MAGNETIC RESONANCE IMAGING IN PROSTATE CANCER: VALUE OF APPARENT DIFFUSION COEFFICIENTS FOR IDENTIFYING MALIGNANT NODULES

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MAGNETIC RESONANCE IMAGING IN PROSTATE CANCER: VALUE OF APPARENT DIFFUSION COEFFICIENTS FOR IDENTIFYING MALIGNANT NODULES
ABSTRACT
The aim of this work was to determine the potential of diffusion-weighted magnetic resonance imaging (DW-MRI) for identifying prostate cancer by comparing apparent diffusion coefficients (ADC’s) from malignant peripheral zone (PZ) nodules with values from non-malignant PZ and predominantly benign central gland (CG). Thirty-three patients with elevated prostate specific antigen (PSA) aged 52-78 years (30 with biopsy proven prostate cancer) underwent endorectal MRI with T2-weighted and echo-planar DW (b = 0, 300, 500 and 800 s/mm²) sequences. ADC’s were measured from 30 malignant PZ nodules (identified on T2-weighting and positive biopsy; median ROI size 41mm²), 33 CG regions (predominantly benign nodules; median ROI size 218mm²) and 18 non-malignant PZ regions (ipsilateral biopsies all benign; median ROI size 54.5mm²). ADC’s were (mean ±sd; mm²/s): malignant PZ nodules 1.30± 0.30X10⁻³, CG 1.46± 0.14X10⁻³ and non-malignant PZ 1.71± 0.16X10⁻³. Differences between all 3 groups were statistically significant (p=0.01 malignant PZ vs. CG; p=0.0001 malignant PZ vs. non-malignant PZ and p=0.0001 CG vs. non-malignant PZ). Using Receiver Operating Characteristic curves, cut-off values of 1.39x 10⁻³ mm²/s differentiated malignant PZ nodules from predominantly benign CG (sensitivity 60%, specificity 76%) and of 1.6 x 10⁻³ mm²/s identified malignant from non-malignant PZ (sensitivity 86.7%, specificity 72.2%). These results suggest that DW-MRI has potential to increase specificity of prostate cancer detection because ADC’s are significantly lower in malignant compared with non-malignant prostate tissue.
INTRODUCTION:
Cancer of the prostate currently accounts for ~30% of new cancer cases [1] and requires 6-8 tissue cores obtained under transrectal ultrasound (TRUS) guidance for diagnosis. T2-weighted magnetic resonance imaging (MRI) delineates prostate cancer as a region of low signal intensity (indicative of a shorter T2 relaxation time constant for tumour) surrounded by high signal intensity (longer T2) of normal peripheral zone tissue [2;3]. However, although the sensitivity of T2-weighted images for tumour detection is high, specificity is poor [4]. Furthermore, the 30% of tumours that occur in the central gland cannot be detected on T2-weighted imaging because it is not possible to differentiate them from the low signal-intensity benign nodules of prostatic hyperplasia. Potential advantages of improved discrimination of malignant tissue in both the peripheral and central zones of the prostate include better local staging performance, increased accuracy in performing biopsy, improved focusing of irradiation for intensity-modulated radiotherapy, improved follow-up of therapy response, and earlier detection of tumour recurrence.

An alternative to T2-weighted 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 [5-8] as well as cancer-related pathologies [9-13]. In cancer imaging, it has been used primarily in characterizing brain tumours [7] and in differentiating brain lesions based on diffusivity of peritumoural edema [14]. However, there are a few recent reports of the utility of DW-MRI in prostate cancer [15-19] where its role appears promising but has not been established. The extensive branching ductal structure of the normal prostate compared
with the highly restricted intracellular and interstitial spaces encountered in prostate cancers produces a substantial differential in apparent diffusion coefficient (ADC) and, thus, the potential for high image contrast. The purpose of this study was to investigate the potential of DW-MRI in identifying malignant nodules by comparing apparent diffusion coefficients (ADC’s) of malignant peripheral zone (PZ) nodules with values from non-malignant PZ and from the central gland (CG), which is primarily composed of benign nodules.
METHODS

Patient population: This was a prospective, single-institution, cross-sectional study with institutional approval by the local research ethics committee. Over an 8-month period, 33 patients with elevated PSA were studied: 30 consecutive patients with low signal intensity lesions within the PZ on conventional T2-weighted images, with TRUS guided biopsy confirmation from that region positive for cancer and 3 patients with no T2-weighted abnormality and no identifiable tumour on biopsy. A minimum of 6 cores was obtained from each patient. The number of positive cores varied from 1-4 and Gleason score varied from 6 to 8. In 6 patients, contralateral tumours identified on biopsy did not correspond to low signal intensity nodules on the T2-W scans; these lesions were not included in the analysis. Patients were aged 52-78 yrs (mean±sd, 68.7 ± 6.5 yrs) with PSA 2.9-72.3 ng/ml (mean±sd, 14.1 ±13.5 ng/ml). All patients had a clinical stage less than or equal to T3N0M0. Patients underwent DW-MRI complementary to the routine staging MR imaging examination of the prostate. MRI was done at a median of 11 weeks following the most recent biopsy (interquartile range 6-24 weeks).

Imaging: Imaging was done on a 1.5-T Intera (Philips Medical Systems, Netherlands) using a balloon design endorectal coil inflated with 50 ml of air. Hyoscine butyl bromide 20 mg was administered intramuscularly to reduce peristalsis. Conventional T2-weighted fast spin echo images were obtained transverse to the prostate and in the two orthogonal planes (FSE 2000/90 ms [TR/effective TE], echo train length 16, 2 signal averages, 20 slices) with a 256X512 matrix; 3mm slice thickness and a 14cm FOV (Fig. 1a, b). In addition, echo-planar diffusion-weighted sequences (DWI 2500/69 [TR/TE]) with b values of 0, 300, 500 and 800 sec/mm² in
three directions were performed transverse to the prostate. This provided an approximately linear spacing of $b$ values, and results in a better fit than using two-points only. The phase-encoding gradient was from left to right in order to minimize motion artifacts in the prostate. Twelve 4mm thick slices (20 cm FOV, matrix 128) provided coverage of the prostate with an image acquisition time of 1min 24secs. Apparent diffusion coefficient (ADC) maps using the combined multidirectional diffusion data were generated using the system software (Fig 1c).

Co-Registration of T2-weighted and diffusion-weighted images: Two sources of misregistration were identified: (i) incorrect determination of the resonance frequency by the scanner in some measurements led to a “rigid body” shift in the phase-encoding direction of the echo-planar images (left-right) (ii) susceptibility inhomogeneities resulted in irregular distortions, e.g. proximal to rectal wall at the air/tissue interface. In our analysis we corrected for the rigid body shift on the DW images in relation to the T2-weighted images by shifting the echo-planar images according to the amount of displaced centre of mass as measured from whole-gland outlines. An outline was drawn around the whole prostate gland on the middle slice of the T2-weighted images selected for the ROI placement. Another outline was drawn around the prostate on the corresponding DW echo-planar image ($b=0$). These outlines were overlaid as shown in Fig. 2a. Centre of mass was calculated for both outlines and relative shifts in the antero-posterior and left-right direction were calculated. The shift in the left-right direction (phase encoding) was used subsequently to align the T2-weighted images and the ADC maps (Fig. 2b). The susceptibility distortion had no preferred direction and was not corrected, but its magnitude was calculated based on residual perpendicular distance between outlines.
**Data Analysis:** Regions of interest (ROIs) were drawn on three consecutive slices of the T2-weighted scans around (1) 30 dominant nodules within the PZ that were low signal-intensity on T2-weighting with positive biopsies (median ROI size 41, quartiles 27, 64.5 mm$^2$), (2) the whole CG representing predominantly benign nodules (median ROI size 218, quartiles 168, 330 mm$^2$) and (3) non-malignant PZ where ipsilateral biopsies were all benign and no T2-W abnormality was identified (median ROI size 54.5, quartiles 43, 62.3 mm$^2$) by a radiologist experienced in endorectal prostate image interpretation (Fig 1b). The urethra was included on the whole CG ROIs as it represented <10% of the CG area and was often difficult to identify separately in larger glands. The measurement ROIs drawn on the T2-weighted images were then overlaid on the aligned ADC maps and mean ADC values obtained from the pixels in all of the 3 slices for each ROI type. This provided an ADC value for malignant PZ, CG and non-malignant PZ for individual patients. As detailed histological analysis of the CG was not available, and since the CG predominantly comprises nodules of benign prostatic hyperplasia (BPH), the ROI encompassing the whole CG was taken to represent benign prostatic nodules.

**Statistical Analysis:** The data was tested for normality using a Shapiro-Francia test. As data was normally distributed, differences in ADC between malignant PZ, CG and non-malignant PZ were calculated using independent samples t-tests and a p value of <0.05 was taken to be significant. A Receiver Operating Characteristic (ROC) curve also was constructed using SPSS (version 11.5 for Windows) and used to examine whether the ADC could be used to differentiate between malignant PZ nodules, CG (predominantly benign nodules) and non-malignant PZ.
RESULTS

Thirty malignant PZ lesions in 33 patients were identified (3 patients had no T2-weighted abnormality and no identifiable tumour on 8 biopsies). A total of 18 patients had all 3 or 4 biopsies from one side classified as no tumour without any associated T2-weighted abnormality (18 non-malignant PZ). One patient had concurrent mild prostatitis noted incidentally on histology.

On the echo-planar diffusion-weighted images, the “rigid body” shift was only in the phase-encoding (left-right) direction (Fig. 2a); this bulk shift was below 1.5mm in 70% of cases and in the range of 1.5-4.3mm in 30% of cases. A bulk shift of 0.11 - 4.28 mm (median 1.10 mm) corrected for the co-registration error. After correction for these rigid body shifts there was residual disagreement between echo-planar and T2-weighted prostate outlines of 1.2±0.5 mm due to susceptibility distortion (Fig 2b). As these were small and variable in direction it was considered unnecessary to attempt to further correction.

ADC values from malignant PZ were 1.30 ± 0.30 x 10^{-3} mm^2/sec (mean ± SD), from CG were 1.46 ± 0.14 x 10^{-3} mm^2/sec and from non-malignant PZ were 1.71 ± 0.16 x 10^{-3} mm^2/sec (Fig. 3). The differences between these regions were statistically significant (malignant PZ vs. CG p <0.01, malignant vs. non malignant PZ p <0.0001, non-malignant PZ vs. CG p <0.0001).

The sensitivity for identifying a malignant PZ nodule using different values for the ADC was plotted against (1-specificity). The area under this ROC curve (Az) indicates the accuracy of using the ADC to identify malignant PZ nodules; the closer
the value is to 1.0, the better the test. When comparing malignant PZ against non-malignant PZ, the Az was 0.89 and a cut-off ADC value of $1.6 \times 10^{-3}$ mm$^2$/s gave 86.7% sensitivity and 72.2% specificity for identifying malignant PZ lesions. When differentiating malignant PZ from CG (predominantly benign nodules), the Az for the ADC’s was 0.67. Using a cut-off ADC value of $1.39 \times 10^{-3}$ mm$^2$/s gave a sensitivity and specificity for the differentiation of malignant nodules from predominantly benign CG tissue of 60% and 76% respectively. Using the cut-off value of $>1.6 \times 10^{-3}$ mm$^2$/s as suggested by the ROC curve as an indicator of no tumour, 4 of 18 PZs classified as “normal” on T2-weighted imaging and biopsy would be recognized as malignant on diffusion-weighted imaging. ADC values in these 4 PZs ranged from 1.51-1.55 $\times 10^{-3}$ mm$^2$/s. Conversely 2 of 30 ROIs classified as “tumour” on T2-weighted imaging and biopsy would not be recognized as malignant on diffusion-weighted imaging. ADC values in these 2 PZs were 1.7 and $1.9 \times 10^{-3}$ mm$^2$/s and are likely to reflect a mixture of tumour and normal tissue within the ROI.
DISCUSSION

Our study shows that ADC values of malignant prostate nodules are significantly lower than in non-malignant prostate tissue and that based on ROC-curve analysis, ADC has potential to improve specificity for detecting malignant nodules. This supports the increasing evidence of the utility of diffusion weighted imaging in prostate cancer detection [15-19]. A previous study using ADC values to identify tumour in the peripheral zone resulted in an area under the ROC curve of 0.84 [20]. However, in that study a line-scan diffusion method was used that is not commonly available on commercial scanners, and absolute T2 values and proton density values were included in the classifier. In our study, we aimed to evaluate the use of echo-planar diffusion-weighted imaging, increasingly provided on clinical MR scanners, for identification of tumour in the prostate.

The mean ADC values of the malignant nodules obtained in this study correlates well with a previous report in which an endorectal coil was used [15], but not with data that was obtained with the use of a phased array coil only [16]. This is likely to be related to selection of regions of interest, rather than to differences in data acquisition. However, poorer signal-to-noise and increased volume averaging with use of a phased array coil, may also have an impact on the ADC analysis. Compared with the previous reports, the ROI size we used was greater. This has the advantage of including the whole of a heterogeneous tumour or benign nodule and avoids bias from radiologist selected ROIs. For evaluation of non-malignant regions where ROI placement is less critical, there is good agreement between our values and those of others [15;16]. In the 6 patients where contralateral tumours identified on biopsy did not correspond to low signal intensity nodules on the T2-weighted scans, foci of
restricted diffusion were visually noted in 2. It was not possible to obtain meaningful ADC values from these regions because of the likelihood of introducing bias in selecting ROIs on the ADC map. In order to obtain an accurate estimation of ADC from a region of tumour, registration of the ADC map with tumour ROIs drawn on whole-mount prostatectomy specimens is needed.

The prostate is composed of several regions of glandular and nonglandular tissue [21]. The non glandular fibromuscular stroma lies anteromedially. The glandular region is divided into three zones (peripheral, transition, central). The transition and central zones comprise the central gland, which is easily distinguishable from peripheral zone (which lies posteriorly and laterally) on T2-weighted MRI. Identification of the 30% of tumours that do not lie within the PZ is not possible on T2-weighting because of the normally low signal intensity of benign nodules and fibrous stroma in the transitional and central zones. We were therefore unable to include these tumours in our malignant ROI’s. Furthermore, the inclusion of some CG tumour within the whole CG ROI may have reduced the sensitivity of our results. Another limitation of this study is that malignant lesions not visible on T2-weighted images have not been included in the analysis. The error inherent in sampling on transrectal ultrasound guided biopsy would make it difficult to place regions of interest over a biopsy-positive location where there was no identifiable MR abnormality with any degree of certainty. As it was not possible to separate benign and malignant nodules within the CG or identify tumours not visible on T2-weighting without histological mapping of the whole-mount radical prostatectomy specimen, a further study to do this is warranted.
The glandular architecture of the normal prostate consists of small, round acini amid loosely woven, randomly oriented stroma. The epithelium is arranged in glands around a central lumen with intervening stroma made up of smooth muscle and fibrous tissue. Microscopically, BPH can involve both glands and stroma, though the former is usually more prominent. The glands are well-differentiated and still have some intervening stroma. In neoplasia, the glands of prostatic adenocarcinoma may be still recognizable as glands, but there is often little intervening stroma and the nuclei are hyperchromatic. These cellular and structural changes have a substantial impact on tissue water diffusion characteristics and on the diffusion-weighted image where image contrast is determined by the random microscopic motion of water protons. Apparent diffusion coefficients derived from these images thus reflect differences in water mobility and potentially can be used to separate nodules based on their cellularity. Malignant nodules are typically more cellular than the nodules of BPH, although there is significant heterogeneity in the latter where glandular BPH nodules, mixed BPH nodules, and stromal BPH nodules with different cellularity may all co-exist. In this study, use of a threshold value of $1.6 \times 10^{-3}$ for ADC could separate benign from malignant PZ with 86.7% sensitivity and 72.2% specificity. Our ADC measurements of tumour and prostate also may be overestimated because of perfusion weighting resulting from the inclusion of a $b$ value of 0. However, we would expect tumour ADC to be overestimated more than that of normal prostate given the greater blood flow rate and vascular volume of tumour [22]. Also, it was not possible to separately identify ADC values in regions of prostatitis, as there was only one patient in this cohort with this histology.
In pelvic imaging, where fast acquisition to ‘freeze’ bulk motion is of paramount importance, single-shot echo-planar sequences are favoured over turbo spin-echo sequences for diffusion-weighted imaging. The disadvantage of using single-shot turbo spin-echo sequences is the low signal-to-noise arising from long echo train length and long effective echo times. Echo-planar sequences also have their limitations and are prone to susceptibility-induced distortion, particularly in prostate imaging where air in the rectum or within the balloon of the endorectal coil causes significant local magnetic field inhomogeneity and susceptibility artefact. These susceptibility effects are much reduced when partially parallel acquisition methods (such as SENSE [23] are used owing to the reduced echo-train length [24]. The measured distortion on our images was only $1.2 \pm 0.5$mm for the boundary of the whole prostate, which is less than the pixel size of the echo-planar diffusion-weighted images, and the distortion of soft-tissue lesions within the prostate would be expected to be less than this. Any inadvertent inclusion of normal tissue within the ROI transferred to the ADC maps would tend to reduce the difference in mean ADC values of tumour, rather than lead to spurious significance. This, together with the unfavourable signal-to-noise ratio in single-shot turbo spin-echo diffusion-weighted images, resulted in our preference for the echo-planar approach.

In this study we opted to use endorectal balloon coils rather than a phased array surface coil as their sensitivity for signal detection compared to a phased array coil is superior up to 5 cm from the coil surface. This provided an adequate signal-to-noise ratio on diffusion-weighted echo-planar sequences whilst also allowing higher spatial resolution for tumour identification on T2-weighted images. Previous data has shown a signal-to-noise advantage of endocavitary coils over phased array coils up to 2 coil
diameters from the coil surface [25]. Unfortunately, endorectal coils are currently not commercially available in phased array versions to permit the use of parallel imaging. It is unlikely that the inflated endorectal coil had any significant influence on ADC values; any such effect would be symmetrical in the peripheral zone. Also the degree of coil inflation (55ml air) was identical in all patients reducing inter patient variability. Although it is possible to reduce susceptibility artefacts from air in the balloon by filling the balloon with perfluorocarbon or water, this requires a double balloon design, and was not possible in the single balloon design endorectal coil used in our study. In our experience patient tolerance for the endorectal procedure is relatively good particularly with short examination times (diffusion-weighted imaging 1.5 min, total examination time 17 min). In no case was the examination terminated or abandoned because of patient discomfort. Use of an endorectal coil in combination with a surface phased array coil would further improve signal detection but this is currently not available on our system.

In future, it may be possible to use DW-MRI as an adjunct to T2-weighted sequences as a diagnostic tool for improving sensitivity of prostate cancer detection. It would complement techniques such as MR spectroscopy and dynamic contrast-enhanced imaging which are increasingly used in tumour detection. It may also be valuable for characterization of highly cellular regions of tumours versus acellular regions, as well as for detecting treatment response, which is manifested as a change in cellularity within the tumour over time.
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REFERENCES


FIGURE LEGENDS

Fig. 1  Patient with prostate cancer: Malignant peripheral zone (PZ, arrows) identified as a low signal-intensity region on conventional T2-weighted image (a) with the low signal-intensity central gland (CG, arrowhead) and high signal-intensity non-malignant PZ (open arrow) clearly identified. Regions of interest outlining the malignant nodule, CG and non-malignant PZ are shown in (b). The malignant nodule is seen as focal area of restricted diffusion (arrow) on the apparent diffusion coefficient (ADC) map (c).

Fig. 2  Outlines of whole prostate gland drawn around the T2-weighted image (black) and corresponding diffusion weighted slice (grey). The outlines are overlaid to show degree of distortion before (a) and after (b) pixel shifting to correct for left-right distortions in the phase-encode direction.

Fig. 3  Box plot comparing ADC values in malignant peripheral zone (PZ), central gland (CG) and non-malignant PZ

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