EVALUATION OF THE POTENTIAL OF DWI IN PROSTATE CANCER DETECTION

Morgan VA, Kyriazi S, Ashley S, deSouza NM
ABSTRACT

Background: Conventional T2W imaging alone has a poor sensitivity for prostate cancer detection. This study therefore evaluated combined T2-W and diffusion weighted (DW)-MRI vs. T2-W MRI alone for identifying tumour in patients with prostate cancer.

Material and Methods: 54 consecutive patients with prostate cancer (46 Stage 1 and 2, 8 stage 3) and sextant biopsies within the previous 3 months were studied. Endorectal MR images were analysed by two radiologists (1 experienced, 1 trainee) blinded to patient information and histopathology. T2-W images were scored first, followed by combined T2-W and isotropic apparent diffusion coefficient (ADC) maps calculated from DW-MRI (b=0, 300, 500 and 800 s/mm²). Gland apex, middle and base for each side were scored negative, indeterminate or positive for tumour. Imaging data for each sextant were compared with histology. Sensitivity, specificity and inter-observer agreement were calculated.

Results: Sensitivity and specificity for tumour identification significantly improved from 50% and 79.6% (T2-W alone, experienced observer) to 73.2% and 80.8% (p<0.001). For the trainee observer there was no improvement (44.3% and 72% T2-W alone vs. 45.1% and 69.2% T2-W plus ADC maps). Inter-observer agreement was moderate for T2-W imaging alone (kappa 0.51), and fair for T2-W plus ADC maps (kappa 0.33).

Conclusion: In an experienced observer, DW-MRI together with T2-W imaging can significantly improve tumour identification in prostate cancer.

Key words: MR diffusion/perfusion, prostate, cancer, imaging
In the assessment of prostate cancer, imaging using conventional T2-W magnetic resonance imaging (MRI) with an external pelvic array coil has a good specificity (90%) but relatively low sensitivity (27.3%) for tumour detection (9). With the higher spatial resolution afforded by use of endorectal receiver coils, the sensitivity and positive predictive value for detection of tumour foci >1cm in diameter with T2-W MRI is relatively high (85.3% and 92.6%, respectively), but this falls dramatically to 26.2% and 75.9% when tumours <1cm diameter are considered (14). Knowledge of disease extent and distribution within the prostate would enable therapy to be tailored to these lesions particularly the use of newer therapeutic modalities such as cryoablation, high intensity focussed ultrasound (HIFU) and intensity modulated radiotherapy (IMRT). Use of MR spectroscopy in conjunction with MRI has improved accuracy for tumour detection in the gland (22), but is time consuming. Techniques such as dynamic contrast enhanced MRI also improve the accuracy of prostate cancer detection (8) but incur an additional intervention and cost.

Another mechanism for developing image contrast is through "apparent diffusivity" (the displacement of tissue water due to random, thermally driven motion over distances of ~1–20 µm) (13). The visualization of changes in the diffusion properties of tissue water with MR imaging has become a useful, multifaceted tool to characterize tissue structure and to identify and differentiate disease processes (1, 4, 5, 12). There are a few recent reports of the utility of diffusion-weighted MRI in prostate cancer where its role appears promising but has not been established (6, 7, 19). It is easy to implement with
short image acquisition times and availability of quantitative data using apparent diffusion coefficient (ADC) values. 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 ADC and, thus, the potential for high image contrast. Furthermore, the ADC values of malignant prostate nodules appear significantly lower than in non-malignant prostate tissue (3, 6, 19). The purpose of this study was therefore to compare the sensitivity and specificity of combined T2-W and diffusion-weighted MRI with T2-W imaging alone in the detection of prostate cancer in the peripheral zone and central gland by comparison with results of sextant biopsies.
MATERIALS AND METHODS

Patients: Patients were recruited prospectively and with the approval of the local research ethics committee. Fifty-six patients with elevated prostate specific antigen (PSA) and histology available from sextant biopsies (as is routine at local diagnostic units) within 3 months of MRI participated in the study. Biopsies targeted mainly the lateral part of the gland to predominantly include peripheral zone, as 70% of cancers arise here (11). In 37 cases, two additional biopsies one from each side were obtained from the mid-gland medially. In two patients with large glands the diffusion weighted imaging did not cover the gland, so it was not possible to correlate their imaging levels with the sextants biopsied. These patients were therefore excluded. In the 54 patients studied, age ranged from 52-80yrs (mean±sd, 67.6 ± 6.4yrs, median 68yrs) with a prostate specific antigen (PSA) 2.3-46 ng/ml (median 9.8, quartiles 6.95 and 14.6 ng/ml). The number of positive cores varied from 1-6 and Gleason grade varied from 6 to 8. Over the study period of 16 months, patients underwent diffusion-weighted sequence complementary to the routine MRI examination of the prostate. MRI was done between 1 and 90 days post biopsy. (median 15 days), as determined by clinical need. 17 patients underwent biopsy within 4 weeks following their MRI. All patients had a clinical stage less than or equal to T3N0M0. (T1=35, T2=11 and T3=8).

MRI: MR studies were performed on a 1.5T Intera (Philips Medical Systems, The Netherlands, gradient performance 30 mT/m 0.2 msec rise time) using a balloon design coil inflated with 55ml of air. Hyoscine butyl bromide was administered intramuscularly immediately prior to MRI to reduce peristalsis. We have found that it produces more effective antiperistalsis than other
agents (e.g. glucagon) and given intramuscularly at a dose of 20 mg does not cause urinary retention. Conventional T2-W fast spin echo images were obtained axial to the prostate and, for diagnostic purposes, in 2 further orthogonal planes sagittal and coronal to the prostate (FSE 2000/90 ms [TR/effective TE], echo train length 16, 6 averages) with a 256x512 matrix, 3mm slice thickness and a 14cm FOV. The axial images alone were used in the analysis. In addition, echo-planar diffusion-weighted sequences sensitized in 3 orthogonal planes (DWI 2500/69 [TR/TE], bandwidth 1860 Hz in the EPI frequency direction with b values of 0, 300, 500 and 800 sec/mm$^2$ were obtained at the same slice positions as the axial T2-W images. The phase encoding was left to right in order to minimise motion artefacts in the prostate. Twelve 4mm thick slices with no interslice gap (20cm FOV, matrix 128 X 128) provided coverage of the prostate with an image acquisition time of 1min 24secs. Isotropic apparent diffusion coefficient (ADC) maps were generated with the system software using all b values and taking an average value for the 3 directions of diffusion sensitization. After the endorectal coil was removed, T1- and T2-W axial images through the whole pelvis were obtained to ascertain the presence of lymphadenopathy. These images were required for clinical diagnostic purposes and did not form part of this study.

Image Analysis: The lower 4 slices covering the prostate on the transverse T2-W images (1.2cm slab, which corresponded to lower 3 slices on the ADC maps) were designated as gland apex, the upper 4 slices on the transverse T2-W images covering the prostate as gland base (1.2cm slab, which corresponded to upper 3 slices on the ADC maps); the slices between them were denoted as mid-gland. This division was arbitrary, but as all glands
included were entirely covered from apex to base within the 12 DW-MR slices, this division corresponded with the histological description. Images were analysed by two radiologists blinded to patient information and histopathology. Observer 1 was specialised in endorectal prostate MRI; observer 2 was a radiology trainee. Images were scored on a 3 point scale where 1 = negative for tumour, 2 = unsure and 3 = positive for tumour. The axial T2-W images were evaluated first, and then the T2-W + ADC maps were scored by simultaneously assessing the ADC maps in conjunction with the T2-W image at that level. A low signal-intensity lesion within the peripheral zone, or a homogenous low signal-intensity lesion with irregular borders and mass-effect within the central gland were considered positive for tumour on T2-weighted images, while these features in combination with a restricted diffusion on the ADC maps were considered positive for tumour on the T2-W + ADC maps.

Statistical analysis: Comparison of each sextant was done of the T2-W images alone with histology and the T2-W + ADC maps data with histology. Sensitivity and specificity, positive and negative predictive values were calculated and compared using a p value of <0.05 to denote statistical significance. A kappa value for interobserver agreement was calculated for T2-W imaging alone and T2-W + ADC maps.
RESULTS

In total, 324 sextant regions were assessed in 54 patients.

For observer 1 on T2-W imaging 108 regions were scored as tumour (score 3), 193 as non-tumour (score 1) while 23 regions were scored as unsure (score 2). On T2-W + ADC maps, observer 1 scored 139 regions as tumour, 176 as non-tumour and 9 as unsure. Thus, for observer 1, it was possible to assign 60.9% of the regions previously scored as unsure (14/23) to tumour or non-tumour categories based on the addition of the ADC maps. For observer 2 on T2-W imaging, 114 tumour lesions were noted (score 3), 201 regions were scored as non-tumour and 9 regions as unsure. On T2-W + ADC maps observer 2 scored 120 regions as tumour, 194 as non-tumour and 9 as unsure. For observer 2 there was no change in the number of lesions assigned to the unsure category with the addition of the ADC maps.

An example of tumour visible on T2-W imaging as well as on the ADC map is seen in Fig. 1, while the Figs. 2 and 3 show tumour detectable preferentially on the ADC map. Alternatively tumour may not be visualized by either technique (Fig. 4). In no case was the tumour seen on the T2-W image and not on the ADC map.

Sensitivity and specificity, positive and negative predictive values for T2-W imaging alone and T2-W + ADC maps are given for each observer in Table 1, with regions scored unsure being considered negative for tumour. There was an improvement in overall accuracy, sensitivity and specificity for observer 1 with the addition of ADC maps to the T2-W images. A breakdown of MR and
histology correlations by sextant for observer 1 is given in Table 2. This shows that the false positives and false negatives with T2-W techniques alone and with T2-W plus DW-MRI were evenly distributed amongst the sextants; the right apex appeared to have a marginally higher number of false negatives. Overall, 11 tumours were seen in the central gland, the remainder being in the peripheral zone.

Interobserver agreement for T2-W imaging alone was moderate (kappa =0.53) (Table 3) and better than for T2-W + ADC maps (kappa =0.334) (Table 4). This difference in interobserver agreement for T2-W alone compared to T2-W + ADC maps was statistically significant (p=0.001). The relatively low agreement for T2-W + ADC maps may be due to lack of familiarity of the untrained observer with the additional new technique.
DISCUSSION

This study shows the potential for improving sensitivity of prostate cancer detection with DWI in early stage disease as our sensitivity for tumour detection by an experienced reader improved from 46.5% to 71% on inclusion of the ADC maps in the evaluation. Other recent reports have also indicated the potential of DW-MRI in prostate cancer but its definitive role remains to be established. At 4.7 T improved prostate tumour detection in transgenic mice using diffusion-weighted imaging compared with T2 mapping has been demonstrated (21). In human in vivo studies, preliminary work on diffusion-weighted imaging of the prostate has shown differences between tissue types warranting clinical investigation (3, 6, 19), and a recent study of 60 patients showed that the addition of DWI to conventional T2-W imaging significantly improved tumour detectability (19).

On conventional T2-W imaging, prostate cancer is mainly recognized as a focal low signal-intensity lesion within the peripheral zone. However, such change also may arise as a result of inflammatory process within the gland (20). Furthermore, malignant lesions isointense with peripheral zone may not be distinguished as tumour. DWI which reflects thermally induced motion is likely to improve identification of tumour in these cases. The glandular normal prostate compared with the highly cellular regions encountered in prostate cancers which result in restricted diffusion within reduced intracellular and interstitial spaces produces a substantial differential in ADC and, thus, the potential for high image contrast. Despite this, there are some lesions that go undetected: in our study 2 patients had no visible lesions on MRI, one with 1 positive mid-gland sextants containing 10% Gleason 3+3 tumour and the
other with 1 positive core containing 15% Gleason 3+3 tumour (Fig 4). With
an experienced observer we identified 32 additional lesions with a combined
T2-W + DWI approach over T2-W imaging alone. The reproducibility of the
technique would have been better evaluated with two experienced observers,
although the experienced reader and the trainee showed moderate
agreement in their interpretation of the T2-W data. The DW-MRI unfamiliar to
both readers was more often correctly interpreted by the experienced
observer. This is likely due to a better understanding of the underlying
principles of the measurement technique by the experienced observer, and
an awareness of the limitations.

Apparent diffusion coefficients derived from DWI images reflect differences in
water mobility and potentially can be used to separate nodules based on their
cellularity. The ADC values of malignant prostate nodules appear
significantly lower than in non-malignant prostate nodules (3, 18). This has
particular implications for identifying the 30% of cancers that arise within the
central gland. 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. As with other studies, the majority of
lesions in this study were identified in the peripheral zone (PZ), where it is
known that 70% of tumours arise (2). Inclusion of central gland lesions is
likely to have reduced the sensitivity of the results because of overlap in the
appearance of the different types of BPH and malignant nodules on DWI (6,
18). Although the use of threshold values to discriminate tumour from non-
malignant tissue has been evaluated in some studies (7), we evaluated the
qualitative use of DW-MRI in a clinical reporting setting and used a simple visual scoring system. It is hoped that in future comparison of DWI with prostatectomy specimens will yield threshold values of ADC that enable differentiation of benign from malignant nodules, particularly in the central gland.

Conventionally, the term intravoxel incoherent motion (IVIM) is used in reference to the microscopic translations that occur in voxels on diffusion-weighted MR images (11), which includes the molecular diffusion of water and the microcirculation of blood (perfusion). Molecular diffusion is determined by the physical boundaries (cell membranes) encountered by mobile protons. Because of the pseudorandom organization of the capillary network at the voxel level, the microcirculation of blood, or perfusion, can also be considered to be an incoherent motion. IVIMs, quantified by the apparent diffusion coefficient (ADC), thus incorporates the effects of both diffusion and perfusion (10, 23). In *in vivo* tissues, reported ADCs have often had higher values than expected (11), which have been attributed to the microcirculation of blood in the capillaries. ADC values of the liver, spleen, kidney, pancreas, and muscle have been shown to be significantly higher than the true diffusion coefficient (D) values estimated with the IVIM theory for these organs (24) indicating the contribution of perfusion to the ADCs of the abdominal solid organs. In the prostate the ADC, D, and perfusion fraction (derived from endorectal single shot echo planar imaging (EPI) DWI with 11 b-values ranging from 0 – 800 s/mm² using two different models) cannot be derived adequately for central gland tissue using a 2-compartment model, but can be used to identify a perfusion component in the peripheral zone, where the true
diffusion coefficient is statistically different from the ADC (17). In the current study, ADC maps that included b=0 were analysed. Thus the effects of perfusion together with diffusion were included on the maps. ADC maps that excluded the b=0 value had a much poorer signal-to-noise ratio (SNR), hence were not used in the analysis. In future use of a b value of 100 would enable production of ADC maps that excluded the effects of perfusion while maintaining a more acceptable SNR for analysis.

For DW-MRI of the prostate, an endorectal coil is required to provide sufficient SNR at 1.5-T. Also, single-shot echo-planar sequences are favoured over turbo spin-echo sequences because of the need to freeze bulk motion. However, the susceptibility-induced distortion to which single-shot EPI is prone can be problematic 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. Our diffusion-weighted images were acquired with an EPI readout and led to some distortion at tissue boundaries where there was a discontinuity in magnetic susceptibility. In addition there was also sometimes a shift in the phase-encode direction owing to a slight offset of the water resonance frequency. We have previously quantified these distortions by comparing the images with standard T2-W spin-echo readout and established that this results in a maximum displacement of 1.2mm in the phase-encode direction (16). Advantages of an EPI sequence however are that it is possible to obtain 12 contiguous 4mm thick slices, giving a supero-inferior coverage of 4.8cm in 1.5min. In all but 2 of our cases this was sufficient to cover the prostate from apex to base. We found a 4mm slice thickness to be optimal because SNR reduction with
thinner slices made interpretation more difficult. In addition, thinner slices would require a greater slice number to cover the prostate, and at the TR used would effectively double acquisition time. Although this meant imperfect matching with the T2-W image slices, this had little effect on the visual comparison undertaken in this study.

We used isotropic ADC maps for our evaluation. A previous report investigating anisotropy within the prostate showed that diffusion in prostate tissue was anisotropic and consistent with the tissue architecture of the prostate fiber orientations namely predominantly in a superior-inferior direction for both the PZ and central gland (CG) (fractional anisotropy (FA) values for the PZ and CG were 0.46 +/- 0.04 and 0.40 +/- 0.08, respectively). However, we have shown in phantom studies that simulation of various noise levels and a plot of fractional anisotropy vs noise results in a continuous increase in fractional anisotropy with decreasing signal to noise. Thus observed fractional anisotropy may well be due to the effects of system noise (15).

Although always reading the T2-W images first potentially causes “sequential” reading bias, it was not possible to read the ADC maps out of context of the anatomical data. Reader variability was greater with the T2-W +DWI combination, indicating that for implementation of this new technique training is essential. Particularly with EPI sequences, artefacts across the prostate from susceptibility effects of neighbouring air may degrade image quality. Additionally, heterogeneity on the ADC maps at the base of the gland around the ejaculatory ducts is common, and likely to result in errors in
untrained observers. At this level where the prostatic base merges with the bladder wall, increased cellularity of normal tissue structure leads to a reduction in ADC values. Another source of error may arise due to blood products causing signal reduction on an EPI image. However, we only saw evidence of post-biopsy hemorrhage on the conventional pelvic T1- and T2-W images in 3 of 54 cases, whilst low signal-intensity from hemosiderin was not evident in any case.

The main limitation of this study is correlation of MRI with sextant biopsy rather than prostatectomy. In prostate biopsies, the apical portion of the gland (close to the penile pulp), the anterior parts of the central gland and the very base of the gland close to the urinary bladder, are regularly undersampled. Despite this limitation, this study shows that use of DW-MRI has diagnostic potential as an adjunct to T2-W sequences and would complement techniques such as MR spectroscopy and dynamic contrast-enhanced imaging which are increasingly used in tumour detection. Validation of these techniques with the results of prostatectomy is needed. DWI may also be valuable for characterization of highly cellular regions of tumours versus acellular regions, as well as for detecting treatment response, manifested as a change in cellularity within the tumour over time.

In conclusion, in an experienced observer, DW-MRI together with T2-W imaging can significantly improve tumour identification in prostate cancer. DW-MRI is routinely available on most MR systems and should be easy to implement as an addition to standard T2-W images. With a single-shot EPI technique, coverage of the whole gland incurs a time penalty of under 2 mins.
However, to achieve an adequate signal to noise ratio at 1.5-T an endorectal coil is required.

REFERENCES


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resonance imaging and $^1$H spectroscopy to increase accuracy in prostate cancer detection. Am J Roentgenol. 2007 Jan;188(1):91-8


### TABLES

**Table 1:** Sensitivity, Specificity, positive and negative predictive values for T2-W imaging alone compared to T2-W plus ADC map for each observer

<table>
<thead>
<tr>
<th></th>
<th>Observer 1</th>
<th>Observer 2</th>
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<tbody>
<tr>
<td></td>
<td>T2-W</td>
<td>T2-W + ADC map</td>
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<tr>
<td>Sensitivity %</td>
<td>50.0</td>
<td>73.2</td>
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<tr>
<td>Specificity %</td>
<td>79.6</td>
<td>80.8</td>
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<tr>
<td>Accuracy %</td>
<td>66.6</td>
<td>77.5</td>
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<td>PPV %</td>
<td>65.7</td>
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<tr>
<td>NPV %</td>
<td>67.1</td>
<td>79.5</td>
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**Table 2:** MRI and histology correlations by sextant for observer 1

<table>
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<th>R base</th>
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<tr>
<td>T2W MRI +</td>
<td>5</td>
<td>4</td>
<td>10</td>
<td>15</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>T2W MRI -</td>
<td>11</td>
<td>34</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>T2W&amp;DW-MRI +</td>
<td>5</td>
<td>8</td>
<td>12</td>
<td>14</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>T2W&amp;DW-MRI -</td>
<td>11</td>
<td>30</td>
<td>12</td>
<td>16</td>
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**Table 3:** Inter observer agreement for the presence of tumour between experienced (observer 1) and trainee (observer 2) for conventional T2-W imaging

<table>
<thead>
<tr>
<th>T2-W alone</th>
<th>Observer 2</th>
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<tr>
<td></td>
<td>+ve Tumour</td>
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<tr>
<td>Observer 1</td>
<td></td>
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<tr>
<td>+ve</td>
<td>76</td>
</tr>
<tr>
<td>-ve</td>
<td>27</td>
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Observed agreement = 78%

Kappa statistic = .511
Moderate agreement

**Table 4:** Inter observer agreement for the presence of tumour between experienced (observer 1) and trainee (observer 2) for conventional T2-W imaging together with apparent diffusion coefficient (ADC) maps

<table>
<thead>
<tr>
<th>T2-W plus ADC maps</th>
<th>Observer 2</th>
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<tbody>
<tr>
<td></td>
<td>+ve Tumour</td>
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<tr>
<td>Observer 1</td>
<td></td>
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<tr>
<td>+ve</td>
<td>78</td>
</tr>
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<td>-ve</td>
<td>56</td>
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Observed agreement = 68.2%

Kappa statistic = .333
Fair agreement
FIGURE LEGENDS

Fig. 1 Focal prostate cancer within the peripheral zone (PZ) on T2-W imaging, diffusion-weighted imaging and on apparent diffusion coefficient (ADC) map: On conventional T2-W image (A, FSE 2000/90 ms [TR/effective TE]) a low signal-intensity lesion representing tumour within the PZ (arrows) is seen. High signal-intensity non-malignant PZ is clearly identified on the opposite side. The malignant nodule is seen as focal area of restricted diffusion (arrows) on the diffusion-weighted image (B, b=800 sec/mm$^2$ and on the ADC map (C, constructed using b values 0, 300, 500 and 800 sec/mm$^2$). Histology from this sextant confirmed malignancy.

Fig. 2 Focal prostate cancer within the peripheral zone (PZ) on diffusion weighted imaging and on apparent diffusion coefficient (ADC) map only: On conventional T2-W image (A, FSE 2000/90 ms [TR/effective TE]) the tumour at the gland apex on the right is not identified. However, it is clearly seen as an area of restricted diffusion (arrows) on the diffusion-weighted image (B, b=800 sec/mm$^2$ and on the ADC map (C, constructed using b values 0, 300, 500 and 800 sec/mm$^2$). Histology from this sextant confirmed malignancy.

Fig. 3 Focal prostate cancer within the central gland (CG) shown on T2-W imaging, diffusion-weighted imaging and on apparent diffusion coefficient (ADC) map: The CG is lower in signal-intensity than the peripheral zone (PZ) on the conventional T2-W image (A, FSE 2000/90 ms [TR/effective TE]) and an ill-defined bulge is seen anteriorly on the left (arrow). This nodule shows marked restriction of diffusion (arrows) on the diffusion-weighted image (B,
b=800 sec/mm²) and on the ADC map (C, constructed using b values 0, 300, 500 and 800 sec/mm²). Histology from this sextant confirmed malignancy.

**Fig. 4** *Focal prostate cancer on histology not identified on T2-W imaging or apparent diffusion coefficient (ADC) map:* On conventional T2-W image (A, FSE 2000/90 ms [TR/effective TE]) there is no focal abnormality within the prostate at the mid-gland level, nor was there evidence of diffusion restriction on the ADC map (B, constructed using b values 0, 300, 500 and 800 sec/mm²). Histology showed a positive core with 15% tumour within the right mid-gland sextant.

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