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Diffusion-weighted Imaging with Relative Signal Intensity Statistical Thresholding for Delineating Prostate Cancer Tumors

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Purpose: We assessed the utility of diffusion-weighted imaging (DWI) with relative signal intensity (rSI) statistical thresholding for delineating prostate cancer tumors.

Materials and Methods: Seventeen patients with prostate cancer underwent DWI before total prostatectomy. We measured standard deviation (SD) of the signal intensity (SI) of the lesser pelvic space at DWI, created rSI maps, displaying signal intensities with SDs of only $> +3$, $> +3.5$, $> +4$, or $> +5$, and assessed correlation between the proportion of cancerous area on the 4 different rSI maps and that on pathological slices.

Results: We could detect prostate cancer on rSI maps for all cases with $SD > +3$, but not 2 cases with $SD > +3.5$, five with $SD > +4$, and eight with $SD > +5$. The correlation coefficients (R) between the proportion of cancerous area on pathological examination and rSI maps were 0.7464 for $SD > +3$ ($P=0.0006$); 0.6469 for $SD > +3.5$ ($P=0.0050$); 0.6459 for $SD > +4$ ($P=0.0051$), and 0.4540 for $SD > +5$ ($P=0.0671$).

Conclusion: DWI-based rSI mapping may be used to delineate the extent of prostate cancer. We achieved best correlation between ratio of cancerous area of the lesser pelvic space on pathological examination and on rSI map using a threshold with $SD > +3$ of the SI.

Keywords: *diffusion-weighted imaging, magnetic resonance imaging, prostate cancer, relative signal intensity*

Introduction

Prostate cancer accounts for approximately 28% of new cancer cases and approximately 11% of cancer deaths in the USA.¹ Accurate delineation of the extent of prostate cancer is important given the emergence of focal therapies.^{2,3} Knowledge of tumor location and extent within the prostate can help direct maximal therapy to the largest focus of tumor and minimize damage to surrounding structures, such as the neurovascular bundles, rectal wall, and neck of the bladder.

Magnetic resonance (MR) imaging plays an important role in the evaluation of prostate cancer. T₂-weighted imaging (T₂WI) is widely used for pre-treatment work-up for prostate cancer, although its

accuracy for detecting and localizing cancer is limited by the similar signal patterns of tumor tissue and benign prostatic hyperplasia, prostatitis, and post-biopsy hemorrhage.^{4,5} Various other techniques, including dynamic contrast-enhanced MR imaging (DCE-MRI), MR imaging spectroscopy, and diffusion-weighted imaging (DWI), may be used to improve the diagnostic utility of MR imaging.

Particularly, DWI has gained widespread popularity for differentiating prostate cancer from non-cancerous tissue.⁴⁻⁷ DWI demonstrates areas with impeded diffusion and reduced apparent diffusion coefficients (ADCs) in cancerous tissue. Advantages of DWI are its relatively short acquisition time and the high contrast resolution between cancer and normal tissue.⁴⁻⁷ DWI with ADC mapping has been shown to improve the diagnostic performance of T₂WI for detecting and localizing pro-

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state cancer.^{6,7} However, there are 3 significant problems with ADC mapping of prostate cancer: there is a non-negligible overlap in ADCs between prostate cancer and surrounding noncancerous tissue; ADC maps tend to be noisy, especially at higher b-values⁸; and calculation of an ADC map requires acquisition of at least 2 images with different b-values. Nevertheless, misregistration between datasets acquired with different b-values may occur as a result of distortions from motion and echo-planar imaging, so exact delineation of the extent of prostate cancer on the ADC map may be difficult and thereby negatively influence planning of focal therapies. Previous work has shown that the signal intensity at high-b-value DWI can be used to detect prostate cancer.⁹ Applying a very high b-value, such as 1500 to 2000 s/mm², rather than the usual 1000 s/mm² can increase contrast between prostate cancer and surrounding noncancerous tissue and improve cancer detectability.⁹ Use of high-b-value DWI instead of ADC maps requires application of only one b-value, avoids issues of image misregistration, and may therefore be useful for delineating the extent of prostate cancer. However, the lack of an anatomical reference to normalize the SI at DWI makes measurements of tumor size highly dependent on the window level and width applied.

We propose using the lesser pelvic space as a reference to determine the relative signal intensity (rSI) of prostate cancer at DWI and herein introduce and assess the utility of DWI with rSI statistical thresholding for delineating cancerous prostate tumors and use histopathology as the reference standard.

Materials and Methods

Patients

Our local institutional review board approved this retrospective study, and all participants provided written informed consent. Patients were included if they had pathologically proven prostate cancer and had undergone prebiopsy and preoperative MR imaging examination of the prostate between August 2008 and April 2010 and total prostatectomy. We excluded patients with previously treated prostate cancer and contraindications to MR imaging, such as implanted pacemaker and claustrophobia. In our institution, patients with clinically suspected prostate cancer undergo MR imaging of the prostate before biopsy as part of the routine work-up.

We included 17 consecutive patients (mean age, 65.8 years; range, 50 to 74 years), five with tubular adenocarcinoma and 12 with adenocarcinoma. The

mean preoperative prostate-specific antigen level of these patients was 11.72 ng/mL (range, 4.02 to 24.75 ng/mL); median Gleason score of maximum cancer lesion was 7 (range, 6 to 9); median clinical stage was T2cN0M0 (range, T2aN0M0 to T2cN0M0); and mean time interval between MR imaging and radical prostatectomy was 68 days (range, 9 to 146 days) (Table 1).

MR imaging

All MR imaging examinations were performed using a 1.5-tesla system (ECHELON Vega, Hitachi Medical Corporation, Tokyo, Japan) and an 8-channel phased-array body coil (RAPID™, Hitachi Medical Corporation, Tokyo, Japan); to avoid possible deformations of the prostate that would complicate planning of focal therapies, no endorectal coil was used. The maximum gradient specifications were 30 mT/m for amplitude and 150 mT/m/s for slew rate. The examination protocol comprised the acquisition of images of the patient's prostate, including seminal vesicles.

Axial fast-spin echo T₂WI was acquired using parameters: repetition time/echo time (TR/TE), 4604/107 ms; slice thickness/gap, 3/0.6 mm; echo factor, 17; bandwidth, 71.2 kHz; field of view (FOV), 270 × 243 mm²; matrix, 384 × 336; in-plane resolution, 0.71 × 0.8 mm²; number of signal averages, 2; and scan time, 3 min 9 s.

Axial diffusion-weighted single-shot spin-echo echo-planar images were acquired using param-

Table 1. Characteristics of 17 patients with prostate cancer

Gleason score of maximum cancer lesion	Datum
6	4
7	10
8	1
9	2
Dimension (mm ²)	
median	100
range	28~1600
Number of tumors in patients	
total	72
median	4
range	1~12
Gleason score	
4	1
5	4
6	30
7	32
8	2
9	3

ters: B1-insensitive fat suppression radiofrequency pulse (H-Sinc¹⁰); TR/TE, 5821/77.2 ms; b-values, 0 and 1500 s/mm²; slice thickness/gap, 3/0.6 mm; parallel acquisition factor, 2.0; echo factor, 81; bandwidth, 250 kHz; FOV, 270 × 270 mm²; matrix, 128 × 128, in-plane resolution, 2.14 × 2.11 mm²; number of signal averages, 12; 200% anti-aliasing; and scan time, 4 min 45 s.

Pathological analysis and matching of pathological specimens to MR imaging data

After resection, each prostate was horizontally sectioned into 5-mm slices that corresponded as much as possible to the 3-mm axial slices of MR imaging.^{7,11} As part of the routine pathological examination of prostate cancer, faculty pathologists in our institution outlined in ink the margins of the areas of cancer on the sectioned prostate slices and measured the areas of cancerous and noncancerous tissue on the slice with the largest area of tumor.

A board-certified radiologist (S.Y.) with 6 years' experience in abdominal MR imaging matched the sectioned pathological slices with corresponding T₂-weighted and DW images without knowledge of the pathological cancerous area. Morphological features of the central zone (CZ), transitional zone (TZ), peripheral zone (PZ), apex and base of the prostate, cysts, calcifications, and urethra were used as landmarks to match the datasets, as described previously.^{7,12,13} Importantly, the MR slice that corresponded to the pathological slice with the maximum area of cancer was used for further analysis, as we will describe.

MR imaging analysis

We placed an arbitrarily shaped region of interest (ROI) in the lesser pelvic space, including the prostate, pelvic and thigh bones, and other normal tissue in the space, on the slice with b-value of 1500 s/mm² (Fig. 1a) and measured the standard deviation (SD) of the signal intensity within this ROI. We created 4 types of rSI maps for each patient that displayed only signal intensities with SDs of > +3, > +3.5, > +4, and > +5 measured in the lesser pelvic space. We also created a fused rSI/T₂ WI (Fig. 1). Subsequently, the observer manually delineated the margins of the prostate and margins of the detected tumor on the rSI maps with SDs of > +3, > +3.5, > +4, and > +5. Areas of high signal intensity on these maps with areas of low intensity on T₂WI were considered to indicate cancerous prostate tissue. For each patient, the observer, who was blinded to patient identity, type of rSI map under evaluation, and histopathological results, compared rSIs in a random fashion between 2

types of parametric maps obtained following a wash-out period of at least one week. Areas of prostate cancer and noncancerous prostate tissue on the 4 different rSI maps were automatically calculated.

Statistical analysis

We calculated the ratio of cancerous area (%) by dividing the area of cancerous prostate tissue by the entire area of prostate tissue, as determined on sectioned prostate slices and 4 different rSI maps, and we summarized the ratios as means with ranges. Correlations between the ratios of cancerous area on sectioned prostate slices and on the 4 different rSI maps were assessed using Pearson's correlation analysis. $P < 0.05$ was considered statistically significant. Statistical analyses were executed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

Results

All MR images were of diagnostic quality and without artifact and distortion that would compromise image evaluation. We could detect the area of prostate cancer as lesions of high signal intensity in all 17 cases on rSI maps with SD > +3 (Fig. 2), but we could not detect it on rSI maps with SDs of > +3.5 in 2 cases, > +4 (5 cases), and > +5 (8 cases). Table 3 and Fig. 3 show the value, mean, and ranges of ratios of cancerous area, and Table 2 delineates the characteristics of these lesions. The ratios of cancerous area were always highest on rSI maps with SD > +3, followed by those with SD > +3.5, > +4, and > +5. Correlation coefficients (R) between ratios of cancerous area on pathological samples and rSI maps were: 0.7464 ($P = 0.0006$) for SD > +3; 0.6469 ($P = 0.0050$) for SD > +3.5;

Table 2. Maximum cancer lesions that could not be detected on > +3.5 SD, > +4 SD, or > +5 SD

Case	Dimension (mm ²)	PSA (ng/mL)	Gleason score	rSI	Pathology
1	528	14.13	7	3.5	adenocarcinoma
2	42	21.00	7	3.5	adenocarcinoma
3	168	7.44	7	4	adenocarcinoma
4	72	8.60	6	4	adenocarcinoma
5	561	4.31	7	4	adenocarcinoma
6	108	5.70	7	5	adenocarcinoma
7	72	5.45	7	5	adenocarcinoma
8	40	9.26	7	5	adenocarcinoma

PSA, prostate-specific antigen; SD, standard deviation; rSI, relative signal intensity

Fig. 1. Fusion between relative signal intensity map (rSI) using a threshold of $> +3$ standard deviation (SD) of the signal intensity (SI) of the lesser pelvic space at diffusion-weighted imaging (DWI) with a b-value of 1500 s/mm^2 (a) and T₂-weighted imaging (T₂WI) (b). The rSI/T₂WI fusion image (c) shows the prostate cancer as a structure with high signal intensity (arrow). Note the region of interest drawn on the DWI with a b-value of 1500 s/mm^2 (a) to determine the SI of the lesser pelvic space.

Fig. 2. Sectioned prostate slice with margins of cancer area outlined in ink (a) and corresponding relative signal intensity (rSI)/T₂-weighted imaging fusion maps with thresholds of $> +3$ standard deviation (SD) (b), $> +3.5$ SD (c), $> +4$ SD (d), and $> +5$ SD (e) of the signal intensity of the lesser pelvic space at diffusion-weighted imaging with a b-value of 1500 s/mm^2 . The rSI map with SD $> +3$ shows the largest area of cancer (best match with the tumor area delineated on the pathological specimen), whereas the rSI map with SD $> +5$ shows the smallest area of cancer.

Table 3. Mean and ranges of cancer area ratios (area of prostate cancer/area of whole prostate) on pathological sectioned prostate slices and relative signal intensity (rSI) maps with thresholds of $> +3$ standard deviation (SD), $> +3.5$ SD, $> +4$ SD, and $> +5$ SD of the signal intensity of the lesser pelvic space at diffusion-weighted imaging with a b-value of 1500 s/mm^2

Dataset	Cancer area ratio (%)	
	Mean	Range
Pathological sectioned prostate slices	13.20	0.5–49.1
$> +3$ SD rSI map	12.65	1.3–52.1
$> +3.5$ SD rSI map	9.88	0.0–46.4
$> +4$ SD rSI map	6.39	0.0–31.6
$> +5$ SD rSI map	3.61	0.0–21.6

Fig. 3. Ratios of cancerous area (area of prostate cancer/area of whole prostate) on relative signal intensity (rSI) maps with thresholds of $> +3$ standard deviation (SD), $> +3.5$ SD, $> +4$ SD, and $> +5$ SD of the signal intensity (SI) of the lesser pelvic space at diffusion-weighted imaging with a b-value of 1500 s/mm^2 . Only on rSI maps with $\text{SD} > +3$ could we detect maximum prostate cancer as lesions of high signal intensity.

0.6459 ($P=0.0051$) for $\text{SD} > +4$; and 0.4540 ($P=0.0671$) for $\text{SD} > +5$ (Fig. 4). In this study, the sensitivity and false negative were: 0.85 and 0.15 for $\text{SD} > +3$; 0.46 and 0.54 for $\text{SD} > +3.5$; 0.26 and 0.74 for $\text{SD} > +4$; and 0.14 and 0.86 for $\text{SD} > +5$.

Discussion

On rSI maps with $\text{SD} > +3$, we could detect all 17 prostate cancers, whereas we could not on maps with SDs of $> +3.5$, $> +4$, and $> +5$, and sensitivity was greater than that of the other maps with $\text{SD} > +3$. Furthermore, correlation between ratios of cancerous area on pathological samples and rSI maps was better when we used a threshold SI of the lesser pelvic space with $\text{SD} > +3$ than with higher threshold values.

Previous studies have shown the advantage of adding DWI to T_2 WI to detect and localize prostate cancer.^{6,7,9} Haider's group⁶ reported that for the entire prostate, sensitivity for localizing prostate cancer was significantly higher ($P<0.001$) with T_2 WI plus ADC maps (81% [120/149]) than with T_2 WI alone (54% [81/149]), and specificity was only slightly lower for T_2 WI plus ADC maps (84% [204/243]) compared with T_2 WI alone (91% [222/243]).

Lim and colleagues⁷ showed greater sensitivity for prostate cancer detection using T_2 -weighted and ADC data (Reader 1, 88%; Reader 2, 81%; Reader 3, 78%) than T_2 WI (Reader 1, 74%; Reader 2, 67%; Reader 3, 67%) for all readers ($P=0.01$ for Reader 1; $P=0.02$ for Readers 2 and 3). Specificity of T_2 -weighted and ADC data was greater than that of T_2 WI for Reader 1 (88% vs. 79%, $P=0.03$) and Reader 2 (89% vs. 77%, $P<0.001$).⁷

Katahira and associates⁹ assessed the effect of using different b-values to detect prostate cancer on native diffusion-weighted images and found sensitivity and specificity: of 52.2 and 80.7% for T_2 WI alone; 61.2 and 82.6% for the combination of T_2 WI and DWI at a b-value of 1000 s/mm^2 ; and 73.2 and 89.7% for the combination of T_2 WI and DWI at a b-value of 2000 s/mm^2 . The combination of T_2 WI and DWI at a b-value of 2000 s/mm^2 achieved the highest diagnostic performance, followed by the combination of T_2 WI and DWI at a b-value of 1000 s/mm^2 .⁹ The study by Katahira's group⁹ is important because it shows that native diffusion-weighted images themselves can be used to detect and localize prostate cancer. Advantages of this approach over the use of ADC maps is that higher b-values can be applied that may improve contrast between prostate cancer and surrounding noncancerous tissue^{8,9} and that only one b-value need be applied, which shortens acquisition time and eliminates potential misregistration issues between datasets obtained with different b-values.

The feasibility of semiquantitative analysis of native DWI as well as its outperformance of quantitative ADC analysis in discriminating benign from

Fig. 4. Scatter plots with ratio of cancerous area on pathological specimen (x-axis) versus ratio on rSI maps with SDs of $> +3$ (a), $+3.5$ (b), $> +4$ (c), and $> +5$ (d) (y-axis), including regression lines. Correlation coefficients (R) between ratio of cancerous area on pathological specimen and ratio on rSI maps were 0.7464 ($R^2 = 0.5572$) for SD $> +3$; 0.6469 ($R^2 = 0.4185$) for SD $> +3.5$; 0.6459 ($R^2 = 0.4173$) for SD $> +4$; and 0.4540 ($R^2 = 0.2062$) for SD $> +5$.

malignant pulmonary nodules have also been demonstrated.¹⁴ The present study applied these concepts to the delineation of prostate cancer, an increasingly important need given the emergence of focal therapies.^{2,3} It is important to realize that sensitivity and specificity figures of diagnostic tests for detecting and localizing prostate cancer cannot be directly translated to the setting of tumor delineation, which requires decisions on a voxel level.¹⁵ The number of investigations of the use of MR imaging for tumor delineation in prostate cancer remains limited.

In a study of 5 patients with prostate cancer who had undergone T_2 WI, DWI (b-values of 500, 1000, and 2000 s/mm^2) with ADC mapping (based on b-values of 500 and 1000 s/mm^2), and DCE-MRI, Groenendaal and associates¹⁵ reported tumor coverage of 44 to 89% by MR imaging-based delineation. The limited tumor coverage by the initial MR

imaging-based delineations could be partly caused by errors created during registration and by errors in the processing of tissue. Retrospective application of a margin of approximately 5 mm to the MR imaging-based tumor delineations yielded tumor coverage of 85 to 100% in all patients.¹⁵ Important differences between the study of Groenendaal¹⁵ and ours are that they did not normalize the SI of native DWI and they did investigate the utility of more than one MR imaging sequence for tumor delineation. Therefore, we cannot directly compare their study results with ours. We applied signal values of DWI (b-values of 1500 s/mm^2) to rSI maps, so rSI maps were displayed regardless of window width and level.

This study had several limitations. First, our sample size was relatively small, and our study design was retrospective. Future prospective studies that include more patients are necessary to validate

the rSI mapping method with a proposed threshold of $> +3$ SD of the signal intensity of the lesser pelvic space. Second, this proposed threshold may be applicable only for the DWI protocol used in this study; particularly, images acquired with different b-values may have different optimal thresholds for rSI mapping. Third, we assessed tumors in a 2-dimensional manner on a single slice, but it would be more appropriate to perform a volumetric analysis using a 3-dimensional tissue processing and registration method.¹⁵ Fourth, although the rSI mapping method with a proposed threshold of $> +3$ SD showed good correlation with pathological examination, no comparison was made with ADC maps or other MR imaging sequences. ADC maps were not created because the 2 b-values of 0 and 1500 s/mm² that we applied would yield an inaccurate ADC as a result of perfusion effects¹⁶ and noise.⁸ Given the increasing use of multiple MR imaging techniques in prostate cancer, it is important that future studies investigate which sequence or combination of sequences best delineates prostate cancer.^{4,5} This importance is also underlined by the results of a recent study that showed great variation in consistency between ADC (based on b-values of 300, 500, and 1000 s/mm²) and DCE-MRI parameter maps with regard to tumor delineation among 21 patients with prostate cancer.¹⁷ Knowledge of the inconsistency between different MR imaging sequences must be considered when planning focal therapies for prostate cancer.¹⁷ Finally, it should be realized that the detection of prostate cancer depends on lesion size and Gleason score; particularly, it may be difficult to detect lesions smaller than 4 mm in diameter on DWI because of the generally low spatial resolution.⁶ In the present study, we could detect the smallest prostate cancer (4 × 4 mm²) on pathological examination on the rSI map with SD $> +3$. However, this method may be limited in detecting and delineating smaller tumors.

In conclusion, DWI-based rSI mapping may be used to delineate the extent of prostate cancer. We found that use of a threshold of $> +3$ SD of the SI of the lesser pelvic space provided the best correlation between ratio of cancerous area on the rSI map and on pathological examination.

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