DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING: A
POTENTIAL NON-INVASIVE MARKER OF TUMOUR AGGRESSIVENESS IN
LOCALIZED PROSTATE CANCER

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INTRODUCTION

Treatment options for localised prostate cancer are many and varied, ranging from immediate radical surgery through to watchful waiting (intervening only if symptoms develop). On the one hand, radical prostatectomy has been shown in a good quality randomised controlled trial to have an overall survival advantage compared with watchful waiting (1). On the other hand, prostate cancer can often behave in an indolent fashion even without treatment, with no effect either on health or longevity (2). In such cases, radical treatment, with its risks of incontinence and impotence, could be worse than the ‘disease’. So, the challenge of managing localised 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 inform 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 a clear survival benefit (1). Patients with low-risk localized disease are typically offered the option of either immediate radical treatment or active surveillance. However, histological evaluation at biopsy requires an invasive procedure and is subject to sampling error. There remains a pressing need for non-invasive markers of prostate cancer behaviour, that can be applied to individual cases at the outset, to identify those requiring treatment, and those who should be monitored in an active surveillance programme with PSA and repeat biopsy.

The best method of imaging prostate cancer is with endorectal T2-weighted magnetic resonance imaging (T2-W MRI). Unfortunately the sensitivity of T2-W MRI alone varies from 60-82%, for disease detection within the gland with a specificity of around 55-70% (8-10). Awareness of clinical data significantly improves reader detection of prostate cancer nodules with endorectal MRI, but 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 centers. The production of citrate is reduced in cancer tissue, while choline is increased, leading to an increased choline to citrate ratio. An attempt to correlate MR spectroscopy with tumour aggressiveness showed that there was a trend toward increasing \((\text{Choline + Creatine})/\text{Citrate}\) with increasing Gleason score but that there was significant overlap between MR spectroscopic imaging parameters at various Gleason grade levels (16). More recently,
dynamic contrast-enhanced MRI has been investigated as a diagnostic tool for prostate cancer detection (17;18), but although the technique is promising, controversies exist around standardization of analysis and reporting. Thus, although MRI is useful in disease staging (19), functional MR indices to date have not been used for predicting disease outcome in prostate cancer.

An alternative to conventional T2-W MRI is to develop image contrast through "apparent diffusivity" (tissue water incoherent displacement over distances of 1–20 µm). Diffusion-weighted magnetic resonance imaging (DW-MRI) has been used in both clinical and research settings for detecting cerebral (20-23) as well as cancer-related pathologies (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 contribution from microcapillary perfusion and Brownian diffusion within the extracellular space. ADCs therefore are directly associated with coherent microvessel density and cellularity (30) with microcapillary perfusion contributing to a “fast” diffusion component and extra- and intracellular water movement over a shorter diffusion path length contributing to a “slow” component.

The purpose of this study was to compare tumour apparent diffusion coefficient (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 06) 44 consecutive patients with clinically localized prostate cancer (on digital rectal examination) referred for routine clinical evaluation in our MR centre underwent DW-MRI in addition to their standard T2-W MRI. We used areas of T2W abnormality validated by biopsy results as positive evidence of tumour.

The patients were classified into 2 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) formed Group 1. Patients with intermediate or high-risk disease (either >= T2b and/or Gleason score >=7, and/or PSA > 10) formed Group 2. MRI was done at a median of 13 weeks (lower and upper quartiles 8.8 weeks and 26.3 weeks) from the most recent biopsy. A minimum of six biopsies (apex, mid-gland and base from each side) were obtained in each case (14 patients has 8 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.

Scanning Methods: MR studies were performed using a 1.5-T Intera (Philips Medical Systems, Netherlands) using a balloon design endorectal coil (Philips Medical Systems, Netherlands) inflated with 55ml of air. Hyoscine butyl bromide 20 mg was administered intramuscularly immediately prior to centering the patient in the scanner 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 contra-indicated in patients with large prostates and urinary retention, given intramuscularly at this dose, we have had no cases of urinary retention in our clinical practice over the last 10 years. Conventional T$_2$-W fast spin echo images were obtained in 3 orthogonal planes (TSE 2000/90 ms [TR/effective TE], echo train length 16, 2 signal averages) with a 256x512 matrix (interpolated to 512 x 512), 3mm slice thickness, no gap and a 14cm FOV (total imaging time 12 mins). Echo-planar DW images (2500/69 [TR/TE]) with b values of 0, 100, 300, 500 and 800 s/mm$^2$ were obtained transverse to the prostate and parallel to the corresponding set of T$_2$-W images. The phase-encoding gradient was from left to right in order to minimize motion artifacts in the prostate. Twelve 4mm thick slices (no gap, 20 cm FOV, matrix 128x128) provided coverage of the prostate with an image acquisition time of 1min 24s.

Data Analysis: The axial T$_2$-W and DW- images were transferred offline for analysis. Regions of interest (ROIs) were drawn on all slices of the T$_2$-W axial scans 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 homogenous low-signal intensity lesion with mass-effect on the T$_2$-W 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. T$_2$-W defined tumour volumes were calculated by multiplying total tumour ROI area by slice 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/mm$^2$, ADC$\text{overall}$), which reflects both perfusion and diffusion components, for $b=0-100$ s/mm$^2$ to reflect the “fast” diffusion component, ADC$_{\text{fast}}$, and over the range $b=100-800$ s/mm$^2$ to reflect the “slow” diffusion component ADC$_{\text{slow}}$. Manufacturer’s software that automatically generates such data was not available on our scanner at the time. The data was 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 T2-W images to correct for rigid body shifts (31). T2-W ROIs were transferred onto the corresponding slices 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 was tested for normality using a Shapiro-Francia test. The distribution of values for MR-defined tumour volume and for ADC$\text{overall}$ were found to be non-normal. These data were therefore log transformed and the log transformed data tested for normality. All other data was normally distributed. A paired t-test 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 ADC$\text{overall}$, ADC$_{\text{fast}}$ and ADC$_{\text{slow}}$ 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 (Figure 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 (32) 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 T2-W MRI after taking the biopsy findings into consideration. In the other 28 lesions, the lesion was easily discernible on the T2-W 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 0.15-12.6cm³ (mean $2.3 \pm 2.8$ cm³, median 1.2 cm³, quartiles 0.68, 3.3 cm³). One sextant in one patient was biopsy positive with no corresponding T2-W abnormality and therefore was not included as a tumour ROI in the analysis. Comparison of ADC values in lesions <1cm³ (n = 10) with those from lesions $\geq$1cm³ (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 (Figure 2a and b). All these lesions were easily identifiable on T2-W 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 $15.7 \pm 30.5$ cm$^3$, median 6.0 cm$^3$, quartiles 1.3, 16.5 cm$^3$). Two sextants in one patient were biopsy positive with no corresponding T2-W abnormality and this region therefore was not included as a tumour ROI in the analysis.

Comparison between low- and high-risk groups: Heterogeneity of ADC was observed within tumour ROIs in all cases (Figures 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$_{\text{fast}}$ ($b=0-100$ s/mm$^2$) and ADC$_{\text{slow}}$ ($b=100-800$ s/mm$^2$) 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$_{\text{fast}}$ and ADC$_{\text{slow}}$ 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$_{\text{fast}}$ ($p=0.013$) and ADC$_{\text{slow}}$ ($p=0.005$) were discriminatory between risk groups. T2-W defined tumour volume also was a significant predictor of risk group ($p=0.002$). Logistic regression showed that ADC$_{\text{slow}}$ enabled correct prediction of risk group 72.7% of the time (area under ROC curve, AUC=0.76) while using log MR-defined tumour volume would enable 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$_{\text{slow}}$ cut-off of 1333 $\times 10^{-6}$ mm$^2$/s gave a sensitivity of 89% and specificity of 58% whilst a cut-off of
1200 \times 10^{-6} \text{ mm}^2/\text{s},\text{ gave a sensitivity of 55%, specificity 95%. Also, for a 77% accuracy of risk prediction using tumour volume, a cut-off of } 3.75\text{cm}^3\text{ gave a sensitivity of 61%, 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 low-risk compared to 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 we used the NCCN criteria to define risk groups rather than Gleason score 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 warranted also in relation to histopathological and clinical outcomes.

The methodology used in our 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 upto 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 ADC_{slow}
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 T2-W low signal intensity lesions are well described not only in cancer, but also in
infection, inflammation and fibrosis, we reduced the likelihood of these lesions
contributing to our ROIs by only including T2-W lesions that had a biopsy from that
sextant positive for tumour. We used sextant biopsies as our 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 T2-W hypointensity can
represent chronic prostatitis rather than tumour. Although we attempted a thorough
correlation, it is possible that in group 1 diffusion weighted abnormalities did not
correspond to tumour foci. In group 2 where tumour volume was large, sampling error is
much less likely. We also ensured that there was no evidence of high signal intensity
within these regions on T1-W scans 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 peripheral zone (31;36;37). In comparison, ADC values of tumour have previously been described as indistinguishable from central gland where hypercellular BPH nodules may have low ADCs (36). We have shown that it is possible to distinguish ADCs in tumour from those in the CG in high-risk patients. This could be of benefit in identifying those with CG tumours that require treatment. The main clinical utility would be to identify adverse disease on DW-MRI that was considered low-risk according to established clinical characteristics. However, if a patient is thought to have high-risk disease on the basis of T stage, Gleason score and PSA, then management unlikely to be influenced by favourable DW-MRI results. DW-MRI has also been shown to do significantly better than T2-W MRI at field strengths of 3T (38), and further benefits are seen when used in combination with dynamic contrast-enhanced imaging (39).

In prostate cancer, tumour volume is recognized as an important predictor of clinical stage and disease outcome: in a multivariate analysis, tumour volume was an independent predictor of PSA recurrence (P = 0.04) (40). In one large study, significant correlations between tumour volumes and known prognostic parameters such as preoperative serum levels of prostatic specific antigen, loss of differentiation, histological grade, lymph node metastasis, and margins were found (41). However, in practice, clinicians place little emphasis on tumour volumes, as reliable measures of tumour volume are not readily available. Estimates of tumour volume derived from radical prostatectomy have been shown to correlate with volumes on T2-W MRI (42), although in some studies (43) and in tumours less than 1cm in diameter, the correlation with tumour size at histology is much poorer (44). In this study tumour volume was
significantly higher in group 2 and confirms the value of both T2-W defined tumour volume and the slow component of ADC in differentiating low from high-risk groups.

There is a major unmet need for markers of prostate cancer behaviour, especially within the low-risk group, and it is in this group of patients where the additional information provided by DW-MRI is likely to be most beneficial. This group of patients are faced with the difficult decision of whether or not to have radical treatment, needing to weigh up the potential survival benefit against the known morbidity. Active surveillance is an approach to the management of localized prostate cancer that aims to avoid over treatment of men with indolent cancers, while still providing treatment with radical intent within a window of curability for those who need it. Active surveillance programmes rely on PSA kinetics and repeat biopsies to risk stratify patients and guide decisions on who needs treatment and when. Hence risk stratification relies to an extent on information obtained from needle biopsy. It is well known that sampling error is a major limitation of needle biopsies. DW-MRI provides information on the whole gland and gives biological information, which may be used in addition to, or as a non-invasive surrogate for, the prognostic information derived from biopsies. Separation of high and low risk lesions has also been described using MRS, which is the only other functional imaging technique where risk stratification has been attempted according to Gleason grade. In Zakian’s study, the area under the curve for separating low from high risk lesions using the maximum Cho+Cr/Cit was 0.8, with overlap between MRS parameters at various Gleason scores (16). Tumour volume was also found to correlate with Gleason score. Investigation of a combination of the slow component of ADC, MRS and tumour volume as a tool in the management of localized prostate cancer therefore is warranted.
A major limitation of this study is the lack of correlation of tumour ROIs with whole mount histopathology. However, our clinical practice is such that these patients largely elect to remain within an active surveillance programme, or in the case of higher risk disease undergo hormone down regulation and radiotherapy. In the high-risk cohort, all lesions were large and easily discernible on T2-W imaging, so the likelihood of error in ROI placement is low. In the low-risk cohort, where 8 lesions were difficult to identify without the biopsy data, the ADC values are likely to have been indistinguishable from adjacent non-malignant PZ or CG. In these cases, the lack of a visually identifiable lesion on the ADC map is also an indicator of the low-risk nature of the lesion. A more problematic feature is that we used the averaged ADC from the entire tumour region, and this was often heterogenous. It may be that the more restricted areas of diffusion within the tumour region are ultimately more predictive of outcome.

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 scan is less than 2 minutes. 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.
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Figure Legends

**Fig. 1** *Patient with low-risk prostate cancer:* Endorectal T2-W 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 central gland are shown in (b). An apparent diffusion coefficient (ADC) map (c) shows the restricted diffusion in the right peripheral zone posteriorly (arrow).

**Fig. 2** *Patient with high-risk prostate cancer:* Endorectal T2-W 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 central gland are shown in (b). An apparent diffusion coefficient (ADC) map (c) shows the restricted diffusion in the right peripheral zone laterally (arrow).

Tables

**Table 1** Patient Characteristics for each of the groups

**Table 2** Calculated mean and standard deviation ADC values in Group 1 (Low-risk) and Group 2 (Intermediate/High-risk). The p values relate to the differences in ADC values between the groups

**Table 3** Slow component of ADC as a predictor of risk group

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