Diffusion-weighted magnetic resonance imaging: a potential non-invasive marker of tumour aggressiveness in localized prostate cancer

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AIM: To evaluate diffusion-weighted magnetic resonance imaging (DW-MRI) as a marker for disease aggressiveness by comparing tumour apparent diffusion coefficients (ADCs) between patients with low- versus higher-risk localized prostate cancer.

METHOD: Forty-four consecutive patients classified as low-[n = 26, stage T1/T2a, Gleason score ≤ 6, prostate-specific antigen (PSA) < 10 (group 1)] or intermediate/high- [n = 18, stage ≥ T2b and/or Gleason score ≥ 7, and/or PSA > 10 (group 2)] risk, who subsequently were monitored with active surveillance or started neoadjuvant hormone and radiotherapy, respectively, underwent endorectal MRI. T2-weighted (T2W) and DW images (5 b values, 0–800 s/mm²) were acquired and isotropic ADC maps generated. Regions of interest (ROIs) on T2W axial images [around whole prostate, central gland (CG), and tumour] were transferred to ADC maps. Tumour, CG, and peripheral zone (PZ = whole prostate minus CG and tumour) ADCs (fast component from b = 0–100 s/mm², slow component from b = 100–800 s/mm²) were compared.

RESULTS: T2W-defined tumour volume medians, and quartiles were 1.2 cm³, 0.7 and 3.3 cm³ (group 1); and 6 cm³, 1.3 and 16.5 cm³ (group 2). There were significant differences in both ADC fast (1778 ± 264 × 10⁻⁶ versus 1583 ± 283 × 10⁻⁶ mm²/s, p = 0.03) and ADC slow (1379 ± 321 × 10⁻⁶ versus 1196 ± 158 × 10⁻⁶ mm²/s, p = 0.001) between groups. Tumour volume (p = 0.002) and ADC slow (p = 0.005) were significant differentiators of risk group.

CONCLUSION: Significant differences in tumour ADCs exist between patients with low-risk, and those with higher-risk localized prostate cancer. DW-MRI merits further study with respect to clinical outcomes.

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Introduction

Treatment options for localized prostate cancer are many and varied, ranging from immediate radical surgery through to watchful waiting (intervening only if symptoms develop). Radical prostatectomy has been shown in a good-quality, randomized, controlled trial to have an overall survival advantage compared with watchful waiting. Conversely, prostate cancer can often behave in an indolent fashion even without treatment, with no effect either on health or longevity. In such cases, radical treatment, with its risks of incontinence and impotence, could be worse than the disease. So, the challenge of managing localized prostate cancer is to distinguish patients with clinically relevant cancers, who may benefit from radical treatment, from the remainder who do not need any intervention. There is a major unmet need for markers of prostate cancer behaviour...
that could be used to support the decision whether or not to offer patients radical treatment.

A conventional approach is to classify cases into risk groups in terms of serum prostate specific antigen (PSA) level, biopsy Gleason score, and clinical T stage.\(^3-5\) and nomograms to risk-stratify patients based on such parameters have been derived.\(^6,7\) These risk groups have been shown to predict the probability of biochemical recurrence after radical treatment, and are used as a guide to treatment decision-making. In particular, patients with intermediate and high-risk localized prostate cancer are typically considered good candidates for immediate radical treatment with surgery or external beam radiotherapy as there is no overall change in reader accuracy, because of an associated increase in false-positive findings.\(^11\) MR spectroscopy has also been used as an adjunct to imaging and improves accuracy of prostate cancer detection,\(^12-15\) but is time-consuming both for image acquisition and subsequent data processing and is not easy to implement in many centres. Therefore, ADCs are directly associated with coherent microvessel density and cellularity\(^20\) with microcapillary perfusion contributing to a "fast" diffusion component and extracellular space. Therefore, ADCs are directly associated with coherent microvessel density and cellularity\(^20\) with microcapillary perfusion contributing to a "fast" diffusion component and extracellular water movement over a shorter diffusion path length contributing to a "slow" component.

The purpose of this study was to compare tumour ADC values between patients with clinically localized prostate cancer classified as low-risk versus those classified as intermediate or high-risk of progression, in order to determine the potential value of DW-MRI as a non-invasive marker of disease aggressiveness.

**Methods**

**Patient population**

This was a prospective, single-institution study with approval from the local research ethics committee. Over a 6-month period (July–Dec 2006), 44 consecutive patients with clinically localized prostate cancer (on digital rectal examination) referred for routine clinical evaluation in our MRI centre underwent DW-MRI in addition to their standard T2W MRI. Areas of T2W abnormality validated by biopsy results were used as positive evidence of tumour.

The patients were classified into two groups according to their risk category, defined using the NCCN criteria. Patients with low-risk localized disease (T1/T2a, Gleason score < 7 and PSA < 10) were in disease staging,\(^19\) functional MR indices to date have not been used for predicting disease outcome in prostate cancer.

An alternative to conventional T2W MRI is to develop image contrast through "apparent diffusivity" (tissue water incoherent displacement over distances of 1–20 \(\mu\)m). Diffusion-weighted (DW) MRI been used in both clinical and research settings for detecting cerebral,\(^20-23\) and as well as cancer-related disease.\(^24-28\) In prostate cancer, DW-MRI is proving useful in tumour detection.\(^29\) The apparent diffusion coefficients (ADCs) derived provide quantitative information on the degree of restriction of water diffusion within tissues, including the contribution from microcapillary perfusion and Brownian diffusion within the extracellular space. Therefore, ADCs are directly associated with coherent microvessel density and cellularity\(^20\) with microcapillary perfusion contributing to a "fast" diffusion component and extracellular water movement over a shorter diffusion path length contributing to a "slow" component.
mid-gland, and base from each side) were obtained in each case (14 patients had eight biopsies and 23 had 12). Patient characteristics are summarized in Table 1. Following MRI, patients were treated as indicated clinically and were either watched under an active surveillance protocol or received neoadjuvant hormonal therapy followed by radiotherapy.

**Imaging methods**

MRI studies were performed using a 1.5 T Intera (Philips Medical Systems, Best, the Netherlands) using a balloon-design endorectal coil (Philips Medical Systems) inflated with 55 ml air. Hyoscine butylbromide (20 mg) was administered intramuscularly immediately prior to centring the patient in the machine in order to reduce peristalsis: this is routine at our institution for abdomino-pelvic MRI and is preferred to glucagon because of more effective antiperistalsis. None of our patients had a previous history of urinary retention. Although it is contraindicated in patients with large prostates and urinary retention, given intramuscularly at this dose, there have been no cases of urinary retention in our clinical practice over the last 10 years. Conventional T2W fast spin-echo images were obtained in three orthogonal planes [TSE repetition time (TR) 2000 ms/echo time (TE) 90 ms, echo train length 16, two signal averages] with a 256 × 512 matrix (interpolated to 512 × 512), 3 mm section thickness, no gap, and a 14 cm field of view (FOV; total imaging time 12 min). Echoplanar DW images (2500/69 [TR/TE]) with b values of 0, 100, 300, 500 and 800 s/mm² were obtained transverse to the prostate and parallel to the corresponding set of T2W images. The phase-encoding gradient was from left to right in order to minimize motion artefacts in the prostate. Twelve 4 mm thick sections (no gap, 20 cm FOV, matrix 128 × 128) provided coverage of the prostate with an image acquisition time of 1 min 24 s.

**Data analysis**

The axial T2W and DW images were transferred offline for analysis. Regions of interest (ROIs) were drawn on all sections of the T2W axial images around the whole prostate, the central gland (CG), and the tumour. The tumour region was identified as a focal low signal intensity lesion or a homogeneous low-signal intensity lesion with mass-effect on the T2W images in a sextant that was biopsy positive for tumour by a radiologist with 10 years experience of prostate MRI. The radiologist had knowledge of the biopsy findings, but did not have access to the DW data and ADC maps. T2W defined tumour volumes were calculated by multiplying total tumour ROI area by the section thickness.

Software written in-house (IDL, ITT-IVS, Colorado, USA) was used to generate isotropic ADC maps over the whole range of b values (0–800 s/mm², ADCoverall), which reflects both perfusion and diffusion components, for b = 0–100 s/mm² to reflect the “fast” diffusion component, ADCfast, and over the range b = 100–800 s/mm² to reflect the “slow” diffusion component ADCslow. Manufacturer’s software that automatically generates such data was not available on the MRI machine at the time. The data were fitted with a single exponential in each case. The centre of mass and whole gland outlines defined on ADC maps were matched with those defined on the T2W images to correct for rigid body shifts.31 T2W ROIs were transferred onto the corresponding sections on the ADC maps. Mean ADC values from tumour, CG, and non-malignant peripheral zone (PZ, whole prostate minus CG and tumour) were calculated.

**Statistical analysis**

The data were tested for normality using a Shapiro–Francia test. The distribution of values for MR-defined tumour volume and for ADCoverall were found to be non-normal. These data were, therefore, log transformed and the log-transformed data tested for normality. All other data were normally distributed. A paired t-test was used to assess within-group differences (between tumour, CG and PZ in the same prostate) and an independent samples t-test with Bonferroni correction to assess differences between means of the two groups were used. Differences in ADCoverall, ADCfast, and ADCslow between tumour ROIs, CG, and non-malignant PZ were calculated and a p-value of <0.05 was taken to be significant. A logistic regression model was used to determine parameters predictive of risk, and a receiver operating characteristic (ROC) curve was subsequently plotted to determine the cut-off value for this parameter.
Results

Group 1

Thirty-six tumour lesions were identified in 26 patients. These were identified as low-signal-intensity lesions in the PZ (Fig. 1a and b) or irregular, homogeneous, low signal intensity lesions in the CG with mass effect. The size, margins, and mass effect of the CG lesions were in keeping with tumour as opposed to fibromuscular nodules of benign prostatic hypertrophy. All the corresponding sextants were biopsy positive for tumour. Eight of these lesions were relatively subtle and required review of the T2W MRI after taking the biopsy findings into consideration. In the other 28 lesions, the lesion was easily discernible on the T2W images, and the biopsy findings were used as confirmatory evidence. In patients with more than one tumour focus, a single tumour ADC was calculated from all tumour voxels. Tumour ROI volume ranged from 0.15–12.6 cm$^3$ (mean 2.3 ± 2.8 cm$^3$, median 1.2 cm$^3$, quartiles 0.68, 3.3 cm$^3$). One sextant in one patient was biopsy positive with no corresponding T2W abnormality, and therefore, was not included as a tumour ROI in the analysis.

Comparison of ADC values in lesions <1 cm$^3$ ($n=10$) with those from lesions ≥1 cm$^3$ ($n=16$) showed no significant difference between the means ($p=0.09$), indicating that partial volume effects in smaller tumours are unlikely to affect the group mean ADC values.

Group 2

Twenty-three tumour lesions were identified in 17 patients (Fig. 2a and b). All these lesions were easily identifiable on T2W MRI as a low signal-intensity mass with a biopsy from a corresponding sextant of the prostate positive for tumour. In patients with more than one tumour focus, a single tumour ADC was calculated from all tumour voxels. Tumour ROI volume ranged from 0.3–132.9 cm$^3$ (mean 15.7 ± 30.5 cm$^3$, median 6 cm$^3$, quartiles 1.3, 16.5 cm$^3$). Two sextants in one patient were biopsy positive with no corresponding T2W abnormality and this region, therefore, was not included as a tumour ROI in the analysis.

Figure 1 Patient with low-risk prostate cancer. Endorectal T2W transverse image (a) shows a well-defined low signal intensity region in the peripheral zone on the right (arrow), within a sextant that was biopsy positive for tumour. A radiologist-determined region of interest around the tumour, whole prostate and CG are shown in (b). An ADC map (c) shows the restricted diffusion in the right peripheral zone posteriorly (arrow).
Comparison between low- and high-risk groups

Heterogeneity of ADC was observed within tumour ROIs in all cases (Figs. 1c and 2c). Isotropic ADC values averaged over the ROI are given in Table 2 for regions of tumour, PZ, and CG. For tumour ROIs, there was a significant difference between the two groups in both the ADC<sub>fast</sub> (b = 0–100 s/mm<sup>2</sup>) and ADC<sub>slow</sub> (b = 100–800 s/mm<sup>2</sup>) components (Table 2). The PZ and CG values did not show any significant differences between groups. There also was a significant difference in both the ADC<sub>fast</sub> and ADC<sub>slow</sub> components between tumour and PZ (p = 0.0001), and between PZ and CG (p = 0.0001) in both groups, and between tumour and CG (p = 0.0001) for group 2, but not group 1 (p = 0.053).

Predictors of disease aggressiveness

ADC<sub>fast</sub> (p = 0.013) and ADC<sub>slow</sub> (p = 0.005) were discriminatory between risk groups. T2W defined tumour volume was also a significant predictor of risk group (p = 0.002). Logistic regression showed that ADC<sub>slow</sub> enabled correct prediction of risk group 72.7% of the time (area under ROC curve, AUC = 0.76), whereas the log MR-defined tumour volume enabled correct prediction of risk group 79.7% of the time (AUC = 0.76; Table 3). However, with the relatively small numbers of patients in this study, these parameters failed to show independent significance. For a 70% accuracy of risk prediction, using a tumour ADC<sub>slow</sub> cut-off of 1333 x 10<sup>-6</sup> mm<sup>2</sup>/s gave a sensitivity of 89% and specificity of 58%, whereas a cut-off of 1200 x 10<sup>-6</sup> mm<sup>2</sup>/s, gave a sensitivity of 55% and specificity 95%. Also, for a 77% accuracy of risk prediction using tumour volume, a cut-off of 3.75 cm<sup>3</sup> gave a sensitivity of 61% and specificity of 88%.

Discussion

This study demonstrates that the slow and fast components of water diffusion within prostate tumours are significantly different in patients with...
Diffusion-weighted MRI in prostate cancer

Table 2  Calculated mean and standard deviation apparent diffusion coefficient (ADC) values in group 1 (low risk) and group 2 (intermediate/high risk)

<table>
<thead>
<tr>
<th>B-values</th>
<th>ADC tumour (×10⁻⁶ mm²/s)</th>
<th>ADC PZ (×10⁻⁶ mm²/s)</th>
<th>ADC CG (×10⁻⁶ mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–800</td>
<td>ADCoverall</td>
<td>ADCfast</td>
<td>ADCslow</td>
</tr>
<tr>
<td>Low-risk</td>
<td>16.56 ± 322</td>
<td>17.78 ± 264</td>
<td>13.79 ± 221</td>
</tr>
<tr>
<td>(n = 26)</td>
<td></td>
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<tr>
<td>High-risk</td>
<td>1501 ± 256</td>
<td>1583 ± 213</td>
<td>1196 ± 158</td>
</tr>
<tr>
<td>(n = 18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-Value</td>
<td>0.24</td>
<td>0.03</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The p-values relate to the differences in apparent diffusion coefficient (ADC) values between the groups. CG, central gland; PZ, whole prostate minus CG.

low-risk compared with those with intermediate or high-risk disease. ADC values thus offer potential for differentiating indolent from aggressive prostate cancers. Water diffusion characteristics are substantially affected by cellular and structural changes within tissues because this parameter is strongly affected by cell density, vascularity, viscosity of extracellular fluid, membrane permeability between intra- and extracellular compartments, active transport and flow, and directionality of tissue/cellular structures that impede water mobility. This study, therefore, confirms that these cellular and structural differences exist between low and high-risk lesions, and that they can be measured non-invasively in vivo. Although ADC values are known to correlate with tissue structure, the NCCN criteria rather than Gleason score were used to define risk groups in order to reduce the effects of biopsy sampling variability and reflect the fact that our ADC values were averaged over the whole tumour ROI. Averaging ADCs over the ROI is a limitation as it does not account for ADC differences within the tumour itself: correlation of these differences with histopathology would be useful. Further study of DW-MRI in localized prostate cancer is also warranted in relation to histopathological and clinical outcomes.

The methodology used in the present study enables calculation of diffusion components weighted to low and high b values. Although some researchers have advocated the use of b values of 1000 s/mm² in order to separate out the slow diffusion components adequately, our data shows that values up to 800 s/mm² are sufficient: use of higher b values merely serves to increase the noise in the acquired data. Ex vivo data show that it is the slow diffusion component that is associated with cell density.33 Thus the ADCslow differences between high and low-risk groups may be due to highly cellular regions in high-risk patients. However, it does not explain why the fast diffusing component traditionally linked with capillary microcirculation should be diminished in the high-risk group. It is possible that microcapillary perfusion is compromised in the high-risk patients because of tumour hypoxia. This is supported by ex vivo findings of increased hypoxia in more aggressive tumour types.34

As T2W low signal intensity lesions are well described not only in cancer, but also in infection, inflammation, and fibrosis, the likelihood of these lesions contributing to our ROIs were reduced by including only T2W lesions that had a positive sextant biopsy. Sextant biopsies were used as the minimum, although it is acknowledged that a larger number of biopsies improves disease detection.35 It is well recognized that biopsies are subject to sampling error, and T2W hypointensity can represent chronic prostatitis rather than tumour. Although a thorough correlation was attempted, it is possible that in group 1 DW abnormalities did not correspond to tumour foci. In group 2, where tumour volume was large, sampling error is much less likely. Evidence of high signal intensity was investigated for within these regions on the T1W images of the whole pelvis taken at the same time to indicate haemorrhage, as this would have affected the ADC measurement. The quantitation of ADC served to eliminate signal variations due to receiver gain and surface coil signal inhomogeneities.

In agreement with previous findings, prostate cancer has a lower ADC value than non-malignant
In conclusion, DW-MRI offers potential as a non-invasive marker of biologically aggressive cancer. Tumour volume and the slow diffusion component appear to be discriminators of higher-risk disease. DW-MRI is simple to implement and the time penalty when added to a standard endorectal staging MRI examination is less than 2 min. However, further work is needed to determine the best cut-off values of ADC. There is a need also to establish the potential of DW-MRI in longitudinal studies in patients on active surveillance in order to determine when to implement treatment.
Acknowledgements

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References