviation was set at 0.5, 1.0, 1.5 and 2.0.

Statistical analysis
The ADC values for cancer lesions and noncancer areas were compared. Among the cancer lesions, the relation between the ADC values and the differentiation types was examined. The two-tailed unequal variance $t$-test was used for ADC values with the zonal location and differentiation type of cancer. For every statistical analysis, significance was considered to exist when $p < 0.05$.

To evaluate the diagnostic performance of the cutoff ADC value for detecting cancer lesions, the sensitivity, specificity, and accuracy were calculated using the ADC values obtained in this study and were compared for four cutoff levels.
Results

The mean and standard deviation of the ADC values of all the cancer lesions \((n = 60)\) was \(1.04 \pm 0.30 \times 10^{-3} \text{ mm}^2/\text{s}\). In the peripheral zone, the cancer lesions \((n = 33)\) and the surrounding noncancer areas \((n = 44)\) had ADC values of \(1.07 \pm 0.35\) and \(1.94 \pm 0.31\) \((x10^{-3}\text{ mm}^2/\text{s})\), respectively \((p < 0.001)\). In the transition zone, the cancer lesions \((n = 27)\) and the noncancer areas \((n = 37)\) had ADC values of \(1.00 \pm 0.22\) and \(1.56 \pm 0.14\) \((x10^{-3}\text{ mm}^2/\text{s})\), respectively \((p < 0.001)\) (Table 1 on page 8). The mean ADC values of the cancer lesions were significantly lower than those of noncancer areas in both the peripheral and transition zones (Fig. 1 on page 7, Fig. 2 on page 8).

The mean ADC value of well-differentiated adenocarcinoma \((n = 27)\), moderately differentiated adenocarcinoma \((n = 27)\), and poorly differentiated adenocarcinoma \((n = 6)\) were \(1.05 \pm 0.33, 1.04 \pm 0.27,\) and \(0.97 \pm 0.30\) \((x10^{-3}\text{ mm}^2/\text{s})\), respectively. No significant differences were observed between the ADC values and the differentiation type of cancer (Table 2 on page 9).

Among the four cutoff levels proposed by using the mean plus multiplied standard deviation of ADC values obtained from the total prostate cancer, the mean value plus single standard deviation \((1.35 \times 10^{-3}\text{ mm}^2/\text{s})\) was found to achieve the best accuracy of 93% with the sensitivity of 88% and specificity of 96% (Table 3 on page 10). In this setting, a false-negative diagnosis of prostate cancer was found for seven lesions, including six for peripheral zone cancer and one for the transition zone cancer. All of the false-negative cancer lesions were also difficult to be detected on T2-weighted and dynamic contrast-enhanced images (Fig. 1 on page 7). A false-positive diagnosis was found in only 4%, which were exclusively in the transition zone composed of benign hypertrophy. The cutoff level of 1.2 (the mean plus a half of standard deviation) was found to yield the highest specificity of 100% among the four cutoff levels.
Fig. 1: Multiple cancer lesions in transition and peripheral zones a: Histopathological map of surgical specimen b: Apparent diffusion coefficient (ADC) map c: T2-weighted image d: Early phase of dynamic contrast-enhanced imaging a Histopathological map of the surgical specimen demonstrated two cancer lesions located in the left anterior portion of the transition zone (arrow, open circle) and the left posterior portion of the peripheral zone (arrowhead, open oval). Histologically, the transition zone cancer proved to be poorly differentiated adenocarcinoma with Gleason score 8 (3 + 5), and the peripheral zone cancer is a well-differentiated adenocarcinoma with Gleason score 6 (3 + 3). b On the ADC map, the transition zone cancer (arrow) had a low ADC value of 0.69 x 10^{-3} \text{mm}^2/\text{s} in comparison with that of the noncancer transition area (1.57 x 10^{-3} \text{mm}^2/\text{s}). The area corresponding to the peripheral zone cancer (arrowhead) had an ADC value of 1.88 x 10^{-3}\text{mm}^2/\text{s}, which was similar to that of the surrounding noncancer areas (1.92 x 10^{-3} \text{mm}^2/\text{s}). c, d The transition zone cancer (arrows) shows a homogeneous low signal intensity area on a T2-weighted image (c) and a high signal intensity area on the early phase of the dynamic contrast-enhanced image (d). The peripheral zone cancer (arrowheads) was not detected on the T2-weighted image (c) or on the dynamic contrast-enhanced image (d).
**Fig. 2:** Cancer lesion in peripheral zone a. Histopathological map b. Apparent diffusion coefficient (ADC) map c. T2-weighted images

a. Histopathological map of the surgical specimen demonstrates cancer lesion in the left peripheral zone (arrows). Histologically, the cancer proved to be poorly differentiated adenocarcinoma with Gleason score 9 (4 + 5).  
b. On the ADC map, the cancer (arrows) had a low ADC value of 0.93 ± 0.22 x 10^{-3} mm²/s. 
c. The cancer shows homogeneous low signal intensity areas (arrows) on T2-weighted images.
Table 1
ADC values for cancer lesions and surrounding noncancer areas

<table>
<thead>
<tr>
<th>Location</th>
<th>Cancer lesion</th>
<th>Noncancer area</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PZ</td>
<td>1.07 ± 0.35 (n=33)</td>
<td>1.94 ± 0.31 (n=44)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>TZ</td>
<td>1.00 ± 0.22 (n=27)</td>
<td>1.56 ± 0.14 (n=37)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total</td>
<td>1.04 ± 0.31 (n=60)</td>
<td>1.77 ± 0.25 (n=81)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Results are the mean ±SD
ADC, apparent diffusion coefficient; PZ, peripheral zone; TZ, transition zone,
Table 2  ADC values according to the histological type of prostate cancer

<table>
<thead>
<tr>
<th>Histological type</th>
<th>ADC value (x10^{-3} mm^2/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>1.05±0.33</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>1.04±0.27</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>0.97±0.30</td>
</tr>
</tbody>
</table>

ADC values are the mean ±SD
The differences were not significant
<table>
<thead>
<tr>
<th>Cutoff ADC level (x 10⁻³mm²/s)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.20 (mean + SD x 0.5)</td>
<td>75</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>1.35 (mean + SD x 1.0)</td>
<td>88</td>
<td>96</td>
<td>93</td>
</tr>
<tr>
<td>1.51 (mean + SD x 1.5)</td>
<td>93</td>
<td>80</td>
<td>86</td>
</tr>
<tr>
<td>1.66 (mean + SD x 2.0)</td>
<td>97</td>
<td>57</td>
<td>74</td>
</tr>
</tbody>
</table>
Conclusion

DISCUSSION

The ADC values for prostate cancer measured in our study were significantly lower than those of noncancer regions, as reported in the previous studies. The ADC value based on DWI is a parameter that reflects diffusion itself as well as tissue properties, such as cell organization, cell density, and microvasculature. Low ADC values in prostate cancer could be attributed to high cellular density, as shown in some brain tumors.

Measurement of ADC values are necessary to evaluate objectively the prostate gland for cancer lesions and for differentiating malignant from nonmalignant lesions. ADC values of noncancer regions in the peripheral zone were high. The normal peripheral zone has loose stroma and a large extracellular space that consists of a network of water-rich ducts and acinus. The transition zone usually shows hyperplastic changes, including glandular and connective tissues, in elderly patients. This is probably the main reason for higher ADC values for the normal peripheral zone than for the nonmalignant transition zone.

The detection of cancer of the prostate gland on the ADC map depends on the conspicuity of the cancer lesions in comparison with the surrounding noncancer areas. In this study, the difference in the ADC values between the cancer and the surrounding noncancer areas was shown to be greater for the peripheral zone than for the transition zone. Therefore, it seems to be more difficult to detect cancer in the transition zone than in the peripheral zone with the ADC map. Furthermore, the noncancer areas in the transition zone usually have a heterogeneous appearance of mixed low and intermediate signal intensity on T2-weighted images.

A cutoff level for the ADC value could play an important role as an objective index for the detection and localization of prostate cancer with the ADC map. The cutoff level should be determined in a way that achieves the best sensitivity, specificity and accuracy in the diagnosis of prostate cancer. In this study, the cutoff level defined as the mean plus a single standard deviation of the ADC value from the total cancer lesions yielded an accuracy as high as 93%. If the mean ADC value plus double or one and a half the standard deviation were used as the cutoff level, the sensitivity could be higher but at the cost of specificity and accuracy. Thus, a cutoff level of $1.35 \times 10^{-3}$ mm$^2$/s defined as the mean ADC value plus a single standard deviation seems to be a reasonable, effective diagnostic indicator for detecting cancer lesions and for differentiating between cancer
and noncancer areas. Furthermore, the cutoff level of $1.20 \times 10^{-3}$ mm$^2$/s defined as the mean ADC value plus a half of a standard deviation could provide the highest specificity of 100%, which means that a low ADC lesion of $1.20 \times 10^{-3}$ mm$^2$/s or less could be malignant with the highest probability.

In the setting of the cutoff level $1.35 \times 10^{-3}$ mm$^2$/s, the false-negative could not be detected on either T2-weighted or dynamic contrast-enhanced images. Most of the false-negative cancer lesions were histologically proven to be a sparsely spread cancer, which seems difficult to detected with MRI, as reported by Langer et al. Mucinous carcinomas can demonstrate scattered clumps of tumor cells within a lake of mucin upon histological examination and should show high signal intensity on T2-weighted images, mimicking cystic hyperplasia. These types of prostatic adenocarcinoma would have intermediate or high ADC values and might not be identified on an ADC map or on T2-weighted or contrast-enhanced images.

The type of differentiation of cancer has shown no significant differences in the ADC values, although poorly differentiated adenocarcinoma did have somewhat lower ADC values than well-differentiated or moderately differentiated adenocarcinoma. Tumors with a high Gleason grade appear to have increased cellular density, which may result in lower ADC values. Precancerous conditions and well-differentiated adenocarcinoma, which pathologically resemble benign tissue, may have ADC values as high as those for benign tissue.

We have also noted that some of the benign hyperplastic nodules in the transition zone have low ADC values and resemble cancer lesions. Information regarding the morphologic appearance on T2-weighted images can help differentiate cancer from noncancer areas for such a false-positive lesion. Hyperplastic nodules tend to be round with a smooth margin and a hypointense pseudocapsule, whereas cancer has an irregular margin and may extend beyond anatomical structures.

A b-value $> 1000$ s/mm$^2$ produces high contrast and a low signal-to-noise ratio (SNR) on DWI. Only tissues with low ADC values appear as hyperintense focal areas, and the contrast between cancer and noncancer is greatly increased. These images may be useful for detecting cancer with apparently low ADC values. However, as the b-value is increased, the TE elongates, the SNR is reduced, and the images are much more affected by susceptibility. Under these conditions, ADC values may not be reliable. To accurately determine tissue properties based on diffusion, original DWI scans require a sufficient SNR and fewer artifacts. To date, ADC maps reconstructed from b values around 800 s/mm$^2$ could have a great advantage over a high-b-value DWI.

Finally, the cutoff level for the ADC value determined on the basis of the results obtained from radical prostatectomy specimens could be a good indicator to offer the high
likelihood of detecting cancer foci. ADC maps using the ADC cutoff level in combination with T2-weighted imaging could provide accurate localization information of prostate cancer. Using this technique, targeted biopsies might detect as many cancers as do systematic biopsies, which could minimize the number of biopsies performed.

There are several limitations in this study, and a large scale prospective study is necessary to investigate how accurate is the cutoff ADC level determined with the surgical specimens in the detection of prostate cancer and in the differentiation of malignant lesions from other nonmalignant lesions.

**Conclusion**

Our study determined that the cutoff ADC level is $1.35 \times 10^{-3} \text{ mm}^2/\text{s}$. This factor may be used to achieve the best accuracy in detection of prostate cancer.
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