DWI and PRECISE criteria in men on active surveillance for prostate cancer: a multicentre preliminary experience of different ADC calculations

Abstract

Purpose: The PRECISE score estimates the likelihood of radiological progression in patients on active surveillance (AS) for prostate cancer (PCa) with serial multiparametric magnetic resonance imaging (mpMRI). A PRECISE score of 1 or 2 denotes radiological regression, PRECISE 3 indicates stability and PRECISE 4 or 5 implies progression.

We evaluated the inter-reader reproducibility of different apparent diffusion coefficient (ADC) calculations and their relationship to the PRECISE score.

Material and methods: Baseline and follow-up scans (on the same MR systems) of 30 patients with visible lesions from two different institutions were analysed by two radiologists. The PRECISE score was initially assessed in consensus. At least six weeks later, to reduce the likelihood of being influenced by the consensus PRECISE reading, each radiologist independently calculated ADC for the following: lesion, non-cancerous tissue and urine in the bladder. Normalised ADC ratios were calculated with respect to normal prostatic tissue (npADC) and urine. Spearman's correlation (ρ), intraclass correlation coefficients (ICC), differences in ADC and ROC curves were computed.

Results: Interobserver reproducibility was very good ($\rho > 0.8$; ICC > 0.90). Lesion ADC (0.91 vs 0.73 $\times$ 10^{-3} mm^2/s; p=0.025) and npADC ratio (0.68 vs 0.53; p=0.012) at follow-up mpMRI were different between patients with radiological regression or stability vs progression. Cut-offs of 0.77 $\times$ 10^{-3} mm^2/s (lesion ADC) and 0.59 (npADC ratio) could differentiate the two groups (area under the curve: 0.74 and 0.77, respectively).

Conclusion: The ADC, npADC ratio and the PRECISE score should be recorded for MRI-based AS.

Keywords: Prostate cancer; Active surveillance; Diffusion Magnetic Resonance Imaging; Molecular imaging.

Abbreviations and acronyms:

PCa: prostate cancer

AS: active surveillance

mpMRI: multiparametric magnetic resonance imaging

PI-RADS: Prostate Imaging Reporting And Data System

DWI: diffusion-weighted imaging

ADC: apparent diffusion coefficient

PRECISE: Prostate Cancer Radiological Estimation of Change in Sequential Evaluation

PSA: prostate specific antigen

T2-WI: T2-weighted imaging

DCE: dynamic contrast-enhanced

ROI: region of interest

PZ: peripheral zone

TZ: transitional zone

IQR: interquartile ranges

ROC: receiver operating characteristic

ICC: intraclass correlation coefficient

1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed solid organ cancer in men in the United Kingdom, with around 40,000 cases diagnosed each year. [1]
Patients with PCa confined to the prostate are classified into low, intermediate and high-risk categories and active surveillance (AS) is recommended for men with low or intermediate-risk disease. [1]
The standard AS programmes include repeated blood tests, digital rectal examination and standard biopsy.

There is compelling evidence that multiparametric magnetic resonance imaging (mpMRI) shows potential in identifying candidates for AS, who may have little benefit from therapy, but still need to be monitored to allow prompt curative treatment if the disease shows signs of becoming harmful (radiological progression). [2–4]
Sanguedolce and colleagues explored which baseline mpMRI features might be helpful for the refinement of AS inclusion criteria in 135 patients and concluded that a Prostate Imaging Reporting And Data System (PI-RADS) score >3 and an index lesion >10mm were strongly associated with patient withdrawal from the AS programme. [5]

Quantitative assessment of the change in diffusion-weighted imaging (DWI) over time is of interest as a way to detect who develop clinically significant disease whilst on surveillance. [4, 6–8] This technique measures the diffusion of water molecules within the extracellular space by the calculation of a quantitative parameter called apparent diffusion coefficient (ADC). [9] Because cancer cells are more tightly packed than benign cells, diffusion of water is restricted in the former and this corresponds to a higher signal on DWI and decreased signal on the ADC map (i.e. a lower ADC value than normal tissue). It has been reported that the ADC is a significant predictor of time to adverse histology on

biopsy or radical treatment for PCa during AS. [10] However, the current reporting of studies of mpMRI during AS lacks rigour and standardisation. [2]

In the UK, the National Institute for Health and Care Excellence guidelines recommend the use of serial mpMRI during AS, but they do not clearly report how often mpMRI should be performed and how serial mpMRI findings should be interpreted. [11]

To address this need, the PRECISE (Prostate Cancer Radiological Estimation of Change in Sequential Evaluation) criteria were published in 2016. [12] The aim of these recommendations, which are based on international expert consensus, is to facilitate robust data collection from serial mpMRI during AS and to distinguish natural variability from changes indicating true radiologic progression of PCa.

The PRECISE criteria recommend scoring the likelihood of radiological progression on follow up scans using a 1-to-5 scale (PRECISE score). A score of 1-2 indicates regression of a previously visible lesion, 3 denotes stability and 4-5 corresponds to radiological progression. (Table 1)

We conducted this pilot study in two academic centres (University College London -UCL- and Sapienza), both highly experienced in prostate mpMRI reporting in order to address the following question: can DWI be used to differentiate those patients whose cancer progresses from those with stable disease?

In order to do this, we firstly evaluated the inter-reader reproducibility of different ADC calculations from serial prostate MR scans and then explored *if* and *how* these are related to the PRECISE score.

2. Material and methods

In this two-centre, retrospective study patient records and MR images were reviewed as part of an audit routinely performed for the internal evaluation of the AS service (Fig. 1).

2.1 Eligibility criteria and study design

All prostate MR examinations were performed between January 2009 and May 2019 and two radiologists (one from each centre; VP and FG with 11 and 7 years of experience in prostate MRI reporting, respectively) were involved in the study. Both radiologists had been actively involved in the discussion and drafting of the PRECISE recommendations in 2016.

Inclusion criteria for this pilot study were: i) biopsy-proven PCa eligible for AS according to guidelines (i.e. Gleason 3+3 or 3+4) [11]; ii) prostate specific antigen (PSA) ≤15 ng/ml; iii) visible lesion on DWI at baseline scoring ≥3 according to the PI-RADS version 2.1 guidelines [13] that was concordant with the histology using the six sectors scheme (i.e. base, midgland, and apex of the right and left prostate gland); iv) same MR scanner (1.5T or 3T, same manufacturer) and protocol for baseline and follow-up scans.

Patients who had any treatment with any 5-alpha reductase inhibitors in the previous 12 months were excluded, as the use of such medications could reduce PCa conspicuity on DWI. [14]

AS entry was defined as the initial diagnosis of PCa on biopsy and the follow-up period is updated to May 2019.

To overcome any selection bias, eligible patients were randomly selected from each database. In this study, baseline MRI was not necessarily the first scan after entry into AS, as some of the patients had been scanned on different systems over the years. A specific inclusion criterion was to include only those patients who had been consecutively scanned on the

same MR system (i.e. same magnet strength and same MR protocol including the same b values for each patient) both for baseline and follow-up scans (i.e. no other scans between them).

At the beginning of the study, the two study radiologists identified the index lesion and assessed the PRECISE score for each patient in consensus. As per PRECISE guidelines, the lesion with the highest PI-RADS score and volume (index tumour) was chosen for analysis, if multiple foci were detected in the same patient. Each PRECISE score was the result of the comparison of visual evaluation (i.e. tumour conspicuity on different mpMRI sequences) and maximum lesion diameter on DWI for the peripheral zone (PZ) and on T2-WI for the transition zone (TZ) (in accordance with the strategy for lesion measurement provided in PI-RADS V 2.1 guidelines) between baseline and follow-up scans.

We applied the following specific interpretation to the PRECISE criteria, as per PRECISE recommendations:

    i)   'PRECISE 3' (i.e. stability): either a scan with a stable lesion over time, or a persistent negative scan

    ii)   'PRECISE 4' (i.e. progression): either a new focal lesion (scored as PI-RADS ≥ 3) in a previous negative scan or a lesion with more suspicious MRI features (volume or conspicuity) since the last scan

In case of only diffuse MRI changes in the prostate gland (as seen in prostatitis, for example), the MR scan was reported as 'negative' for the presence of focal lesions.

In order not to introduce any bias, the ADC was not measured at this stage (i.e. the ADC did not influence the assessment of the PRECISE score). Each PRECISE score and lesion location were recorded on a separate spreadsheet by an independent observer. Then, at least 6 weeks later, each radiologist was provided with the list of cases (including the

lesion location but not the PRECISE score) and the set of anonymised MR images of each patient in order to measure the ADC according to the region of interest (ROI) drawn by each radiologist independently. As per PRECISE recommendations, the radiologists were privy only to PSA, initial biopsy result and tumour location.

2.2 MR imaging technique

Three different scanners were used: one 1.5T (Avanto, Siemens, Erlangen, Germany) and one 3T systems (Achieva, Philips, Best, The Netherlands) at UCL and a 3T system (Discovery MR750, GE Healthcare, Milwaukee, USA) at Sapienza all using a multichannel surface phased-array body coil and no endorectal coils.

The protocols in both centres included T2-weighted (T2-WI), DWI (b values: 0, 100, 500, and 1000 s/mm^2, and long b sequence: 1,400 s/mm^2 for 1.5T or 2,000 s/mm^2 for 3T scanners) with ADC map calculation, and dynamic contrast enhanced (DCE) imaging, in accordance with international guidelines. [13, 15, 16]

2.3 Image analysis

All MR imaging data sets were reviewed using commercial image viewing software (Osirix X MD® v. 10.0.4; Geneva, Switzerland).
Image quality was adequate to evaluate the ADC in all scans.

All the available sequences (T2-WI, DWI and DCE) were used to accurately locate the lesion and median ADC values were obtained from ROIs traced on the ADC maps. The ROIs were positioned making reference to where the lesion was most conspicuous on the high b value sequence on DWI. The slice for the ROI had been previously identified in consensus during the initial session for the assessment of the PRECISE score.

In order to select an optimal reference for ADC normalisation, the two study radiologists copied and pasted another ROI of the same size in the non-cancerous PZ or TZ zone (according to tumour location) on the same slice in mirror position, and another ROI in the urine in the bladder lumen (Fig.2).

These additional values were recorded and used to generate two parameters: the normalised prostatic ADC (npADC) and the normalised urinary ADC (nuADC) ratios, according to the formula: ADC (tumour)/ADC (reference).

The concept of normalisation for ADC values is very important in order to minimise the variability between MR scanners and systems. As far this study is concerned, the npADC is more discriminating than the single ADC value from the lesion, as one advantage of using the ADC from the non-cancerous prostate as reference is that measurements are made easier with ROIs used for calculation placed on the same level of slice and because it is assumed that the adjacent tissue is subjected to the same field heterogeneity and susceptibility effects than the lesion.

Necrosis, blood vessels, and areas containing artefacts from bowel peristalsis were excluded from the ROIs.

2.4 Statistical analysis

Clinical and demographic data are reported using descriptive statistics. Continuous variables are expressed by median and interquartile ranges (IQR) and categorical data by frequencies and percentages.

Interobserver consensus and agreement in measuring ADC was evaluated by Spearman's correlation and intraclass correlation coefficients, and graphically inspected by Bland-Altman plots with confidence intervals at level 0.95. Measurements were averaged between the two observers for further analyses.

Significant differences in ADC values and ratios between baseline and follow-up scans were verified using Kruskal-Wallis test statistics. Receiver operating characteristic (ROC) curves were generated and the areas under the curves were compared in order to differentiate between PRECISE 2 and 3 (i.e. radiological regression or stability) vs PRECISE 4 and 5 (i.e. radiological progression).

To detect a difference of the median change of all parameters, between baseline and follow-up scans in the two groups we performed unpaired T-test.

P values < 0.05 were considered to indicate a significant difference.

All statistical analyses were performed using SPSS (version 25; SPSS, Chicago, Illinois, USA).

3. Results

A total of 30 patients (fifteen scanned on 1.5T and fifteen on 3T MR systems) were included in this study.
The median interval between baseline and follow-up mpMRI was 14 months (IQR: 12–18.75).
There were 26/30 (87%) lesions in the PZ and 4/30 (13%) in the TZ.
The median ROI size (averaged between the two readers) was 15 mm^2 (IQR: 0.11–0.24) for baseline and 20 mm^2 (IQR 0.14-0.41) for follow-up mpMRI.

Table 2 shows the descriptive characteristics of all men included in the study. Overall, there were two (6%) PRECISE 2, fourteen (47%) PRECISE 3, eleven (37%) PRECISE 4 and three (10%) PRECISE 5 cases.
At present 8/30 patients (27%) have received treatment. Of these, two (25%) have been treated with radical prostatectomy, five (63%) with focal therapy and one (12%) with radiotherapy.

The interobserver reproducibility between the two readers was very good both for baseline and follow-up ADC calculations, as shown by the high Spearman's rank and intraclass correlation coefficients (Table 3) and as graphically displayed in the Bland-Altman plots (Fig. 3). Given the high inter-reader reproducibility, the measurements were averaged between the two observers and used for the subsequent analyses.

The overall median ADC values and normalised ADC ratios stratified by each PRECISE score at baseline and follow-up mpMRI are reported in Table 4. Splitting the overall population into radiological regression or stability (i.e. PRECISE 2 and 3) and radiological progression (i.e. PRECISE 4 and 5), significant differences were observed for lesion ADC and npADC ratio at follow-up mpMRI (p=0.025 and p=0.012, respectively), while

there were no differences for all parameters at baseline and for the other values at follow-up mpMRI (Table 5).

There were no differences of the change in all parameters between baseline and follow-up scans according to radiological regression or stability (i.e. PRECISE 2 and 3) vs radiological progression (i.e. PRECISE 4 and 5) (Table 6).

The median lesion ADC and npADC ratio for each PRECISE score and according to radiological regression or stability (i.e. PRECISE 2 and 3) vs radiological progression (i.e. PRECISE 4 and 5) at follow-up mpMRI are graphically displayed in Fig. 4.

According to ROC curves analysis (Fig. 5), a cut-off of 0.77×10^{-3} mm^2/s for lesion ADC (AUC: 0.74; sensitivity: 68% and specificity: 64%) and a cut-off of 0.59 for npADC ratio (AUC: 0.770; sensitivity: 81% and specificity: 71%) could differentiate between PRECISE 2 and 3 and PRECISE 4 and 5.

4. Discussion

There is a need for reliable risk-assessment tools that can support the assessment of stability for patients on AS, and MRI-derived parameters such as the ADC represent an encouraging step in this direction.

The main finding from our study is that the absolute ADC value of the lesion and the npADC ratio (normalised to non-cancerous prostatic tissue) on follow-up imaging are significantly different according to the presence of radiological progression, defined as per PRECISE recommendations (i.e. PRECISE 2 and 3 *vs* PRECISE 4 and 5).

First of all, there is evidence supporting the role of the ADC as a non-invasive, quantitative tool for detection and follow-up of PCa, and a number of studies have shown that ADC values are inversely correlated with the Gleason score (i.e. PCa aggressiveness). [17, 18]

DWI is an essential component of mpMRI of the prostate and several previous studies have evaluated the utility of this technique also during AS. [4] Morgan and colleagues [19] investigated the change in tumour volume over time in 151 patients on AS to determine whether baseline ADC and ADC changes were predictive of tumour growth. They concluded that change in T2-WI volume correlates with a change in ADC, and ADC may be used to identify patients with clinically significant growth, suggesting a 5.8% reduction in ADC as a possible threshold (specificity: 77%; sensitivity:54.9%) for indicating volume progression.
One of the biggest limitations in DWI is the inter-observer variability when assessing the ADC, and reader experience is very important at this regard. We found in our study that two expert radiologists had a very good agreement in calculating the ADC values both at baseline and follow-up mpMRI.

At present, there are no clear recommendations on how (e.g. drawing a single region of interest or by planimetry) and which (absolute vs normalised) ADC values should be calculated.

It is known that absolute ADC values vary from one MR system to the other and that they are dependent on the number of b values acquired. There is also considerable inter- and intra-patient variability. [20]

We aimed to minimise these drawbacks by including only those patients who had been scanned on the same MR system (i.e. same magnet strength and same MR protocol including the same b values) at both time points. We also used the ratio of tumour ADC to that of normal prostatic tissue for overcoming the variability in absolute ADC values (i.e. we assume that the variability of ADC in normal prostatic tissue is equivalent to that within tumours).

Different authors have investigated the potential role of the ADC ratio in the evaluation of PCa using different reference standards for ADC normalisation, including normal prostatic tissue [17] and urine in the bladder.[21]

We found a significant difference for radiological progression (defined as PRECISE 2 and 3 vs PRECISE 4 and 5) for tumour ADC (0.91 vs 0.73 x 10^{-3} mm^2/s; p=0.025) and the npADC ratio (0.68 vs 0.53; p=0.012) at follow-up mpMRI, but no significant results were observed at baseline mpMRI. No difference was seen at baseline and follow-up mpMRI when tumour ADC was normalised to urine in the bladder (nuADC), even though a trend towards statistical significance was observed at follow-up mpMRI (0.52 vs 0.38, p=0.007).

This means that we cannot yet infer that baseline ADC values can predict the likelihood of radiological progression, and further research is needed at this regard.

In addition to the aforementioned results, we should recall that both biopsy and PSA measurements are prone to variability (sampling errors

and natural PSA fluctuation), and there is need of novel markers to detect PCa progression on AS, including image-derived parameters.

To date, no standard ADC cut-offs have been established to assess the radiological progression, but our study provides a first answer to this, as we found two optimal cut-offs to discriminate between radiological stability and radiological progression (ADC: 0.77×10^{-3} mm^2/s and npADC ratio 0.59). Henderson and colleagues [10] reported that ADC is a significant predictor of AS disqualification (i.e. time to adverse histology on biopsy or radical treatment) over nine years of follow up, as patients with a baseline ADC < 972 mm^2/s in their AS cohort progressed, on average, seven years earlier. However, differently from our study, the ADC was calculated only on baseline MRI and they did not perform any kind of ADC normalisation.

Our findings hint that the ADC from follow-up DWI could assist in the identification of patients with radiological progression (who should be biopsied or offered treatment) and, at the same time, could help in identifying those without radiological progression (who could benefit from a more conservative approach, i.e. clinical and mpMRI follow up).

A number of methodological limitations apply to our study.
First is the relatively small cohort of patients, but we aimed to conduct a pilot study on a specific cohort where we minimised the variability related to magnet strengths, vendors and protocols. Fifteen patients (50%) were exclusively scanned on a 1.5T and the other fifteen (50%) exclusively on a 3T scanner, using always the same machine and the same protocol for each patient. In order to achieve good quality results and reliable ADC values, it is fundamental that the MR systems are regularly checked, and the MR protocols adhere strictly to the PI-RADS v. 2.1 guidelines. Therefore, good communication between the radiologist and the radiographer is essential, and if there are artefacts that can compromise DWI quality (e.g. rectal air), measures should be taken to rectify the

problem and the sequence should be repeated, as recommended in the PI-RADS v. 2.1 guidelines.

The second limitation is the absence of tissue verification by means of radical prostatectomy, but this is common in AS cohorts. Only 12/30 (40%) patients in our population underwent rebiopsy (eight of whom with a targeted approach), but resampling was often triggered by apparent tumour growth on mpMRI or by adverse PSA kinetics without MRI changes. However, this study was specifically designed to investigate the correlation of ADC with radiological progression, which was exclusively based on MR features and not on histological progression.

There were only four lesions in the TZ (that is more heterogeneous than the PZ from a histological point of view) and it is possible that different evaluations would have arisen if the number of TZ lesions had been higher.

Moreover, due to the inclusion criteria requiring visible lesions on DWI at baseline and follow up, there were no scans scored as PRECISE 1. This is why we created two groups (PRECISE 2 and 3 *vs* PRECISE 4 and 5) that were fairly balanced in terms of population (16 *vs* 14), without altering the clinical message behind (i.e. patients with radiological stability could be followed up without the need of resampling, differently from those showing radiological progression).

Lastly, it should be noted that changes in ADC and an increase in subjective tumour conspicuity (that is one of the main drivers for defining radiological progression in the PRECISE score) are closely correlated, as the ADC map is the main way of assessing most tumours (especially in the PZ).

In conclusion, our initial results hint that the ADC correlates with radiological progression, in line with previous studies [14, 22]. In addition to this, the calculation of the npADC ratio using our method (Fig. 6) could be easily performed during daily clinical practice and used as an additional image-derived quantitative parameter that can assist the Radiologist in

the assessment of radiological progression by means of PRECISE score. The ADC, npADC ratio and the PRECISE score should be recorded for MRI-based AS.

Acknowledgements

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Table 1: Assessment of likelihood of radiological progression on magnetic resonance imaging in men on active surveillance for prostate cancer (PRECISE score)

Table 2 - Descriptive characteristics for each man included in the study (n=30)

Table 3 – Spearman's rank correlation (ρ) and intraclass correlation coefficients at baseline and follow-up mpMRI

Table 4 - ADC values (x10^{-3} mm^2/s) and normalised ADC ratios stratified by PRECISE score at baseline and follow-up mpMRI

Table 5 - ADC values (x10^{-3} mm^2/s) and normalised ADC ratios stratified by grouped PRECISE score (i.e. radiological regression/stability -PRECISE 2 and 3- vs radiological progression -PRECISE 4 and 5-) at baseline and follow-up mpMRI

Table 6 – Differences of the median change (Δ)of all parameters between baseline and follow-up scans stratified by grouped PRECISE score (i.e. radiological regression/stability vs radiological progression).

Figure 1 - Diagram indicating multiparametric MRI schedule undertaken based on baseline MRI status. The timing of MRI on active surveillance was based on both baseline risk and changes during follow up.

Figure 2 – Multiparametric magnetic resonance imaging of a 77-year-old patient with biopsy-proven prostate cancer in the left midgland peripheral zone. T2-weighted (A), dynamic-contrast enhanced (B) and diffusion weighted (C) imaging confirm the presence of the lesion (arrows). Three different regions of interest (of the same size and area) from the apparent diffusion coefficient map were drawn on the lesion and normal prostatic tissue (D) and on the urine in the bladder (E).

Figure 3 - Bland-Altman plots representing the interobserver reproducibility between the two readers for the different ADC and normalised ADC ratio values, both at baseline (A, B, C) and at follow-up magnetic resonance imaging (D, E, F). The centre line represents the mean of differences, the top line shows the upper 95% limit of agreement, and the bottom line shows the lower 95% limit of agreement, with the mean difference between the long- and short-axis measurements (±1.96 times the standard deviation).

Figure 4 - Boxplots showing lesion ADC (A, B) and normalised prostatic ADC (npADC) values (C, D) at follow-up magnetic resonance imaging as function of each single PRECISE score (A, C) and according to radiological regression/stability (PRECISE 2 and 3) or radiological progression (PRECISE 4 and 5) (B, D).

Figure 5 - ROC curves for the detection of radiological progression on the basis of lesion ADC (blue, long-dashed line) and normalised prostatic ADC (npADC) (red, short-dashed line) values at follow-up magnetic resonance imaging.

Figure 6 – Multiparametric magnetic resonance imaging of a lesion in the peripheral zone on T2-weighted imaging (A, arrow) and ADC map (B-C) and in the transitional zone on T2-weighted imaging (D, arrow) and ADC map (E-F) from two different patients on active surveillance for prostate cancer. The image includes the median ADC values (lesion -blue circles- and non-cancerous tissue -yellow and green circles-) obtained from the different regions of interest, and the corresponding npADC ratios for the lesion in the peripheral (C) and transitional (D) zone.