Combined Diffusion-Weighted and Dynamic Contrast-Enhanced MRI for Prostate Cancer Diagnosis—Correlation With Biopsy and Histopathology

Piotr Kozlowski, PhD,1–3* Silvia D. Chang, MD,1,3,5 Edward C. Jones, MD,1,4,7 Kenneth W. Berean, MD,4,6 Henry Chen,1 and S. Larry Goldenberg, MD1,2,8

Purpose: To determine whether the combination of diffusion-weighted (DW) and dynamic contrast-enhanced (DCE) MRI provides higher diagnostic sensitivity for prostate cancer than each technique alone.

Materials and Methods: Fourteen patients with a clinical suspicion of prostate cancer underwent endorectal MRI on a 1.5T scanner prior to transrectal ultrasound (TRUS)-guided biopsies. The average values of the apparent diffusion coefficient (ADC, calculated from b-values of 0 and 600), Ktrans, ve, maximum gadolinium (Gd) concentration, onset time, mean gradient, and maximum enhancement were determined. Correlation with histology was based on biopsy (six patients) and prostatectomy specimen (eight patients) results. The Tukey-Kramer test was used for statistical analysis.

Results: The average values of all MRI parameters, except ve and maximum Gd concentration, showed significant differences between tumor and normal prostate. The sensitivity and specificity values were respectively 54% (35–72%) and 100% (95–100%) for the ADC data, and 59% (39–77%) and 74% (63–83%) for the DCE data. When both ADC and DCE results were combined, the sensitivity increased to 87% (68–95%) and specificity decreased to 74% (62–83%).

Conclusion: All but two DW- and DCE-MRI parameters showed significant differences between tumor and normal prostate. Combining both techniques provides better sensitivity, with a small decrease in specificity.

Key Words: diffusion-weighted MRI; dynamic contrast-enhanced MRI; prostate cancer; endorectal coil; histopathology


MAGNETIC RESONANCE IMAGING (MRI) has been used to diagnose prostate cancer, with varying success, for over a decade (1). Although the development of endorectal coils significantly improved the image quality required for accurate diagnosis (2), the sensitivity and specificity of this technique have been variable (3) and its diagnostic value for staging prostate cancer remains under investigation (4). Therefore, several MRI-based techniques have been investigated recently with the aim to improve tumor delineation and thus provide more reliable staging and the ability to predict the grade of tumor. Two such techniques—dynamic contrast-enhanced (DCE) MRI and diffusion-weighted (DW) MRI—have shown particularly promising results.

DCE-MRI has been shown to significantly improve tissue characterization, and both the dynamic parameters of the contrast enhancement (e.g., onset time, rate of enhancement, etc.) and the pharmacokinetic modeling parameters have been used to differentiate between cancer and normal tissue in the breast (5), bladder (6), and bone (7). DCE-MRI has been quite successful in diagnosing and staging prostate cancer in the peripheral zone (PZ) (8–12); however, there appears to be some overlap in the enhancement patterns between the tumor and the transitional zone (10). This technique is also useful for identifying equivocal capsular penetration to assess the involvement of the seminal vesicles.
(9), and can be used to monitor neoadjuvant hormonal therapy (13). There are, however, conflicting reports as to whether DCE-MRI correlates well with histological grades of prostate carcinoma (8,10,14).

In addition to characterizing tissue based on proton density (PD) and relaxation properties (T1 and T2), MRI is capable of measuring molecular diffusion of water in vivo. Molecular diffusion is a process in which molecules move along random paths. When a strong magnetic field gradient is present, this random motion results in irreversible dephasing of the MR signal, making diffusion a dominant source of contrast in the MR image (15). Diffusion of water molecules in tissue is affected by the presence of cellular structures that provide barriers to free movement, and can therefore be used to characterize these structures and their changes in pathology (16). Early applications of DW-MRI in cancer diagnosis have been limited to brain tumors, largely because of the extreme sensitivity of this technique to bulk motion. However, recent advances in MR hardware development, particularly fast gradient coils, created the possibility of using ultrafast MRI techniques in a standard clinical setting. DCE-MRI studies of focal liver masses showed lower apparent diffusion coefficient (ADC) values in malignant masses as compared to benign masses and cysts (17). In another study, DW-MRI showed lower ADC values in mucin-producing tumors of the pancreas and pseudocysts as compared to serous cysts and cerebrospinal fluid (18). This technique was also used to show a significant perfusion contribution to the ADC values in the abdominal organs and hepatic lesions (19). Within last few years several studies have been published in which DW-MRI was applied to prostate cancer diagnosis (20–23).

The studies noted above showed that both DCE- and DW-MRI provide important information about the tumor microenvironment that may help to improve the diagnostic capability of traditional T2-weighted MRI. The purpose of the current pilot study was to investigate whether further gains could be made by combining the two techniques. Specifically, we correlated both DCE- and DW-MRI techniques with histology to test the hypothesis that the combination of these techniques would provide higher diagnostic sensitivity than each technique alone.

**MATERIALS AND METHODS**

**Patient Selection and Histology**

The study was approved by the institutional human ethics board, and all participants gave signed consent prior to entering the study. Fourteen patients with a high clinical suspicion for prostate cancer (elevated serum prostate-specific antigen (PSA) and/or prostate nodule detected during digital rectal examination) with no prior treatment were recruited for this prospective study. The subjects underwent the MRI examination prior to transrectal ultrasound (TRUS)-guided biopsies.

TRUS biopsies of the prostate were performed on an Acuson 128XP/10 scanner (Acuson Computed Sonography, Mountain View, CA, USA). The patients were examined with grayscale imaging in the axial and sagittal planes with a 5 MHz transrectal probe. Prophylactic antibiotics and local anesthetic were administered to patients before the prostate biopsies were performed. Systematic octant biopsies were obtained from the following locations in the PZ: left base, right base, left lateral mid-gland, left medial mid-gland, right medial mid-gland, right lateral mid-gland, left apex, and right apex. In one case a repeat biopsy was obtained from a suspicious area noted on the MR images, which confirmed the MR finding.

The radical prostatectomy specimens, obtained from eight of 14 patients with biopsy-proven carcinoma, were all dissected and examined histopathologically in a uniform manner. The external surfaces were inked and the seminal vesicles were amputated. Apical and bladder neck tissues were removed as 0.5-cm-thick tissue doughnuts. The remainder of the prostate gland was then dissected with serial transverse cuts perpendicular to the posterior capsule, at 0.4–0.6 cm intervals, from inferior to superior. The entire prostate gland was submitted for histological examination on hematoxylin and eosin (H&E)-stained slides. Each transverse slice was mapped for prostate adenocarcinoma, maintaining the identity of the right, left, anterior, and posterior locations. The amount of carcinoma in the tissue section, by surface area, was microscopically semiquantitatively scored as follows: 0 = no carcinoma; 1 = <10% carcinoma; 2 = 10–25% carcinoma; 3 = 25–75% carcinoma; and 4 = >75% carcinoma. In addition, tumors identified with both biopsies and radical prostatectomy were assigned a Gleason score (24).

**MRI Examinations**

All MRI experiments were carried out on a 1.5T GE Signa Horizon clinical MRI scanner (General Electric, Milwaukee, WI, USA) equipped with an echo-speed self-shielded gradient set (max. gradient strength = 23 mT/m, max. rise time = 120 mT/m/msec). MRI signals were acquired with an integrated endorectal pelvic phased-array coil (Medrad, Pittsburgh, PA, USA). Fast spin-echo (FSE) T2-weighted images (TR = 4450 msec, TE = 96 msec, FOV = 14 cm, slice thickness = 5 mm with no gap, 256 × 192 matrix, four averages) were acquired in axial and coronal orientations to provide anatomical details of the prostate gland. The slice thickness of 5 mm was chosen for the T2-weighted images to allow direct comparison with the DW and DCE images. Positions of 10 axial slices were then selected to cover the entire gland and were used for the DW- and DCE-MRI scans.

DW-MRI data were acquired using a single-shot FSE sequence developed at the University of California–San Francisco (FOV = 24 cm, slice thickness = 5 mm with no gap, BW = 31 kHz, TR = 8000 msec. TE = 87.5 msec, flip angle = 90°. echo train length = 128, 128 × 128 matrix, 16 averages, b-value = 600 sec/mm²). Four sets of images were acquired in each scan with no diffusion gradient and with the diffusion gradient in the x, y, and z directions.

DCE-MRI was performed using a multislice fast spoiled gradient recalled (FSPGR) sequence (FOV = 24 cm, slice thickness = 5 mm with no gap, TE = 3 msec,
TR = 18.5 msec (T1) or 120 msec (PD), flip angle = 25° (T1) or 8° (PD), 256 × 128 matrix). PD images were acquired prior to the injection of the contrast agent to allow calculations of the T1 values and subsequently the contrast agent concentrations in the tissue (25). A series of T1-weighted images were acquired prior to and following a bolus injection of Gadodiamide (Omniscan, Nycomed-Amersham, Norway; dose: 0.1 mmol/kg injected within 10 seconds followed by a 20-mL flush of normal saline). Three baseline images were acquired just prior to the injection and an additional 42 were obtained following the injection, with a time resolution of 22 seconds per time point. The total time the patients spent in the magnet during the MRI examinations was approximately 60 minutes.

Data Processing

All MRI data were processed offline with a software package developed in-house using Matlab (The MathWorks Inc., Natick, MA, USA).

ADC values were calculated from two DW-MR images acquired with b = 0 and 600 sec/mm² (26). The ADC maps were reconstructed by calculating ADC values in each pixel of each slice. The average ADC values of the tumors were calculated from regions of interest (ROIs) defined as the hypointense areas in the PZ on ADC maps, since previous studies showed lower ADC values in tumors as compared to normal PZ (21,22,27–29). The mean diffusivity was calculated as an average of ADCx, ADCy, and ADCz.

From the DCE-MRI data time-signal intensity parameters, as defined in Ref. 10, were calculated in each pixel of each slice to produce maps of the maximum enhancement (ME), onset time (OT), and mean gradient (MG). In addition, a two-compartment pharmacokinetic model (30) was used to extract Ktrans, extracellular extracellular space (ve) and maximum tissue gadolinium (Gd) concentration from the time-contrast agent concentration curves (31). The fitting was performed in each pixel of each slice within ROIs that included the prostate gland. The criteria for fit acceptance were that 1) the average difference between the measured and the fitted data was less than 0.5; 2) 0.0 < Ktrans < 5.0 [mL/mL/min]; and 3) 0.0 < ve < 1.0 (32). Pixels that did not meet all of these criteria were excluded from the calculation of the average parameter values, and were set to zero for display purposes on the parametric maps. The average values of DCE parameters of the tumors were calculated from the ROIs defined as the hyperintense areas in the PZ on the Ktrans maps. These ROIs corresponded to the fast-enhancing areas in the Gd-DTPA concentration maps.

Control ADC and DCE parameter values were calculated from ROIs defined in the areas that were deemed normal based on both T2-weighted MR images and histology results. T2-weighted images, ADC, and Gd-DTPA concentration maps were coregistered using control point registration with four manually defined control points identifying anatomical features of the prostate gland visible on all three images. For each control point pair, a normalized cross-correlation calculation was performed on an 11 × 11 pixel area centered around the control point. The control point was then moved to the pixel of highest correlation to optimize positioning. From the optimized control points, 3 × 3 transformation matrices were calculated and applied to the different image types to compensate for translation and rotation. ROIs encompassing normal PZ and central gland (CG) were defined on T2-weighted images and then transferred to the parametric maps to calculate the average values for all MRI parameters.

Correlation with histology was based on the results of biopsy and (if available) the radical prostatectomy results. The locations of the tumors in MRI data were mapped to standard octant biopsy sites (MRI slices 1–3 correspond to the base of the gland, 4–7 to the mid-gland, and 8–10 to the apex). Locations within the base and apex were specified as left or right. For the mid-gland four locations were specified as the left mid-lateral, left mid-medial, right mid-medial, and right mid-lateral. Since our experimental setup did not allow for a direct comparison between histological slides and MR images, histological results obtained from the entire glands following radical prostatectomy were also mapped to the standard octant biopsy sites in a similar fashion.

Sensitivity and specificity were assessed based on the presence or absence of tumor in the standard octant biopsy sites. The presence of tumor was confirmed by the biopsy and/or histology results, i.e., the locations where the histology showed the presence of the tumor were considered positive even when biopsy was negative for that site. The diffusion data were considered positive for the presence of tumor in a specific biopsy site if the ADC map showed a hypointense area in that site. Similarly, the DCE data were considered positive if the Ktrans map showed a hyperintense area in the biopsy site. The combined DW and DCE data were considered positive for the presence of tumor if the results of either technique were positive. The hypo- (hyper-) intense areas were defined as the areas with lower (higher) intensity as compared to the intensity within the PZ in the same map. This assessment was carried out visually by two independent readers, and the results from both readers were identical.

Statistical analysis of differences between prostate carcinoma (PCa), benign PZ, and benign CG was carried out using a Tukey-Kramer test.

RESULTS

The average age of the 14 subjects in the study was 60.3 years (range = 48–71 years), and the average value of serum PSA was 9.4 ng/mL (range = 4.3–46 ng/mL). Biopsies acquired from four subjects were negative for carcinoma and MRI data acquired from these subjects did not show any abnormalities. Data from these subjects were included in the overall analysis. Biopsies from the remaining 10 subjects were positive for carcinoma, and eight of these subjects underwent radical prostatectomy. Out of 32 tumors identified by biopsy and histology, 25 had a Gleason score of 7, and seven had Gleason score of 6.

Figure 1 shows typical MRI data acquired from one of the subjects. The reconstructed ADC map shows a hy-
The average values of all MRI parameters from PCa, normal PZ, and normal CG are presented in Table 1. The PCa values presented in the table were determined only from areas that were confirmed as prostate cancer by both MRI and histology. All MRI parameters, with the exception of extravascular extracellular space ($v_e$) and maximum concentration of Gd-DTPA, showed significant differences between cancer and benign PZ. In addition, the average values of $ADC$, $K_{trans}$, and mean gradient within PCa were significantly different from benign CG. Only the average value of $ADC$ showed a significant difference between normal PZ and CG.

When correlated with histology, the ADC data showed 54% (35–72% at 95% confidence level) sensitivity and 100% (95–100% at 95% confidence level) specificity. The DCE data showed a similar sensitivity of 59% (39–77% at 95% confidence level) but a lower specificity of 74% (63–83% at 95% confidence level). When both the ADC and DCE results were combined, the sensitivity increased to 87% (68–95% at 95% confidence level) while specificity decreased to 74% (62–83% at 95% confidence level).

**DISCUSSION**

The results of our pilot study confirm the notion that either DW- or DCE-MRI can be used for noninvasive prostate cancer diagnosis, albeit with somewhat limited sensitivity. The ADC values measured in our study in the normal PZ and CG, and PCa generally correspond well with previously published values (21,23,33,34). The only exception is a study by Gibbs et al (20), which reported much higher ADC values compared to other studies. However, that study, unlike the majority of other studies (including ours), did not use an endorectal RF coil for signal reception, and therefore the signal-to-noise ratio (SNR) may have played a role in the much higher ADC values reported. We validated our DW-MRI method with phantoms, and used signal averaging to ensure sufficient SNR on DW-MR images with the diffusion-sensitizing gradient switched on.

With the relatively low b-value employed in our study ($b = 600 \text{ sec/mm}^2$), the measured ADC primarily reflects the diffusion coefficient of extracellular water (20). It has been shown that low ADC values in brain tumors are associated with high cellular density (35), and one may expect a similar dependence in prostate tumors. Therefore, one can speculate that the differences in ADC values between normal PZ, normal CG, and PCa are likely related to differences in the volume and tortuosity of extracellular space between these structures. The normal prostate gland consists of a network of water-rich ducts and acini supported by stroma. The morphology of ducts and acini is similar in the PZ and CG; however, the stroma is much looser in the PZ than in the CG, resulting in larger extracellular space (36). This is likely the main reason for higher ADC values in the PZ compared to the CG. In the PCa loose stroma is replaced by densely packed malignant epithe-
used combined DW- and DCE-MRI before; however, their main goal was to separate highly ductal tissues (PZ and glandular BPH) from less ductal tissues (CG and stromal BPH), and they did not provide any direct correlation between MRI and histology in their study. Our results show that the sensitivity of combined DW- and DCE-MRI is significantly improved over that of each technique alone, with a small decrease in specificity. This suggests that both techniques provide complementary information about the morphology and pathology of prostate tissue. Indeed, in the majority of cases we noticed that the areas of low ADC did not entirely coincide with the fast-enhancing areas in DCE-MRI (see Fig. 1a). This is likely because the areas of low ADC are associated with high cellular density with lower extracellular space (35), whereas high contrast enhancement is attributed to areas with high microvesSEL density and leaky vasculature (10,11) characteristic of tumor tissue. Since both types of tissue are present within tumor, the combined ADC and DCE-MRI techniques are more likely to provide accurate cancer detection, as was found in our study.

It is reasonable to expect that the combined DW- and DCE-MRI techniques may provide a more reliable way to noninvasively grade tumors, as compared to these and other MRI techniques alone. Indeed, tumors of higher Gleason grade appear to have increased cellular density (24), which will likely result in lower ADC values. Higher-grade tumors also have fewer ducts, and since Noworolski et al (34) suggested that combined DW- and DCE-MRI can distinguish between highly ductal and less ductal tissues within the prostate (34), one would expect this technique to improve tumor grading. The range of Gleason scores in our study was limited to 6 and 7, with the majority of tumors having a score of 7. This prevented any correlation between MRI parameters and the Gleason score. One of the limitations of the current study is the small number of patients (N = 14) involved. A larger study group of patients with a much broader range of tumor grades, and a direct correlation between histological sections and corresponding MR images are required to test whether a correlation between the MRI parameters and the Gleason score exists. The ideal diagnostic technique would be highly specific for malignancy and highly sensitive for biologically significant cancers. We believe that the combined

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>ADC (10^{-3}mm²/second)</th>
<th>K^trans (minutes⁻¹)</th>
<th>v_e</th>
<th>Max. Conc. (mM)</th>
<th>Max. Enh.</th>
<th>OT (minutes)</th>
<th>Mean. Grad.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PZ</td>
<td>1.5730 ± 0.2700</td>
<td>0.598 ± 0.560</td>
<td>0.382 ± 0.148</td>
<td>0.274 ± 0.115</td>
<td>1.218 ± 0.245</td>
<td>0.741 ± 0.133</td>
<td>1.008 ± 0.659</td>
</tr>
<tr>
<td>CG</td>
<td>1.3750 ± 0.1670</td>
<td>0.596 ± 0.288</td>
<td>0.443 ± 0.084</td>
<td>0.314 ± 0.059</td>
<td>1.431 ± 0.190</td>
<td>0.737 ± 0.090</td>
<td>1.004 ± 0.311</td>
</tr>
<tr>
<td>PCa</td>
<td>0.9930 ± 0.1580</td>
<td>1.263 ± 0.544</td>
<td>0.326 ± 0.131</td>
<td>0.257 ± 0.099</td>
<td>1.463 ± 0.218</td>
<td>0.644 ± 0.089d</td>
<td>2.297 ± 1.023a,b</td>
</tr>
</tbody>
</table>

aPCa significantly different than PZ (P < 0.001).
bPCa significantly different than CG (P < 0.001).
cCG significantly different than PZ (P < 0.05).
dPCa significantly different than PZ (P < 0.05).

ADC = mean diffusivity, Max. Conc. = maximum concentration of Gd-DTPA, Max. Enh. = maximum enhancement, OT = onset time, Mean Grad. = mean gradient, PZ = normal peripheral zone (DW MRI: N = 18, DCE MRI: n=24), CG = normal central gland (N = 15), PCa = tumor (DW MRI: N = 16, DCE MRI: N = 24).
REFERENCES