Contents lists available at ScienceDirect

European Journal of Radiology Open

Correlation of apparent diffusion coefficient ratio on 3.0 T MRI with prostate cancer Gleason score

Jyoti Rajeev[b,c], Jain Tarun Pankaj[b,*], Haxhimolla Hodo[a,c], Liddell Heath[a], Barrett Sean Edward[d]

[a] Department of Urology, The Canberra Hospital, Garran, ACT, Australia
[b] Universal Medical Imaging, Canberra, Calvary Hospital, Bruce, Australia
[c] Australian National University, Canberra, ACT, Australia
[d] The Canberra Hospital, Garran, ACT, 2606, Australia

ARTICLE INFO

ABSTRACT

Introduction: The purpose was to investigate the usefulness of ADC_{ratio} on Diffusion MRI to discriminate between benign and malignant lesions of Prostate.

Methods: Images of patients who underwent in-gantry MRI guided prostate lesion biopsy were retrospectively analyzed. Prostate Cancers with 20% or more Gleason score (GS) pattern $3 + 3 = 6$ in each core or any volume of higher Gleason score pattern were included. ADC_{ratio} was calculated by two reviewers for each lesion. The ADC_{ratio} was calculated for each lesion by dividing the lowest ADC value in a lesion and highest ADC value in normal prostate in peripheral zone (PZ). ADC_{ratio} values were compared with the biopsy result. Data was analysed using independent samples T-test, Spearman correlation, intra-class correlation coefficient (ICC) and Receiver operating characteristic (ROC) curve.

Results: 45 lesions in 33 patients were analyzed. 12 lesions were in transitional zone (TZ) and 33 in perpheral zone PZ. All lesions demonstrated an ADC_{ratio} of 0.45 or lower. GS demonstrated a negative correlation with both the ADC value and ADC_{ratio}. However, ADC_{ratio} ($p < 0.001$) demonstrated a stronger correlation compared to ADC value alone ($p = 0.014$). There was no significant statistical difference between GS $3 + 4$ and GS $4 + 3$ mean ADC_{tumour} value ($p = 0.167$). However when using ADC_{ratio}, there was a significant difference ($p = 0.032$). ROC curve analysis demonstrated an area under the curve of 0.83 using ADC_{ratio} and 0.76 when using ADC_{tumour} value when discriminating Gleason 6 from Gleason ≥7 tumours. Inter-observer reliability in the calculation of ADC ratios was excellent, with ICC of 0.964.

Conclusion: ADC_{ratio} is a reliable and reproducible tool in quantification of diffusion restriction for clinically significant prostate cancer foci.

1. Introduction

Diffusion weighted imaging (DWI) is one of the important components of the multi-parametric MRI (mpMRI) examination of the prostate. DWI can be quantitatively measured by Apparent Diffusion Coefficient (ADC). There is wide evidence in current literature that clinically significant prostate cancer foci demonstrate a reduction in apparent diffusion coefficient (ADC_{tumour}) and show restricted diffusion relative to normal prostate tissue [1,2]. ADC_{tumour} values obtained from these maps correlate inversely with the histologic Gleason score for the tumour [3–5] and are also associated with clinical outcomes [6,7].

According to the latest Prostate Imaging Reporting and Data System (PIRADS) version 2 guidelines, interpretation and scoring of DWI and ADC maps on mpMRI examination is based primarily on qualitative visual assessment of the signal intensity of a lesion compared with that of the surrounding normal prostatic tissue in the same anatomic zone, to determine a significant reduction in ADC value within a suspected lesion [2,8].

The guidelines acknowledge substantial overlap of ADC values among different pathologies in prostate like stromal hyperplasia, low-grade cancer, and high-grade cancer. Also, there is substantial variability in ADC values depending on multiple technical factors such as vendor, field strength, and DWI acquisition parameters [2,8]. The ADC values of Prostate Cancer (PCa) also vary according to age and race of the patient [9]. There is no agreed ADC_{tumour} value cut-off that could be reliably used to determine abnormally low ADC within a lesion [4,5]. Nonetheless, in PI-RADS version 2, a threshold of 750–900 mm^2/s is suggested as lesions with an ADC value that is less than this range tend
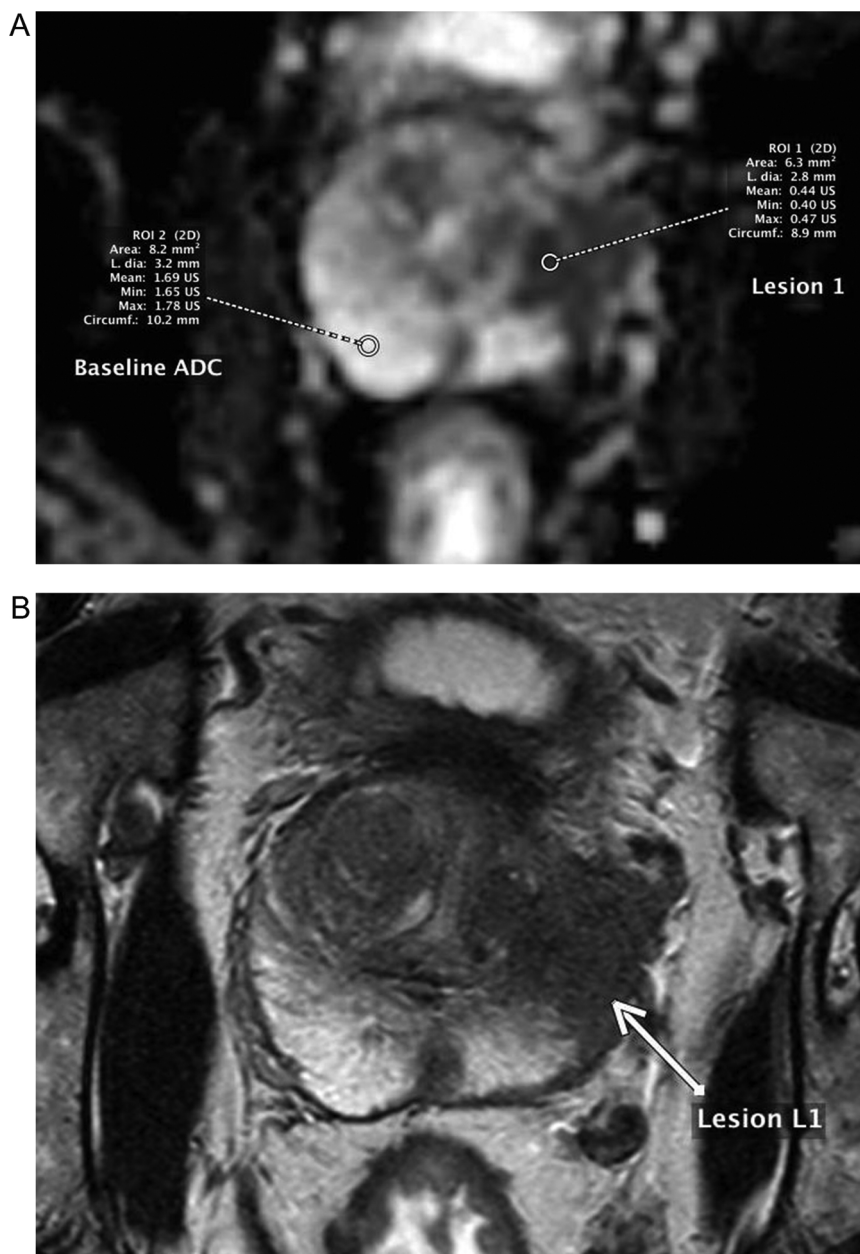
Fig. 1. A. Peripheral Zone lesion with Gleason score 4 + 5 tumor. Axial ADC image with ADC ratio of 0.26. B. Corresponding Axial T2 image of a TZ/PZ lesion.

to represent clinically significant prostate cancer. However, given the noted variability, it has been recommended that each center should identify its own thresholds that are based on internal data and comparisons with histopathologic findings. [2,8]. This independent verification of appropriate threshold can be difficult to establish. Also, comparison between studies from two different centres would be difficult. Previous studies have shown wide variation in ADC_{tumour} values of both PCa as well as normal prostate [10].

A ratio of ADC values (ADC_{ratio}) between a lesion and the background prostate can potentially negate these external factors and provide a more accurate representation of change in the diffusion in a tumour with respect to normal tissue. We calculated ADC_{ratio} for each lesion by dividing the lowest ADC value in a lesion and highest ADC value in PZ of normal prostate.

The aim of this study is to investigate the usefulness of ADC_{ratio} values of a prostatic lesion to background prostate parenchyma to discriminate between benign and malignant lesions. Also, we aim to establish whether ADC_{ratio} is easily reproducible.

2. Material and methods

2.1. Patients

Our institutional review board (Human research and ethics committee) approved this retrospective study. We searched our database for lesions that underwent in-gantry MRI guided biopsy between February 2013 and December 2014. 229 lesions that were biopsied via in-gantry MR guided biopsy were retrospectively evaluated. Significant lesions were considered to be lesions which demonstrated 20% or more Gleason score (GS) pattern 3 + 3 = 6 in each core or any volume of higher Gleason score pattern. Finally, 45 lesions in 33 patients were included in the analysis. 33 tumours were in peripheral zone, and 12 were in transitional zone. Patient cohort characteristics are demonstrated in Table 2. All the MRI studies were performed before any prostate biopsy (biopsy-naïve lesions). Median PSA in this cohort was 7.8 ng/mL (range 1.8–26.0) and mean age was 67 years (range 49–81 years).

Table 1
Spearman rho Correlation between ADC Measurements and Gleason Score Overall for All Tumours and Stratified by Zonal Origin.

Spearman Rho		
Zone	ADC tumour	ADC ratio
Peripheral	− 0.441 (p = 0.01)	− 0.561 (p = 0.001)
Transitional	− 0.211 (p = 0.50)	− 0.402 (p = 0.19)
Overall	− 0.365 (p = 0.014)	− 0.511 (p ≤ 0.001)

2.2. Diffusion weighted (DWI) MRI technique

All MRI examinations were performed on our 3.0-T system (Ingenia, Philips Healthcare, Netherlands). Axial single-shot echo-planar diffusion-weighted imaging (DWI) (FOV: 16 cm, TR range: (4000–5000), TE: 75 ms, Flip angle: 90°, 6 signal averages, Sense (parallel imaging factor) 2, 3 mm slice thickness with no inter-slice gap, voxel size of 1.8×1.8 mm, B factor: 0, 100, 600, 1800s/mm^2) was performed with reconstruction of the apparent diffusion coefficient (ADC) map using a standard mono-exponential. B0 was excluded from ADC calculations to avoid perfusion artifacts. T2-weighted images in 3 planes, Axial T1-weighted and dynamic contrast enhanced images were also obtained in all the patients to complement diffusion-weighted images. The total examination time was approximately 40 min.

2.3. In-gantry MRI guided biopsy technique

A team comprising of an experienced Radiologist (RJ) and single Urologist (HZH) performed in-gantry MRI guided core biopsies on all the patients included in this study using Invivo DynaTRIM device (Invivo Inc., Gainesvile, FL, USA). Prebiopsy MRI scan was performed and the co-ordinates of the target lesion were analyzed with DynaCAD's interventional planning software to enable accurate targeting. MRI compatible needle was introduced by transrectal route through a needle sleeve which works as a guide as well as fiducial marker. Biopsy samples were obtained by using an MR-compatible, 18-gauge fully automatic core-needle double-shot biopsy gun (Invivo) with a needle length of 175 mm and a tissue core sampling length of 17 mm. Five core biopsy samples were obtained from each lesion.

2.4. DWI analysis

All the lesions were marked for two readers (RJ, LH) who retrospectively analysed them on DWI scans. The lowest ADC value within each lesion was calculated by drawing multiple circular region of interest (RoI) of 5–10 mm^2 in each lesion and then the lowest value was selected as ADC$_{tumour}$. Similarly, multiple RoI were drawn within normal peripheral zone (PZ) tissue displaying normal signal characteristics on T1 and T2WI to calculate highest ADC value. Areas of low T2 signal were excluded while calculating ADC of normal prostate to avoid any area of scarring and inflammation. Areas of high T1 signal were excluded to avoid haemorrhage. The ADC$_{ratio}$ was calculated for each lesion by dividing the lowest ADC value in a lesion and highest ADC value in normal prostate in PZ.

Radiologist (RJ-first reader with experience of reading over 2000 prostate MRI examinations at 3.0 T) as well as a urology registrar (LH-second reader, with no significant experience in reading mpMRI examination of prostate) independently calculated ADC$_{ratio}$ for each lesion (Fig. 1). Both the readers were blinded to the actual biopsy result. The ADC$_{ratio}$ was then analyzed with respect to the histological findings from the biopsy.

2.5. Statistical analysis

Intraclass correlation coefficient analysis was conducted to determine the reliability of calculating the ADC$_{ratio}$. Mean ADC$_{tumour}$ and ADC$_{ratio}$ scores were compared using independent samples T-test. Spearman correlation was used to measure the strength of relationship between ADC measurements (both ADC$_{tumour}$ and ADC$_{ratio}$) and the observed Gleason score. Receiver operating characteristic (ROC) curve analysis was calculated to assess the ability to discriminate between different Gleason scores based on ADC$_{tumour}$ value and ADC$_{ratio}$. A P value of < 0.05 was considered statistically significant for all statistical analyses performed. Statistical analysis was performed using software SPSS 24 (IBM).

3. Results

45 tumours were included in the present study. 33 tumours were in peripheral zone, and 12 were in transitional zone. All Gleason 3 + 3 = 6 lesions and higher demonstrated an ADC$_{ratio}$ of 0.45 or lower. Of the 12 transitional zone lesions, the highest ADC$_{ratio}$ value was 0.43. Of the 33 peripheral zone lesions, the highest ADC$_{ratio}$ was 0.45.

Inter-rater reliability in the calculation of ADC ratios was excellent, with an intra-class correlation coefficient of 0.964.

There was no significant statistical difference between Gleason 3 + 4 and Gleason 4 + 3 mean ADC$_{tumour}$ value (p = 0.167), however when using ADC$_{ratio}$ there was a significant difference (p = 0.032).

The association between the ADC measurements and the observed Gleason score demonstrated a negative correlation when using both the ADC$_{tumour}$ value (−0.365) as well as the ADC$_{ratio}$ (−0.511). These relationships were both significant (p = 0.014 and p = < 0.001) respectively. The ADC ratio demonstrated a stronger correlation when compared with the ADC$_{tumour}$ value alone. This trend was observed when stratified by zonal origin, and is presented in Table 1.

ROC curve analysis (Fig. 2) demonstrated an area under the curve of 0.83 using ADC$_{ratio}$ and 0.76 when using ADC$_{tumour}$ value when discriminating Gleason 6 from Gleason ≥7 tumours. The area under the curve decreased for both ADC$_{tumour}$ value and ADC$_{ratio}$ when discriminating between Gleason 3 + 4 and Gleason 4 + 3 tumours (0.66 and 0.72 respectively).

4. Discussion

We found that tumour foci in both TZ and PZ show reduction of ADC values compared to the normal prostate. There is progressive reduction of both ADC$_{tumour}$ as well as ADC$_{ratio}$ values with increase in the GS (Fig. 3). The ADC$_{ratio}$ demonstrated a stronger correlation when compared with the ADC$_{tumour}$ value alone. This correlates well with results of previous studies [11–14].

While the present study is underpowered due to a low N, we have demonstrated that the ADC$_{ratio}$ is not inferior to the ADC$_{tumour}$ in discriminating GS 7 (3 + 4) and GS 7 (4 + 3) tumours. The trend observed is that the ADC$_{ratio}$ may in fact be superior to the ADC$_{tumour}$, and as such further investigation is required. The trend observed in this study was consistent with findings from Boesen et al. [14].

It has been established that patients with GS 7(4 + 3) tumours have

Table 2
Patient characteristics.

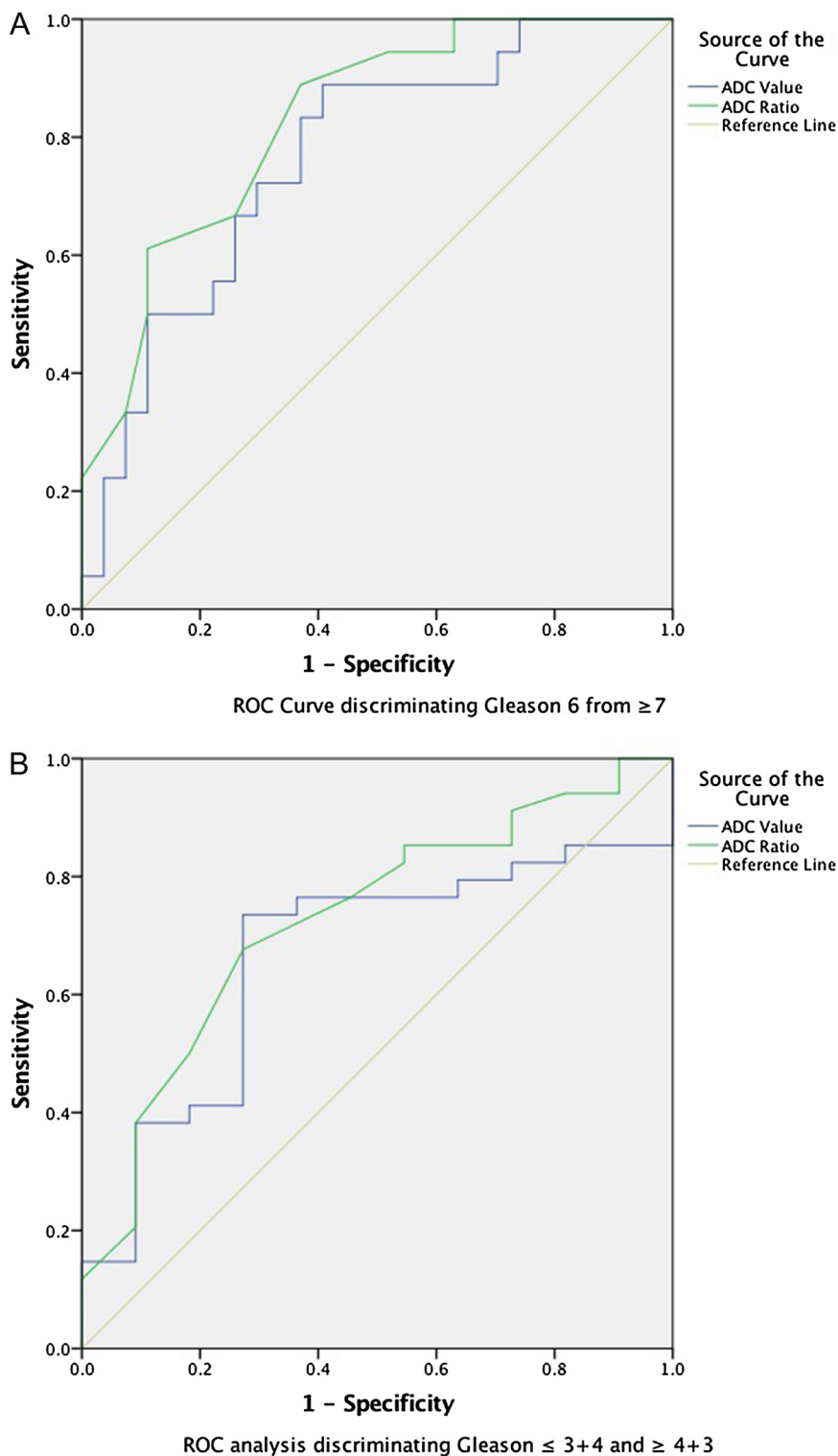| Mean age of patients	67 years (range 49–81 years)
PSA level	7.8 ng/mL (range 1.8–26.0)
Lesion size median	11 mm (range 7–23 mm)
Location of lesions	33 in PZ, 12 in TZ
Gleason score (GS) of lesions	GS 6 = 18
	GS 7 (3 + 4) = 16
	GS 7 (4 + 3) = 5
	GS 8 = 5
	GS 9 = 1

Fig. 2. ROC-curve analysis for determining tumor aggressiveness (GS) using ADC tumor value and ADCratio for all tumors to discriminate between (A) GS 6 and GS ≥ 7 and between (B) GS ≤ 7(3 + 4) and GS ≥ 7(4 + 3).

a worse prognosis [15,16].

ROC curve analysis demonstrated an area under the curve (AUC) of 0.83 using ADC_{ratio} and 0.76 when using ADC_{tumour} value when discriminating Gleason 6 from Gleason ≥7 tumours. This compares with AUC of 0.8 using ADC_{ratio} and 0.73 when using ADC_{tumour} value as per the study of Boesen et al. [14].

We chose a small RoI size of 5–10 mm^2 to try and find an area of the lowest ADC value in a lesion, as lower ADC values have shown to

correspond to higher Gleason grade [3–5]. Larger RoI including majority of a lesion may potentially cause averaging of the ADC values. Other investigators have used different size of RoI. Barrett et al. used ROI of mean size 30 mm^2 in the PZ and 33 mm^2 in the TZ, although there was a wide size range [12]. Boesen, Lebovici and Cobelli et al. used a RoI encompassing the tumour centre while avoiding tumour edges [11,13,14]. Interestingly, all these studies also found ADC_{ratio} to be more useful than ADC_{tumour} values in diagnosis of PCa. There has
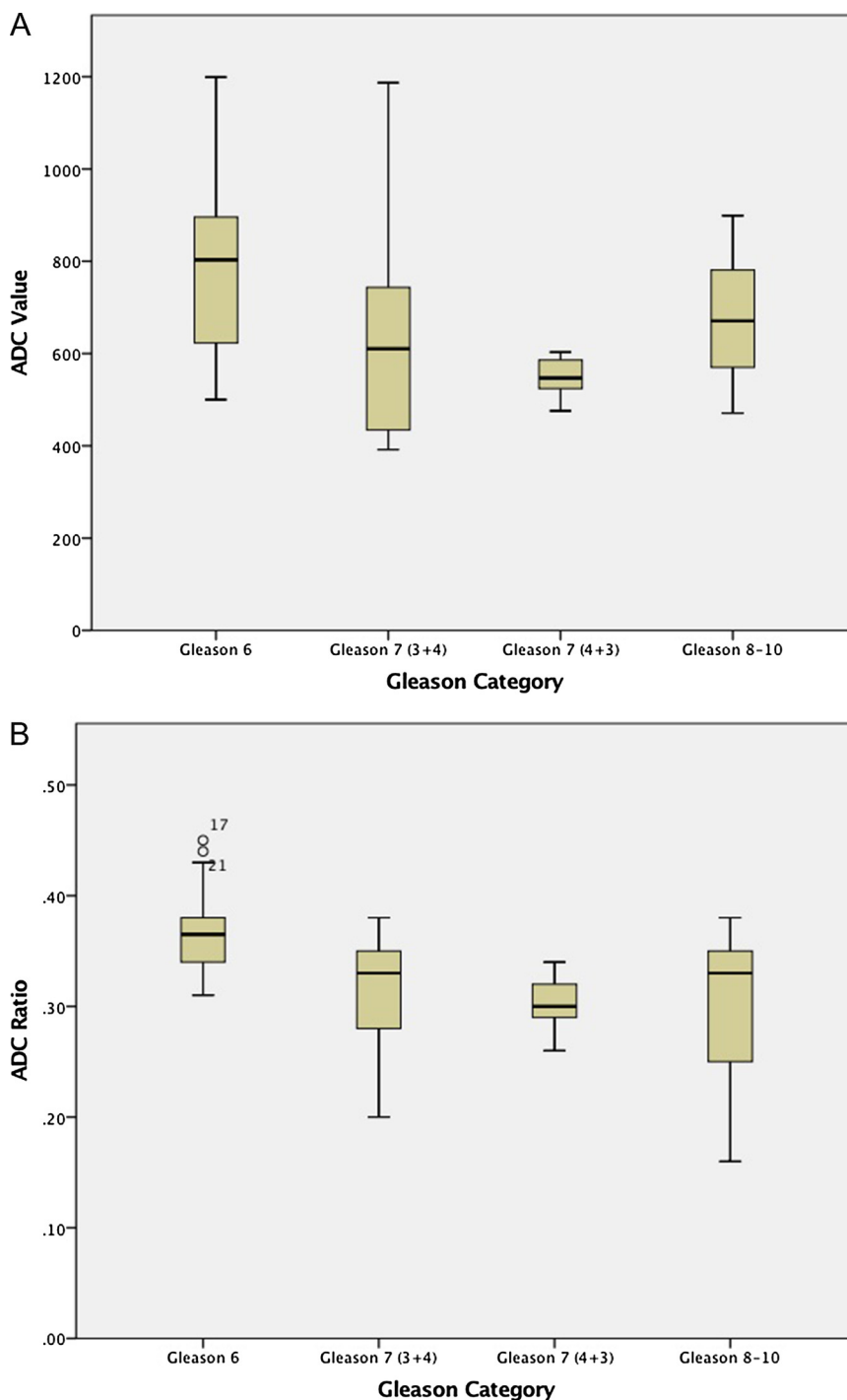
Fig. 3. Correlation of ADC$_{tumour}$ and ADC$_{ratio}$ values with Gleason score.
A and B, Box-and-whisker plots show correlation of ADC$_{tumour}$ values (A) and tumor ADC$_{ratio}$ (B) with Gleason score. Top and bottom of boxes represent 25th and 75th percentiles of data, with line in box representing median value.

been no study in literature demonstrating the appropriate size of a RoI that should be obtained for ADC measurements.

The biggest challenge for this study was to determine reproducibility of ADC$_{ratio}$ while considering a range of reader experience. Inter-reader reliability in the calculation of ADC ratios was excellent, with an intra-class correlation coefficient of 0.964. Due to its simplicity, ADC$_{ratio}$ has potential to become a universal tool in determining reduction in ADC while evaluating mpMRI studies. Lesion to normal prostate ADC$_{ratio}$ is easily calculated and can be used in daily practice without having the need to use new software or formulae.

The previous studies in literature evaluating ADC$_{ratio}$ have used different methods to obtain pathology samples. Lebovici et al. [11] used results of transrectal ultrasound guided biopsy with 20 cores to retrospectively identify a sector with positive Gleason result, rather than targeting a particular lesion identified on mpMRI on biopsy naïve patients with MRI in gantry biopsy, as in our study. Ultrasound guided core biopsy [13] and histopathological examination of prostatectomy specimen [12–14] have also been used. Regardless of the method of acquiring pathology specimen, ADC$_{ratio}$ has been proven to be useful in all these studies.

Use of ADC_{ratio} as a parameter may improve tumour characterization, may provide a greater standardization and may allow a more robust comparison between different centers and across MRI platforms [12–14].

One of the strengths of our study is performance of ingantry MRI guided biopsy (MRGB) on all lesions, enabling accurate targeting of the prostate lesions. MRGB has been shown to be superior to Transrectal Ultrasound guided biopsies [17]. Also, all the MRI examinations were performed using state of the art 3T MRI with DWI scans including high B value of $1800s/mm^2$. Acquisition of "High b-value" images utilising a b-value of more than $1400s/mm^2$ has been recommended in the latest PIRADS v2 guidelines [8].

Our study has several limitations. The first is limitation inherent to retrospective analysis. The final pathology on radical prostatectomy would be a more accurate gold standard. Also, the sample size is small. A study with larger number of patients would be needed to further evaluate the usefulness of ADC_{ratio} and determine universally acceptable cut-offs. Besides, our study is based on analysis of mpMRI images, which is unable to distinguish all significant PCa lesions [18]. Detection rates can be influenced by tumour Gleason score, histological volume, histological architecture and location [19].

5. Conclusion

ADC_{ratio} has a potential to be a reliable and reproducible tool in quantification of diffusion restriction for clinically significant PCa foci. Due to its simplicity, it could replace the current practice of visual analysis of ADC_{tumour} reduction, and provide a more accurate objective tool. Our results add to the growing evidence of usefulness of ADC_{ratio} for MRI diagnosis of PCa.

Conflicts of interest

None.

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