Prostate Cancer Detection in Patients With Total Serum Prostate-Specific Antigen Levels of 4–10 ng/mL: Diagnostic Efficacy of Diffusion-Weighted Imaging, Dynamic Contrast-Enhanced MRI, and T2-Weighted Imaging

OBJECTIVE. The purpose of this study is to evaluate the utility of T2-weighted imaging, dynamic contrast-enhanced MRI (DCE-MRI), and diffusion-weighted imaging (DWI) for detecting prostate cancer in patients with total serum prostate-specific antigen (PSA) levels of 4–10 ng/mL, which is referred to as the “gray zone.”

MATERIALS AND METHODS. Fifty patients with gray-zone PSA levels underwent MRI before biopsy. According to the sites of biopsy, the prostate was divided into eight regions on MRI scans. These regions were evaluated individually for the following features: detectability of prostate cancer on per-region and per-patient bases, and relationship between tumor size and positive or negative MRI findings for tumor detection.

RESULTS. On a per-region basis, the sensitivity and specificity of tumor detection were 36% and 97% for T2-weighted imaging, 43% and 95% for DCE-MRI, 38% and 96% for DWI, and 53% and 93% for the combined method of MRI, respectively. The sensitivity of combined MRI to detect tumor was significantly higher than those of the individual methods (p < 0.001 to p = 0.001). Tumor size was significantly larger in regions with positive MRI findings than in regions with negative MRI findings (p = 0.004). On a per-patient basis, sensitivity and specificity of combined MRI to detect prostate cancer were 83% and 80%, respectively.

CONCLUSION. Combined T2-weighted imaging, DWI, and DCE-MRI findings appear to be potentially useful for detecting and managing prostate cancer, even when performed for patients with gray-zone PSA levels.
Diagnostic Efficacy of Combined MRI in Detecting Prostate Cancer

Materials and Methods

Patient Characteristics

This retrospective study was approved by the institutional review board, and the need for informed consent from patients was waived.

A total of 54 men with gray-zone PSA levels underwent MRI of the prostate within 3 months before TRUS-guided biopsy between January 2006 and December 2009 in our institution. Four patients were excluded because of incomplete MRI examination (n = 2) or cryptogenic intraprostatic hemorrhage (n = 2). Thus, 50 men (mean age, 70 years; range, 40–84 years) were included in this study. Mean PSA level was 6.84 ng/mL (median, 6.68 ng/mL; range, 4.06–9.94 ng/mL). The mean interval between biopsy and MRI was 23 days (range, 1–87 days). None of the patients was diagnosed with prostate cancer before MRI.

A total of 12 specimens (eight from the PZ and four from the TZ) were taken from each patient. During TRUS-guided systematic prostate biopsy by an urologist with 15 years of experience in prostate biopsy.

MRI

After intramuscular administration of glucagon to decrease intestinal peristalsis, prostate MRI was performed in all patients under fasting conditions. MRI was performed with a 1.5-T MRI scanner (Signa Excite High speed, GE Healthcare) with a maximum gradient amplitude of 33 mT/m and a maximum slew rate of 77 mT/m/s. A body coil was used for signal excitation, with a multichannel phased-array torso coil (catalog no. S75292E, GE Healthcare) for signal reception.

MRI protocols included axial and coronal T2-weighted fast spin-echo (FSE) imaging, axial T2-weighted echo-planar imaging (EPI), axial DWI, axial DCE-MRI, and axial unenhanced and contrast-enhanced T1-weighted FSE imaging. Axial DWI was performed using a multisection spin-echo single-shot EPI sequence. ADC maps were reconstructed by calculating the ADC in each pixel of each slice. DCE-MRI was performed using an FSE sequence or a 3D T1-weighted gradient-echo liver acquisition with volume acceleration (LAVA) sequence. Data acquisition for DCE-MRI began simultaneously with initiation of IV injection of gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma) at 0.1 mmol/kg body weight at a rate of 3 mL/s via a power injector (Sonic Shot 50, Nemoto Kyorindo), followed by a 40-mL saline flush at 3 mL/s as a gadopentetate dimeglumine injection. Multiphase DCE images were obtained every 30 seconds for 150 seconds in an FSE sequence (six phases) or every 20 seconds for 120 seconds in a LAVA sequence (seven phases) without breath-holding by patients.

The acquisition parameters for the MRI pulse sequences are listed in Table 1.

Image Interpretation and Data Analysis

Two radiologists with 11 and 7 years of experience in prostate MRI conducted a consensus review of MRI examinations for the 50 patients. The reviewers were aware that patients had been referred for MRI on suspicion of prostate cancer with PSA levels of 4–10 ng/mL but were blinded to all other clinical and histopathologic findings. Furthermore, the reviewers were blinded to the findings of the other sequences at the time of review.

Intraprostatic hemorrhage was considered to be present when an area of signal hyperintensity was identified within the prostate gland on T1-weighted imaging. Two patients who were diagnosed with intraprostatic hemorrhage on T1-weighted imaging were excluded from this study because of the limited accuracy caused by bleeding for tumor localization of prostate cancer on MRI.

According to the sites of biopsy, the prostate gland was divided into eight regions on MRI scans [19, 26] (Fig. 1). To distinguish PZ and TZ, reviewers mainly used T2-weighted MRI scans, because zonal anatomy of the prostate can be seen only on these images [27]. Landmarks used to distinguish PZ and TZ were the urethra, capsule

### Table 1: MRI Parameters Used in the Current Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sequence</th>
<th>T1-Weighted FSE</th>
<th>T2-Weighted FSE</th>
<th>T2-Weighted EPI</th>
<th>DWI (Single-Shot EPI)</th>
<th>DCE-MRI (FSE)</th>
<th>DCE-MRI (LAVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR (ms)</td>
<td></td>
<td>425</td>
<td>3600</td>
<td>2500</td>
<td>5000</td>
<td>350</td>
<td>4.7</td>
</tr>
<tr>
<td>TE (ms)</td>
<td></td>
<td>9.3</td>
<td>102</td>
<td>80</td>
<td>63.8</td>
<td>9</td>
<td>2.2</td>
</tr>
<tr>
<td>Bandwidth (kHz)</td>
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<td>31.2</td>
<td>20.8</td>
<td>250</td>
<td>250&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31.2</td>
<td>62.5</td>
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<td>Echo-train length</td>
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<td>16</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
<td>NA</td>
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<tr>
<td>Matrix size</td>
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<td>320 × 256</td>
<td>320 × 320</td>
<td>256 × 256</td>
<td>128 × 192</td>
<td>256 × 128</td>
<td>288 × 192</td>
</tr>
<tr>
<td>FOV (cm)</td>
<td></td>
<td>24 × 24</td>
<td>24 × 24</td>
<td>24 × 24</td>
<td>36 × 36</td>
<td>27 × 27</td>
<td>35 × 35</td>
</tr>
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<td>No. of acquisitions</td>
<td></td>
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<td>4</td>
<td>8</td>
<td>8</td>
<td>1</td>
<td>0.78</td>
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<tr>
<td>Slice thickness (mm)</td>
<td></td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Interslice gap (mm)</td>
<td></td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>Parallel imaging factor</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Scan time</td>
<td></td>
<td>2 min 42 s</td>
<td>4 min 47 s</td>
<td>2 min 43 s</td>
<td>2 min 40 s</td>
<td>3 min (30 s × 6 phases)</td>
<td>2 min 20 s (20 s × 7 phases)</td>
</tr>
</tbody>
</table>

Note—Diffusion-weighted imaging (DWI) was performed with motion-probing gradient pulses applied sequentially along three orthogonal orientations with two b factors (0 and 800 s/mm<sup>2</sup>). DCE-MRI = dynamic contrast-enhanced MRI, EPI = echo-planar imaging, FSE = fast spin-echo, LAVA = liver acquisition with volume acceleration, NA = not applicable.

<sup>a</sup>Frequency-encoding direction.
of the prostate gland, and the surgical pseudo-
capsule. In the PZ, sections through the bladder
neck and proximal prostatic urethra were consid-
ered as the base, whereas the prostatic apex was
defined by the doughnut-shaped appearance of the
distal prostatic urethra. The remainder of the PZ
was considered as the middle [28]. These regions
were evaluated individually with regard to the
detectability of prostate cancer. Prostate cancer
was localized independently on each MRI study
according to standard criteria. On MRI scans, le-
sions fulfilling the following criteria were regarded
as prostate cancer: first, on T2-weighted imaging
(FSE or EPI or both), a circumscribed round or tri-
angular-shaped area in the PZ with homogeneous
signal hyperintensity on DWI and with focal sig-
nal hypointensity on the ADC map relative to back-
ground prostatic parenchyma; or finally, on DCE-
MRI, an area with focal early enhancement until
the third phase in the FSE sequence or the fourth
phase in the LAVA sequence (60 seconds after ad-
ministration of contrast medium). In the interpre-
tation of images from DWI and DCE-MRI, we
referred to T2-weighted imaging, to confirm ana-
tomic positions after the assessment of each image.

The tumor site on each MRI scan was consid-
ered to match histologic findings if the tumor de-
picted on the image was present in the same region
of the prostate indicated in the pathology report
and was localized independently on each MRI scan.
That is, base right in peripheral zone (PZ) (1), middle
right and far lateral right in PZ (2 and 3), apex right
in PZ (4), ventral and dorsal right in transition zone
(TZ) (5 and 6), base left in PZ (7), middle left and far
lateral left in PZ (8 and 9), apex left in PZ (10), and
ventral and dorsal left in TZ (11 and 12) as biopsy sites
were designated as base right (Area 1), middle
right (Area 2), apex right (Area 3), TZ right (Area 4),
base left (Area 5), middle left (Area 6), apex left
(Area 7), and TZ left (Area 8), respectively. (Reprinted
with permission from [19])

**TABLE 2: Detection of Prostate Cancer Using Various MRI Methods in 50 Patients With Gray-Zone Prostate-Specific
Antigen Levels**

<table>
<thead>
<tr>
<th>MRI Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-region basis (n = 400)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2-weighted imaging</td>
<td>36 (37/103)</td>
<td>97 (289/297)</td>
<td>82 (326/400)</td>
<td>82 (37/45)</td>
<td>81 (289/355)</td>
</tr>
<tr>
<td>DWI</td>
<td>38 (39/103)</td>
<td>96 (286/297)</td>
<td>81 (325/400)</td>
<td>78 (39/50)</td>
<td>82 (286/350)</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>43 (44/103)</td>
<td>95 (282/297)</td>
<td>82 (326/400)</td>
<td>75 (44/59)</td>
<td>83 (282/341)</td>
</tr>
<tr>
<td>Combined MRI</td>
<td>53 (55/103)</td>
<td>93 (277/297)</td>
<td>83 (332/400)</td>
<td>73 (55/75)</td>
<td>85 (277/325)</td>
</tr>
<tr>
<td>Per-patient basis (n = 50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2-weighted imaging</td>
<td>60 (21/35)</td>
<td>87 (13/15)</td>
<td>68 (34/50)</td>
<td>91 (21/23)</td>
<td>48 (13/27)</td>
</tr>
<tr>
<td>DWI</td>
<td>69 (24/35)</td>
<td>87 (13/15)</td>
<td>74 (37/50)</td>
<td>92 (24/26)</td>
<td>54 (13/24)</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>74 (26/35)</td>
<td>80 (12/15)</td>
<td>76 (38/50)</td>
<td>90 (26/29)</td>
<td>57 (12/21)</td>
</tr>
<tr>
<td>Combined MRI</td>
<td>83 (28/35)</td>
<td>80 (12/15)</td>
<td>82 (41/50)</td>
<td>91 (29/32)</td>
<td>67 (12/18)</td>
</tr>
</tbody>
</table>

Note—Data are percentages, with values used to calculate these percentages provided in parentheses. DCE-MRI = dynamic contrast-enhanced MRI, DWI = diffusion-weighted imaging, NPV = negative predictive value, PPV = positive predictive value.

*Combined MRI refers to combined use of T2-weighted imaging, DWI, and DCE-MRI.

Statistical Analysis

Differences in sensitivity, specificity, PPV, and NPV between any two MRI methods were tested using the McNemar test. The Mann-Whitney U test was used to determine significant differences in indexes of tumor size and Gleason score for pathologically diagnosed prostate cancer between regions of positive and negative MRI findings. Statistical analyses were performed using SPSS software (version 17.0, SPSS). All statistical tests were two sided, and p values of 0.05 or less were considered indicative of a significant difference.

**Results**

**Prostate Biopsy Results**

TRUS-guided prostate biopsy revealed prostate cancer in 35 of 50 patients (70%) and in...
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103 of 400 regions (26%). Among the 103 positive regions, 74 (72%) were located in the PZ and the rest were in the TZ. PZ lesions consisted of 19 in the base, 33 in the middle, and 22 in the apex. The median Gleason tumor score was 7 (range, 6–10), and the mean index for tumor size was 0.31 (range, 0.06–0.94).

Detection of Prostate Cancer

Sensitivity, specificity, accuracy, PPV, and NPV on both a per-region basis and a per-patient basis are shown in Table 2. On a per-region basis, the sensitivity of combined MRI to detect tumor was higher than those for T2-weighted imaging, DWI, and DCE-MRI individually (53% vs 36–43%), although specificity was slightly decreased (93% vs 95–97%). Sensitivity differed significantly between T2-weighted imaging and combined MRI (p < 0.001), between DWI and combined MRI (p < 0.001), and between DCE-MRI and combined MRI (p = 0.001). Specificity differed significantly between T2-weighted imaging and combined MRI (p < 0.001), between DWI and combined MRI (p = 0.004), and between DCE-MRI and combined MRI (p = 0.031). No significant differences were observed for any other pairwise comparisons.

On a per-patient basis, sensitivity, specificity, accuracy, PPV, and NPV of combined MRI to detect prostate cancer were 83%, 80%, 82%, 91%, and 67%, respectively, showing the increase of sensitivity and PPV and the decrease of specificity and NPV compared with those on a per-region basis. The sensitivity of combined MRI to detect tumor was higher than those for T2-weighted imaging, DWI, and DCE-MRI individually (83% vs 60–74%), although specificity was equivalent or slightly decreased (80% vs 80–87%). Sensitivity differed significantly between T2-weighted imaging and combined MRI (p = 0.008). No significant differences were observed for any other pairwise comparisons.

Comparison of Tumor Size and Gleason Score Between Regions of Positive and Negative MRI Findings of Prostate Cancer

The index of tumor size was significantly larger in regions of positive MRI findings (0.36 ± 0.20) than in regions of negative MRI findings (0.25 ± 0.19; p = 0.0004). Actually, the mean total cancer length in regions of positive and negative MRI findings was 6.7 mm and 3.6 mm, respectively. Conversely, the Gleason score for regions of positive MRI findings (7.17 ± 0.83) was comparable to that for regions of negative MRI findings (7.45 ± 1.34), with no significant difference.

Tumor Detection by Three MRI Methods in Prostate Cancer With Positive MRI Findings

Positive MRI findings were seen in 55 of 103 regions (53%). These lesions could be diagnosed only on T2-weighted imaging in five regions, only by DWI in two regions, only by DCE-MRI in nine regions, by both T2-weighted imaging and DWI in four regions, by both T2-weighted imaging and DCE-MRI in two regions, by both DWI and DCE-MRI in seven regions, and by all three methods in 26 regions (Figs. 2–4).

Discussion

Our region-based analysis using 1.5-T prostate MRI for the detection of prostate cancer in patients with gray-zone PSA levels showed that sensitivity was low (36–53%), specificity was very high (93–97%), and accuracy, PPV, and NPV were moderately high (81–83%, 73–82%, and 81–85%, respectively). Sensitivity was significantly higher for combined MRI (53%) than for T2-weighted imaging, DCE-MRI in seven regions, and by all three methods in 26 regions (Figs. 2–4).
Several factors can be considered contributory to the decreased sensitivity for prostate cancer detection in patients with gray-zone PSA levels. First, in our results, tumor size rather than Gleason tumor score showed a significant difference between regions of positive and negative MRI findings. Because spatial resolution would be a limiting factor for imaging small tumors, higher resolution may increase the sensitivity, especially in the low-resolution study such as DWI. Second, a recent study of 18 patients with almost gray-zone PSA levels (range, 2.27–10.99 ng/mL; median, 4.59 ng/mL) reported that the degree of intermixed normal tissue within the prostate cancer affects ADC values and T2 properties [30]. That is, although ADC values and T2 signal intensities are low in dense prostate tumors, they resemble those of normal prostatic tissue in sparse tumors [30]. Furthermore, among the 55 lesions with positive MRI findings in the present study, 16 (29%) were diagnosed by only one of the three MRI methods of T2-weighted imaging, DCE-MRI, and DWI. This finding suggests that the contribution of tissue characteristics such as morphologic changes on T2-weighted MRI, tumor vascularity on DCE-MRI, and water diffusion showing the degree of cellular density on DWI varies among prostate tumors in patients with gray-zone PSA levels [31]. Therefore, in prostate cancer with gray-zone PSA levels, both tumor size and tissue heterogeneity may limit the detectability of tumor by combined MRI using T2-weighted imaging, DWI, and DCE-MRI.

The decrease in detectability induced by such unfavorable factors may be overcome by using an endorectal coil to provide a substantial increase in the signal-to-noise ratio [32] or by the addition of MRSI to provide metabolic information about prostate tissue [15, 31, 33]. However, these techniques are disadvantaged by the discomfort associated with coil insertion, long acquisition time, and possible variability in results depending on shimming or postprocessing [18, 31] and may thus be unsuitable for daily clinical use in the detection of prostate cancer. A recent prospective study with 3-T MRI comparing a body-array coil and an endorectal coil reported that T2-weighted MRI with an endorectal coil had significantly higher image quality and tumor detectability in comparison with a body-array coil [34]. On the other hand, the ranges of ADC values of prostate cancer obtained using 1.5-T MRI (600–1000 s/mm²) were almost equivalent whether an endorectal coil (0.96–1.45 × 10⁻³ mm²/s) [21, 35, 36] or body-array coil (0.93–1.21 × 10⁻³ mm²/s) was used [18, 37, 38]. Compared with region-based analysis, patient-based analysis showed increased sensitivity (60–83%) and PPV (90–92%), almost equivalent accuracy (68–82%), and decreased specificity (80–87%) and NPV (48–67%). In particular, both the high sensitivity and the moderate NPV on combined MRI will help urologists to decide whether to perform prostate biopsy or follow up using PSA in patients with gray-zone PSA levels.
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Fig. 4—72-year-old man with PSA level of 8.07 ng/mL and positive results of transrectal biopsy. Transverse MRI of prostate indicated Gleason score of 6 in transition zone (TZ) left region. A, T2-weighted fast spin-echo (FSE) image (3600/102) shows benign hyperplastic nodules (arrows) as heterogeneous hypointense lesions with hyperintense spots in TZ right and TZ left regions. B, Diffusion-weighted image shows TZ cancer (arrow) as focal signal hyperintensity in TZ left region. C and D, No areas of focal early enhancement suggestive of prostate cancer were observed on dynamic contrast-enhanced MRI using FSE sequences of first (unenhanced; C) and third (D) phases. Left TZ cancer could thus be detected only on diffusion-weighted imaging.

Some limitations in the current study warrant consideration. First, in this study, MRI findings were not compared with the results of step-section tumor mapping using the whole prostate after radical prostatectomy. Some subjects diagnosed as cancer-free by systematic TRUS-guided prostate biopsy may thus actually have had prostate cancer. Second, the sample size might have been too small to compare detectability among individual methods of MRI. Third, the use of two different sequences in DCE-MRI might have influenced the tumor detectability of DCE-MRI. Fourth, in this study, prostate biopsy was performed only systematically. Additional biopsy targeting the lesion with positive MRI findings might have increased the detectability of prostate cancer. Finally, because this study was designed as a retrospective investigation, subject selection might have shown sampling biases, such as postponement of prostate biopsy for various clinical reasons by patients or urologists. Such selection bias might be associated with the relatively high prevalence (70%) of biopsy-proven prostate cancer among patients with gray-zone PSA levels in this study. Further prospective investigations with larger patient populations in whom there is a direct correlation between findings on histologic sections and corresponding MRI studies are needed to clarify the clinical value of prostate MRI in detecting tumors in patients with gray-zone PSA levels.

In conclusion, these results indicate that an MRI protocol including T2-weighted imaging, DWI, and DCE-MRI can provide clinically useful information to urologists confronting the problem of managing patients with gray-zone PSA levels. Combined T2-weighted imaging, DWI, and DCE-MRI findings appear to be potentially useful for detecting and managing prostate cancer, even if they are performed for patients with gray-zone PSA levels.

References

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37. Kim CK, Park BK, Kim B. High-b-value diffusion-weighted imaging at 3 T to detect prostate cancer: comparisons between b values of 1,000 and 2,000 s/mm². AJR 2010; 194:172 [web]; W33–W37.