Threshold-based parametric analysis of diffusion-weighted magnetic resonance imaging at 3.0 Tesla to identify men with prostate cancer

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Abstract: The aim of this study is to determine the accuracy of three apparent diffusion coefficient (ADC) threshold values in detecting prostate cancer (PCa) prior to prostate biopsy. Sixty men with clinical suspicion of PCa underwent endorectal diffusion-weighted magnetic resonance imaging (DW-MRI) at 3.0 Tesla (T). Three ADC threshold values (tADC: 1.0, 1.2 and 1.4 × 10⁻³ mm²/s) were sequentially applied to ADC maps for the detection of malignant lesions in the prostatic peripheral zone (PZ). Segment-based and patient-specific PCa detection performance of these tADC values was correlated with the histopathological results from the subsequent 12-core transrectal ultrasound (TRUS)-guided biopsy. Mean of ADC and area size of the identified malignant region of interests (ROIs) were recorded. Accuracy for PCa detection was assessed by receiver operating characteristic curves. 1.0 × 10⁻³ mm²/s of tADC provided 79% sensitivity, 97% specificity and 93% positive predictive value for PCa. Area size of the malignant ROI was a good independent factor for PCa detection (Area under curve, AUC = 0.85). ROI area size 0.2 cm² was identified as the best performing cut-off values for the detection of PCa. Refined detection criteria combining area size ≤0.2 cm² and ADC <1.0 × 10⁻³ mm²/s increased the detection performance. In conclusion, threshold-based parametric evaluation of DW-MRI at 3.0 T can detect PZ PCa accurately prior to biopsy.

Keywords: diffusion-weighted magnetic resonance imaging (DW-MRI); prostatic neoplasm; early detection of cancer; receiver operating characteristic (ROC) curve; histology


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Prostate cancer (PCa) patients are treated with a risk-adjusted patient-specific method that is designed to improve the control of cancer while reducing the risk of treatment-related effects. There is a growing demand for individualized treatment plans, which necessitates the accurate characterization of the location, extent and aggressiveness of the tumor[1]. By following the European Association of Urology Guidelines, diagnosis of PCa is based on transrectal ultrasound (TRUS)-guided biopsy performed in patients with either an elevated prostate specific antigen (PSA) and/or an abnormal clinical examination (digital rectal examination.

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However, only 25%–30% of men with a moderately elevated PSA (4–10 ng/mL) have prostate cancer confirmed at biopsy and therefore many biopsies may ultimately prove unnecessary[3]. In order to reduce the unnecessary biopsy rate, new clinical tools and strategies are required. There has been a great interest in determining the presence or absence of tumor non-invasively with combined anatomical and functional magnetic resonance imaging (MRI)[4].

MRI is well-validated for local staging of PCa using qualitative assessment, including high-resolution T2-weighted (T2W) images once the diagnosis has been established by TRUS biopsy[5]. The combination of T2W imaging and functional techniques have also been proposed for detection purpose[6]. Amongst the three functional parametric techniques available, diffusion-weighted (DW)-MRI has substantial advantages over the other two, i.e., dynamic contrast enhanced-MRI and magnetic resonance spectroscopy (MRS), because it does not require intravenous contrast and is relatively simple to implement. The software also generates apparent diffusion coefficient (ADC) maps. Variations in cellular structure between benign and malignant tissue manifest as differences in water diffusion. These differences can be exploited to improve PCa detection either qualitatively or quantitatively by measuring changes in ADC to potentially measure the aggressiveness of the tumor[7].

There is a poor agreement on the value of 3.0 Tesla (T) over 1.5 T, the use of an endorectal coil (ERC), image acquisition parameters and data processing[8]. Other unresolved issues include variations in the appearance of different parts of the prostate on T2W imaging, inhomogeneous diffusion characteristics within different parts of the prostate, particularly at the prostatic base where increased cellularity may result in area-specific ADC values and the absence of an absolute cut-off value differentiating benign from malignant tissue[5]. Finally, the relevance of abnormalities detected on DW-ADC maps in treatment algorithms either in the absence of proven tumor on TRUS or in patients with low Gleason score on biopsy remains controversial.

ADC maps are readily used for the parametric analysis of DW-MRI, although the diffusion characteristics within the prostate are inhomogeneous[9]. No consensus exists for the cut-off ADC value differentiating benign from malignant prostate tissue and factors such as increased cellularity at the prostatic base which result in area-specific ADC values must be considered[10]. ADC values below $1.0 \times 10^{-3}$ mm$^2$/s[10-14], $1.2 \times 10^{-3}$ mm$^2$/s[15] and $1.4 \times 10^{-3}$ mm$^2$/s[16,17] have all been correlated to the presence of PCa. In this study, we evaluated the objective parametric assessment of ADC maps acquired at 3.0 T using these three predetermined cut-off levels to determine whether ADC values could independently predict presence or absence of tumor as compared to TRUS biopsy.

**Materials and methods**

**Study design**

60 consecutive patients with clinical suspicion of PCa (abnormal screening of PSA/DRE) were recruited in this study based on the Institutional Review Board protocol (Table 1). Exclusion criteria included a history of PCa, previous prostate biopsy and standard contraindication to MRI. After informed and written consent, patients underwent DW-MRI at 3.0 T with an ERC. All patients had 12-core TRUS-guided biopsy within one week of MRI without knowledge of the imaging results. Image analysis and histological assessment were carried out independently.

**Biopsy technique and histopathological interpretation**

Two 15 mm cores were taken from each of 6 peripheral zone (PZ) segments (base, mid-gland and apex on each
side) using a standard TRUS approach. Cores were processed, analyzed and reported according to the international guidelines [18]. The final pathological report (standard institutional report) documented histological findings according to where the cores were taken from.

Image acquisition

All MRI scans were performed on a Philips Achieva 3.0 Tesla scanner (Philips Medical Systems) using a 6-channel surface coil placed on the lower abdomen in combination with a disposable ERC (Medrad Inc.), inflated with a 100% (w/v) barium sulphate suspension. High-resolution T2W images of the prostate and seminal vesicles were acquired in 3 planes while DW images were acquired in axial orientation using 6 b-values (0, 50, 150, 300, 500 and 800) (Table 2). ADC maps were generated automatically with the manufacturer’s software using all b-values except b = 0, to avoid perfusion-related effects. Scan-time for T2W and DW-imaging was 10 and 6 minutes, respectively.

Data processing

Parametric analysis was performed on a dedicated workstation using OsiriX image processing software (Version 3.9.1). The prostate was virtually divided into six segments: (base, mid gland and apex bilaterally) to match the segment-based biopsy sampling procedure. Figure 1 shows the image for each step of the data analysis process. The peripheral and transition zone as identified on T2W axial image within each segment (Figure 1A) was manually delineated (Figure 1B). Threshold ADC (tADC) values of 1.0, 1.2 and 1.4 × 10⁻³ mm²/s were sequentially applied to the delineated region (central zone excluded). All pixels with values above tADC were removed from the image. Remaining pixels with an ADC at or below tADC were evaluated as a ROI for a candidate malignant lesion and that segment was labeled as “DW malignant” (Figure 1C). When ROIs overlapped two (or more) segments, both (or all) were reported as “DW malignant”. Segments within which no pixels at or remained below threshold values were labeled as “DW benign”.

Prostate cancer detection performance

The results of DW-MRI based assessment of segments as “DW malignant” or “DW benign” were compared to the histopathological report for this segment obtained at biopsy. “DW malignant” segments correlating with a positive biopsy result were considered as truly malignant. “DW benign” segments correlating with a negative biopsy result were considered as truly benign. The ability of DW-MRI in detecting PCa was analyzed in two ways: 1) segment-by-segment (6 segments per patient, N = 360), and 2) patient-by-patient (N = 60). Patients with at least one DW malignant segment were labeled as having PCa. For each analysis, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for the detection of PCa were calculated for each tADC value. Accepting the biopsy result as gold standard, a receiver operating characteristic (ROC) curve analysis was performed to evaluate the accuracy of PSA alone and each tADC value in detecting PCa.

ROI for candidate malignant lesions

Location, area size, mean ADC and standard deviation of ROI identified as candidate malignant lesions at each tADC were recorded. Mean ADC and area size values were compared between truly malignant and benign segments (Mann-Whitney test). Mean ADC values were correlated to Gleason score (Pearson correlation). An ROC curve analysis was performed to evaluate the accuracy of ROI area size in detecting PCa. The best cut-off value was determined by identifying the largest sensitivity and specificity product value obtained from each ROC curve.

Refined detection criteria

The best performing tADC and best cut-off value for ROI area size were combined to define the refined detection criteria. These criteria were retrospectively applied to evaluate their performance in PCa detection. Sensiti-

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Repetition time (msec)</th>
<th>Echo time (msec)</th>
<th>Field of view (mm)</th>
<th>Recon resolution (mm)</th>
<th>Flip angle (degrees)</th>
<th>Slice thickness (mm)</th>
<th>Inter-slice gap (mm)</th>
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</thead>
<tbody>
<tr>
<td>T2-W TSE</td>
<td>3831</td>
<td>110</td>
<td>140</td>
<td>0.2 × 0.2 × 3.00</td>
<td>90</td>
<td>3.00</td>
<td>0</td>
</tr>
<tr>
<td>Axial</td>
<td>4540</td>
<td>110</td>
<td>140</td>
<td>0.2 × 0.2 × 3.00</td>
<td>90</td>
<td>3.00</td>
<td>0</td>
</tr>
<tr>
<td>Sagittal</td>
<td>4951</td>
<td>110</td>
<td>140</td>
<td>0.2 × 0.2 × 3.00</td>
<td>90</td>
<td>3.00</td>
<td>0</td>
</tr>
<tr>
<td>Axial DW-MRI</td>
<td>3746</td>
<td>69</td>
<td>160</td>
<td>1.1 × 1.1 × 2.73</td>
<td>90</td>
<td>2.73</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2 MRI parameters

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Figure 1 Representative image for each step of the data analysis process. (A) T2-weighted axial image for anatomical identification of the peripheral zone; (B) corresponding apparent diffusion coefficient (ADC) map and outline of the peripheral zone; (C) pixel values above the applied $1.0 \times 10^{-3}$ mm$^2$/s tADC appear black on the ADC map, leaving the outline of a potentially malignant lesion; (D) representation of the superimposed lesion area identified at each ADC threshold (tADC) value.

Statistical analysis

Statistical analysis was performed using Prism, Version 5.01 (GraphPad Software Inc. CA). A $p$ value of <0.05 was considered statistically significant. Data presented as mean ± standard deviation.

Ethics statement

This study received ethical approval from our institution.

Results

Identification of malignant segments

We first analyzed the ADC maps of each generated segment (6/patient, $N = 360$) for the presence of pixels with ADC values below the applied tADC and identified a total of 86 DW malignant segments. The progressive inclusion of pixels with higher ADC values through increased tADC improved the sensitivity for the identification of histologically-confirmed (truly) malignant segments (79% at $1.0 \times 10^{-3}$ mm$^2$/s; 91% at $1.2 \times 10^{-3}$ mm$^2$/s; 98% at $1.4 \times 10^{-3}$ mm$^2$/s) but was associated with loss of specificity (97% at $1.0 \times 10^{-3}$ mm$^2$/s; 89% at $1.2 \times 10^{-3}$ mm$^2$/s; 71% at $1.4 \times 10^{-3}$ mm$^2$/s) (Table 3). The lowest tADC of $1.0 \times 10^{-3}$ mm$^2$/s yielded the best PPV (79%), while the NPV was high for all three values ($1.0 \times 10^{-3}$ mm$^2$/s: 94%; $1.2 \times 10^{-3}$ mm$^2$/s: 97%; $1.4 \times 10^{-3}$ mm$^2$/s: 99%). Accuracy was the highest at $1.0 \times 10^{-3}$ mm$^2$/s (93%). The detection performance was not influenced by the segment location (Chi-square, $p = 0.79$). The ROIs identified in DW malignant segments were next analyzed. The ROIs mean ADC values were significantly lower in DW malignant segments correlating with a positive
Table 3 Segment-based prostate cancer detection performance of the ADC threshold value

<table>
<thead>
<tr>
<th>Biopsy-positive</th>
<th>ADC threshold value (× 10⁻³ mm²/s)</th>
<th>DW malignant</th>
<th>DW benign</th>
<th>DW malignant</th>
<th>DW benign</th>
<th>DW malignant</th>
<th>DW benign</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>68 (Truly malignant)</td>
<td>18</td>
<td>78 (Truly malignant)</td>
<td>8</td>
<td>84 (Truly malignant)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>78 (Truly malignant)</td>
<td>8</td>
<td>244 (Truly benign)</td>
<td>80</td>
<td>194 (Truly benign)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>84 (Truly malignant)</td>
<td>2</td>
<td>194 (Truly benign)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Sensitivity      | 79% (68/86)                        | 91% (78/86) | 98% (84/86) |
| Specificity      | 97% (266/274)                      | 89% (244/274) | 71% (194/274) |
| Positive predictive value | 89% (68/76) | 72% (78/108) | 51% (80/164) |
| Negative predictive value | 94% (266/284) | 97% (244/252) | 99% (194/196) |
| Accuracy         | 93% (334/360)                      | 89% (322/360) | 77% (278/360) |

Figure 2 Receiver operating characteristic (ROC) curve for the identification of truly malignant segments following apparent diffusion coefficient threshold values (tADC) analysis at 1.0, 1.2 or 1.4 × 10⁻³ mm²/s tested by different cut-off points of (A) the mean ADC value and (B) the area size of the identified candidate malignant lesion region of interest (ROI). The ROC curve for prostate specific antigen (PSA) is provided for comparison. Area under curve (AUC) values are provided.

biopsy (truly malignant segment) than those correlating with a negative biopsy (truly benign segment) at 1.2 and 1.4 × 10⁻³ mm²/s (Mann-Whitney; p < 0.0001) but not at 1.0 × 10⁻³ mm²/s (p = 0.23). ROC curves showed increasing performance for detection of PCa with increasing tADC value. Detection performance was higher than that of PSA (Figure 2A). The area under the curve (AUC) were 0.63 (p = 0.22), 0.83 (p < 0.001) and 0.89 (p < 0.001) at 1.0, 1.2 and 1.4 × 10⁻³ mm²/s, respectively, compared to 0.54 (p = 0.56) for PSA. Mean ADC values were furthermore significantly correlated with Gleason scores 6–8 (3 + 3, 3 + 4, 4 + 3, 4 + 4) at 1.0 × 10⁻³ mm²/s (r = −0.9792, p = 0.0208) and 1.2 × 10⁻³ mm²/s (r = −0.9819, p = 0.0100) but not at 1.4 × 10⁻³ mm²/s (r = −0.9545, p = 0.1900) (Figure 3). Significant differences in mean ADC values between the Gleason scores were noted at all threshold values (Mann-Whitney, p < 0.01) but the Gleason score specific ADC values could not be established. Similarly, the ROIs area sizes measured at each tADC value were significantly larger in DW malignant segments correlating with a positive biopsy (truly malignant segment) than those correlating with a negative biopsy for tADC of 1.2 and 1.4 × 10⁻³ mm²/s (Mann-Whitney; p < 0.0001) but not 1.0 × 10⁻³ mm²/s (p = 0.2328) (Table 4). ROI area size demonstrated a good diagnostic performance (Figure 2B), with an AUC of 0.85 (p = 0.001) at 1.0 × 10⁻³ mm²/s, 0.88 (p < 0.001) at 1.2 × 10⁻³ mm²/s and 0.87 (p < 0.001) at 1.4 × 10⁻³ mm²/s.
Detection of prostate cancer in men

We re-analyzed the data on a patient-specific basis (N = 60). The sensitivity for the detection of PCa was high at all three tADC values (94% at 1.0 × 10^{-3} mm²/s; 94% at 1.2 × 10^{-3} mm²/s; 100% at 1.4 × 10^{-3} mm²/s) but specificity was lost with increasing threshold value (98% at 1.0 × 10^{-3} mm²/s; 70% at 1.2 × 10^{-3} mm²/s; 26% at 1.4 × 10^{-3} mm²/s) (Table 5). The tADC of 1.0 x 10^{-3} mm²/s had the highest specificity (98%), PPV (94%), NPV (93%) and accuracy (92%).

Detection performance of refined detection criteria

We finally examined the combination of ROI size and tADC of 1.0 × 10^{-3} mm²/s since this tADC provided the best balance between sensitivity and specificity, PPV, NPV and accuracy to determine whether the detection criteria for PCa could be refined. Further analysis of the ROC for ROI area size identified 0.20 cm² as the best cut-off area size value for the detection of PCa (sensitivity 79.5%; specificity 93.3%; likelihood ratio 11.92). Applying these values (ADC value <1.0 × 10^{-3} mm²/s with area size <0.20 cm²) as a refined PCa detection criteria in our cohort, we achieved a sensitivity of 88.3% (76/86), specificity of 93.3% (272/274), PPV of 97% (69/71) and NPV of 94% (272/289) in segment-based analysis. On patient-specific analysis, these refined detection criteria had a sensitivity of 96.6% (31/33), specificity 88% (24/27), PPV 82% (23/28) and NPV 86% (24/28).

Table 4 Mean apparent diffusion coefficient (ADC) and area size of the region of interest (ROI) of the candidate malignant lesions detected at each threshold level

<table>
<thead>
<tr>
<th>ADC threshold value (× 10^{-3} mm²/s)</th>
<th>1.0</th>
<th>1.2</th>
<th>1.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC All</td>
<td>0.9 ± 0.22</td>
<td>0.98 ± 0.16</td>
<td>1.16 ± 0.17</td>
</tr>
<tr>
<td>Biopsy-positive (Truly malignant)</td>
<td>0.80 ± 0.22</td>
<td>0.94 ± 0.16</td>
<td>1.05 ± 0.16</td>
</tr>
<tr>
<td>Biopsy-negative</td>
<td>0.88 ± 0.12</td>
<td>1.09 ± 0.08</td>
<td>1.27 ± 0.10</td>
</tr>
<tr>
<td>p value (Mann-Whitney)</td>
<td>p = 0.2328</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Area size</td>
<td>0.35 ± 0.35</td>
<td>0.50 ± 0.44</td>
<td>0.59 ± 0.49</td>
</tr>
<tr>
<td>Biopsy-positive (Truly malignant)</td>
<td>0.38 ± 0.36</td>
<td>0.63 ± 0.46</td>
<td>0.87 ± 0.51</td>
</tr>
<tr>
<td>Biopsy-negative</td>
<td>0.096 ± 0.07</td>
<td>0.16 ± 0.08</td>
<td>0.30 ± 0.25</td>
</tr>
<tr>
<td>p value (Mann-Whitney)</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

The mean ± SD were calculated for all tumor regions identified and for those correlating with biopsy-positive and biopsy-negative regions. A Mann-Whitney test was used to compare the mean values between biopsy-positive and biopsy-negative regions.
Table 5 Patient-based prostate cancer detection performance of the apparent diffusion coefficient (ADC) threshold value

<table>
<thead>
<tr>
<th>ADC threshold value (× 10^{-3} m^2/s)</th>
<th>Biopsy-positive</th>
<th>Biopsy-negative</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Accuracy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>1.0</td>
<td>1.2</td>
<td>1.4</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>2</td>
<td>30</td>
<td>2</td>
<td>32</td>
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<td>32</td>
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<td></td>
<td>2</td>
<td>25</td>
<td>8</td>
<td>19</td>
<td>20</td>
<td>7</td>
<td>20</td>
</tr>
</tbody>
</table>

Sensitivity: 94% (30/32) 94% (30/32) 100% (32/32)
Specificity: 98% (25/27) 70% (19/27) 26% (7/27)
Positive predictive value: 94% (30/32) 79% (30/38) 62% (32/52)
Negative predictive value: 93% (25/27) 90% (19/21) 100% (7/7)
Accuracy: 92% (55/60) 82% (49/60) 65% (39/60)

Discussion

Current screening and diagnostic tools for PCa have imperfect profiles and may result in men being both under- and over-diagnosed\[^{4}\]. A reliable, non-invasive and robust diagnostic tool such as MRI could potentially benefit men with suspected PCa\[^{19,20}\]. As the majority of significant PCas are visible on DW, potential roles include selection of a suitable area for biopsy and incorporation into an image-guided approach where registration of real-time TRUS images with MRI data allows accurate needle placement, thus eliminating the randomness of TRUS-guided biopsy and increasing the likelihood of positive biopsy\[^{21–23}\]. Although qualitative interpretation of DW images is useful, subjective and has a significant inter-observer variability, it cannot be applied to predict tumor grade\[^{17,24}\]. On the other hand, ADC values generated from multiple b-values give an objective measurement of tissue diffusion and are a surrogate for tumor aggressiveness\[^{5,25}\]. The values broadly change inversely with Gleason score and the trend is lower in higher stage of disease, although there are some overlaps between benign and malignant tissue\[^{5,25,26}\].

Gains in sensitivity with higher tADC values would be expected to be offset by lower specificity and a balance between these outcome parameters is required. To address these issues, we applied three sequential ADC threshold levels (tADC of 1.0, 1.2 and 1.4 × 10^{-3} mm^2/s) in 360 segments across 60 patients to determine whether quantitative assessment at 3.0 T could identify malignant lesions within the prostatic PZ prior to prostate biopsy. At 1.2 × 10^{-3} mm^2/sec, the sensitivity and specificity for cancer detection was 91% and 89%, respectively, with a negative predictive value of 97% for segment-based analysis. For patient-specific analysis, the sensitivity and specificity were 94% and 70%, respectively. While tADC of 1.2 × 10^{-3} mm^2/s gives excellent cancer detection, a significant number of segments with ADC values below this value would be correlated with a negative biopsy.

Potential reasons include overlap of ADC values for tumors and other pathological processes conditions which are also known to restrict diffusion (e.g., chronic inflammation, hyperplasia and calcification)\[^{1,27}\]. Potentially, sampling error due to the random nature of TRUS biopsy could in part account for this overlap, a factor that has been cited in favor of using MRI to not only identify potential tumors in high risk patients with negative biopsy results but also to guide subsequent biopsy. We also observed that optimal parametric DW-MRI interpretation benefits from the combination of both the mean ADC value and the minimum lesion size. The measurement of the diameter of suspicious tumor lesions on DW-MRI was indeed proposed as an important parameter to consider for the prediction of insignificant PCa\[^{28}\]. ROC analysis identified an ROI area size of 0.20 cm^2 as the best cut-off for the detection of PCa. Combination of this value with a tADC of 1.0 × 10^{-3} mm^2/s into a refined detection criteria increased specificity (89% to 99%) and PPV (72% to 97%), albeit at the expense of a slight decrease in both sensitivity and NPV. We observed a significant negative correlation between Gleason score and mean ADC values at all tADC values. While we were unable to determine Gleason score specific ADC values, we observed unexpected mean ADC values in Gleason 9 biopsies (N = 5), which was higher than that of Gleason 8 lesions, though the small patient numbers preclude a meaningful comparison.

Neither the distribution of tumor within segments nor detection performance was statistically different across the 6 prostate segments in our study. Apparently, they differ from few published studies where the prostatic
base was associated with higher false positive rates\textsuperscript{29}. This may be explained by the higher spatial resolution afforded by 3.0 T imaging, especially with an ERC, which may make definition between prostatic and surrounding tissue less challenging. It also suggests that DW-MRI identifies PZ PCa with a high degree of accuracy independent of tumor location.

Our study has several limitations. We traded the ease of dual-functional sequence MRI without an ERC for a single functional study acquired with an ERC at 3.0 T with the knowledge that it would require additional set-up and physician time, increased cost and some discomforts which might not sit well with screening program philosophy. In the absence of controlled trials and based on the best available information, an advisory group of the European Society of Urogenital Radiology (ESUR) drafted consensus recommendations for screening of PCa with MRI. Faced with differences between centers such as field strength, use of an ERC, use of dynamic contrast-enhancement and spectroscopy, they recommended multi-parametric MRI techniques incorporating two functional techniques (DW-MRI, DCE or spectroscopy) in addition to T2W imaging for screening of PCa. Although the ERC clearly boosts signal, the consensus group noted that the use of an ERC was not essential at 3.0 T due to the signal boost from the higher field strength. Nonetheless, we opted to place an ERC to maximize signal-to-noise in this study in order to compensate for the fact that we adopted a single functional study only (DW-MRI). Although the cost and inconvenience of an ERC are significant, our approach of T2W imaging plus a single functional (DW-MRI) sequence at 3.0 T is simple and can be readily implemented into clinical algorithms, with the longer preparation time and cost of the coil offset by shorter and less complex examination shall avoid the use of contrast agent and spectroscopy which normally require complex post-processing.

While the performance of parametric DW-MRI was robust, our results must be interpreted within the known limitations of 12-core biopsy, which may underestimate the Gleason score in up to 29\% of cases\textsuperscript{30} and the modest number of patients included in this study. Like most previous studies, our study did not address central gland (central zone) tumors which account for up to 30\% of all PCa, however, as TRUS biopsy routinely targets the peripheral gland we were bereft of a reference standard for the central zone\textsuperscript{11}. Image and data processing using this objective parametric analysis technique was modestly time-consuming which may hinder its application in routine clinical care. Further evaluation of the constraints associated with this approach is necessary. In the future, automatic color-look-up-tables corresponding to specific ADC values could be developed providing acquisition parameters (field strength, b-values use of specific coils) are standardized\textsuperscript{32}. This would aid rapid, objective image review and facilitate rapid identification of malignant lesions by virtue of their ADC values alone or alongside qualitative analysis.

**Conclusion**

We have shown that parametric DW-MRI at 3.0 T can objectively detect tumor prior to TRUS-guided prostate biopsy. The high NPV of 94\% at $1.0 \times 10^{-3}$ mm$^2$/s adds further the weight supporting of a DW-MRI role in detecting PCa. Despite its limitations, it is considerably more accurate than PSA alone and a promising tool for not only the screening of peripheral zone PCa but potentially also for characterizing its aggressiveness. This concept is particularly important in the context of over-diagnosis and over-treatment of clinically insignificant cancers. However, large-scale adequately powered randomized and standardized studies are needed to determine whether Gleason score specific ADC values can be established. If this could be achieved, incorporation of ADC values into a diagnostic algorithm in combination with other clinical parameters (such as PSA and DRE) might ultimately allow low-risk patients to forego biopsy. Additionally, patients undergo a policy of active surveillance who observed declination in the ADC values baseline during serial follow-up might signal an imperative for change to active treatment.

**Author contributions**

Diarmuid C Moran collected the data and together with Laure Marignol conducted the data analysis. Andrew J Fagan developed the image acquisition protocols. Eoin Gaffney conducted pathological assessments. Ruth Dunne, Dearbhaill O’Driscoll and James FM Meaney conducted radiological assessments. All the authors were involved in study design and the construction of the patients’ cohort.

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Conflict of interest

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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