'Importance of Apparent Diffusion Cofficient of prostate cancer in mpMRI and correlation with Gleasons score'

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ABSTRACT

Back ground: The Gleason score is a crucial factor in assessing prostate cancer. It provides valuable information about the aggressiveness of the cancer based on its microscopic appearance. The Gleason score is assigned by a pathologist after examining prostate biopsy samples under a microscope. It ranges from 6 to 10, with higher scores indicating more aggressive cancer. This Study have explored the relationship between Gleason score and Apparent Diffusion Coefficient.

Aims & Objective: prospective analysis of mpMRI images and relevant clinical data from patient with prostate disease. The differences in ADC between different GS group were compared,and the efficacy of ADC in PCa diagnosis were analysed..
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Method: This study was conducted on 36 prostate cancer patient who undergo mpMRI exam followed by radical prostatectomy from certain period. ADC maps were calculated with monoexponential fitting per voxel of DW images at various b value and T-test /ANOVA was used to compare the means of continuous variables like ADC value between different Gleason's score.

Result: Significant correlations between MR imaging and tissue components were found at region-based analysis using linear mixed-effects models for all ROIs (PZ and TZ ROIs). The lumen and stroma density was positively correlated with the normalized T2-weighted MR imaging signal intensity and ADC, while the epithelium and epithelial nucleus density was negatively correlated (P,.01).

Conclusion: Significant correlations were observed between MR imaging parameters ADC and tissue components. Higher ADC positively correlated with benign tissue features (lumen and stroma) and negatively correlated with cancerous components (epithelium and epithelial nucleus).

Introduction:

Prostatic cancer is one of the cancers which potentially curable disease. Traditional diagnostic methods, such as prostate-specific antigen (PSA) testing and transrectal ultrasound-guided (TRUS) biopsy, have limitations. PSA testing lacks specificity, leading to false positives and unnecessary biopsies, while TRUS-guided biopsy can miss clinically significant cancers due to its random sampling nature. This diagnostic challenge necessitates the exploration of more advanced and reliable imaging techniques. To a certain extent, this quality addresses the limitation mentioned earlier. This study uses DWI techniques to assess the diagnostic efficacy.

The current gold standard for diagnosing PCa is achieved through adherence to the guidelines of the European Association of Urology [1]

However, the invasive nature of biopsy procedures can lead to a cascade of potential complications. Recent years have seen the ascendance of non-invasive biopsy procedures.The most effective way to diagnose prostate cancer using conventional T2-weighted imaging is by staging for the presence of extracapsular extension and seminal vescical invasion .With the evolution of multiparametric magnetic resonance imaging (mpMRI) technology, a consortium of directives now advises that all men with suspected disease should be tested**.[**2,3]

These evaluations encompass a suite of imaging sequences,encompassing T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI),and dynamic contrast enhancement. **The European Society of Urogenital Radio is working together to** standardize the acquisition, interpretation, and reporting of mpMRI findings .**the** American College of Radiology and the Ad Me Tech Foundation **have released version 2.1(2019)** of **the** prostate imaging and reporting data system.[4]

Functional magnetic resonance imaging techniques, including diffusion-weighted imaging (DWI), have become more widely accepted in recent years.By providing more specific information on tumor locations, MRI could expand its role in non-invasive characterization of prostate cancer.[5-10]Several recent studies have shown that DWI can help differentiate between malignant and benign prostatic tissue based on lower apparent diffusion.[5-6]

The reduction in diffusion in prostate carcinoma is believed to be caused, at least partly Water molecule movement in the extra cellular space is hindered by the highly cellular enviro nment of neoplastic tissue. The reported ADC values of prostate cancer in the peripheral zone range between 0.93 and 1.38 103 mm2/s.[7] This variability in ADC values is significant. Prostate cancer's heterogeneous tissue composition maybe partially responsible for this variab ility in ADC values. [8]

In addition, it investigates how ADC values are related to the Gleason score (GS), which is a crucial diagnostic parameter.

The progression of prostate cancer is linked to Gleason grades 1-5.

Gleason scores are also used to describe tumours as low grade (Gleason score 6), intermediate grade (Gleason score, 7), or high grade (Gleason score).

A higher likelihood of prostate cancer recurrence is associated with more aggressive tumors [7]

PI-RADS have a significant problem due to their inherent subjectivity in assessing the risk and dimensions of lesions, Thus, it falls short in its ability to reliably predict disease outcomes. The apparent diffusion coefficient (ADC) value, on the other hand, provides a quantitative metric that imbues the assessment process with a degree of objectivity.To some extent, this quality addresses the limitation mentioned earlier.[8]

this present study utilizes DWI techniques to examine the diagnostic efficacy of ADC values regarding low to intermediate-risk PCa. Additionally, it investigates the relationship between ADC values and the Gleason score (GS), an essential diagnostic parameter.

Material and method:

Patients

This prospective study was conducted on 50 cancer patients who undergo mpMRI exam followed by radical prostatectomy from certain period. The period between prostatectomy after imaging will be 7-30days.

MR imaging Protocol

T2-weighted and DW MR imaging were performed with a 3-T MR imager (Achieva TX; Philips Healthcare) using a cardiac coil (In Vivo; Philips Healthcare, Gainesville, Fla) and an endorectal coil (BPX 30; Medrad, Indianola, Pa). T2- weighted MR imaging has a resolution of 0.27 3 0.27 mm. ADC maps were calculated with monoexponential fitting per voxel of DW images at various b values. High-b-value DW images were acquired with a b value of 2000 sec/ mm2. T2-weighted and high-b-value DW MR imaging are normalized to reduce MR imaging signal inhomogeneity between MR imaging sections and patients per MR imaging section.

Tissue Specimen Preparation

The patient-specific mold (PSM) was created from the presurgical MR images from each patient and by using three-dimensional computer-aided design software (Dassault Systems SolidWorks, Waltham, Mass) and a three-dimensional printer (Dimension Elite 3D Printer; Stratasys, Eden Prairie, Minn). In the PSM, sectioning slots are positioned to match the location of the MR imaging sections. After prostatectomy, whole-mount tissue slices were cut in the mold and were stained with hematoxylin-eosin for histopathologic evaluation. Each tissue slice was digitized on a standard bright-field optical microscope (Aperio Technologies, Vista, Calif) at a magnification of 320 (resolution of 0.504 3 0.504 mm).

Image Registration

Image Registration The PSM helps orient the tissue specimen and maintain the shape of the prostate, but tissue preparation (eg, fixation) introduces deformation. The endorectal coil also deforms the prostate during MR imaging (absent in the specimen). In-house semiautomated registration software, implemented in OncoNav software (Center for Interventional Oncology, National Institutes of Health, Bethesda, Md), enables accurate registration based on the outer contours and internal fiducial structures within the prostate . The registration result is visually inspected to ensure that the overall shape and anatomic landmarks (urethra, ejaculatory ducts, benign prostatic hyperplasia nodules) at histology match the identified regions (peripheral zone [PZ], transition zone [TZ], and tumor). Also, ADC and high-b-value DW images undergo rigid registration with T2-weighted MR images using the MR imaging coordinate information.

The surgical procedure used for prostate removal in this study is typically a radical prostatectomy. This can be performed via different approaches, including open surgery (retropubic or perineal), laparoscopic surgery, or robot-assisted laparoscopic surgery.

Tissue Sampling for Histopathology

- Gross Examination- Upon arrival in the pathology lab, the fixed prostate specimen is examined grossly. The prostate is weighed, and its dimensions are recorded. The outer surface is inspected for any visible lesions or abnormalities. The specimen is then inked to mark the surgical margins, ensuring that any close or involved margins can be identified histologically.
- Sectioning- The prostate is serially sectioned (usually in 3-5 mm slices) perpendicular to the urethral axis. This ensures that the entire prostate is systematically examined, and the sections correspond to the anatomical zones (peripheral, central, transition zones).
- Special attention is given to any palpable or visually identifiable lesions, which are sampled more extensively.

- Tissue Embedding: The sliced tissue sections are placed into cassettes and dehydrated through a series of alcohol baths, cleared in xylene, and embedded in paraffin wax. This process makes the tissue firm enough to be thinly sliced for microscopic examination.
- Microtomy: Thin sections (about 4-5 micrometers thick) are cut from the paraffin-embedded blocks using a microtome. These sections are then mounted on glass slides.

-Staining: The mounted tissue sections are stained using Hematoxylin and Eosin (H&E), which provides contrast between different tissue components and highlights cellular structures.
- Additional immunohistochemical (IHC) stains, such as Prostate-Specific Antigen (PSA) or Alpha-Methylacyl-CoA Racemase (AMACR), may be used to further characterize the cancer cells and confirm the diagnosis.

Reporting:
- The findings are compiled into a detailed histopathological report, which includes the Gleason score, tumor stage, margin status, and any other relevant pathological features.
- This report is used to correlate with the preoperative Multi-Parametric MRI findings for further analysis in the study.

Data Collection
- Imaging Data was collected, stored and accessed and use of software for image analysis (e.g., radiomics tools).
- Clinical Data: like patient demographics, clinical history, PSA levels were collected in patient information sheet

Histopathological Data:
- Recording of Gleason scores, tumor stages, and any relevant histological features.

Statistical Analysis-

T-Test/ANOVA was used to compare the means of continuous variables like ADC values between different Gleason score groups. MR imaging signal intensity and tissue component density were normalized by z score transformation to standardize the slopes of the mixed-effects models. The significance of the slopes was tested against zero. Statistical significance of MR imaging signal intensity and tissue component density in discriminating different histopathologic areas was determined with the Wilcoxon rank-sum test. A significance level of .05 was used for statistical testing.

Ethical Considerations

The study was approved by Institutional Ethics Committee (IEC) and written Informed Consent was taken from each participant after thoroughly explaining the objectives of the study and it is only for research purpose and assured them about the anonymity and confidentiality.

Results:

Clinical data: This study enrolled 50 patients, age between 45 to 70 years, PSA1 4 to more than 20 ng/ml. and radical proctectomy done.

Table 1: Gleason Score versus MR Imaging and Tissue Component Density

MR Imaging Sequence and Tissue Component	PZ and TZ	PZ	TZ
Sequence			
T2 weighted	20.08 6 0.20 (.45)	20.26 6 0.23 (.04)	0.27 6 0.30 (.11)
ADC	20.14 6 0.18 (.15)	20.20 6 0.19 (.05)	0.33 6 0.49 (.21)
High *b* value	0.21 6 0.16 (.02)	0.23 6 0.17 (.02)	0.19 6 0.51 (.47)

Gleason score was associated with MR imaging and DHA. Normalized T2-weighted MR imaging signal intensity and ADC were not significantly correlated with Gleason score ($P<0.05$) when all ROIs (PZ and TZ tumor ROIs) were taken into account. Gleason score had a negative correlation with lumen density and a positive correlation with high-b-value DW imaging. $P>0.05$ indicated that no significant correlations were seen between the density of the epithelium, stroma, or epithelial nucleus. However, there were geographical variations in the correlation between MR imaging and Gleason score. For example, the Gleason score in the TZ was positively correlated with ADC and normalized T2-weighted MR imaging, however the Gleason score in the PZ was adversely correlated with these measures (20.26 vs. 0.27; slope for ADC). The Gleason score was only strongly linked with normalized T2-weighted MR imaging.

Figure 1- Graphs show relationship between MR imaging and tissue component density in region- and voxel-based analysis. Slopes of the linear mixed-effects models are computed for the whole prostate. Region and voxel denote the slopes for region- and voxel-based analyses, respectively. Increasing the size of a window (1, 3, 5, or 7 mm) yields a stronger association. T2W = T2 weighted.

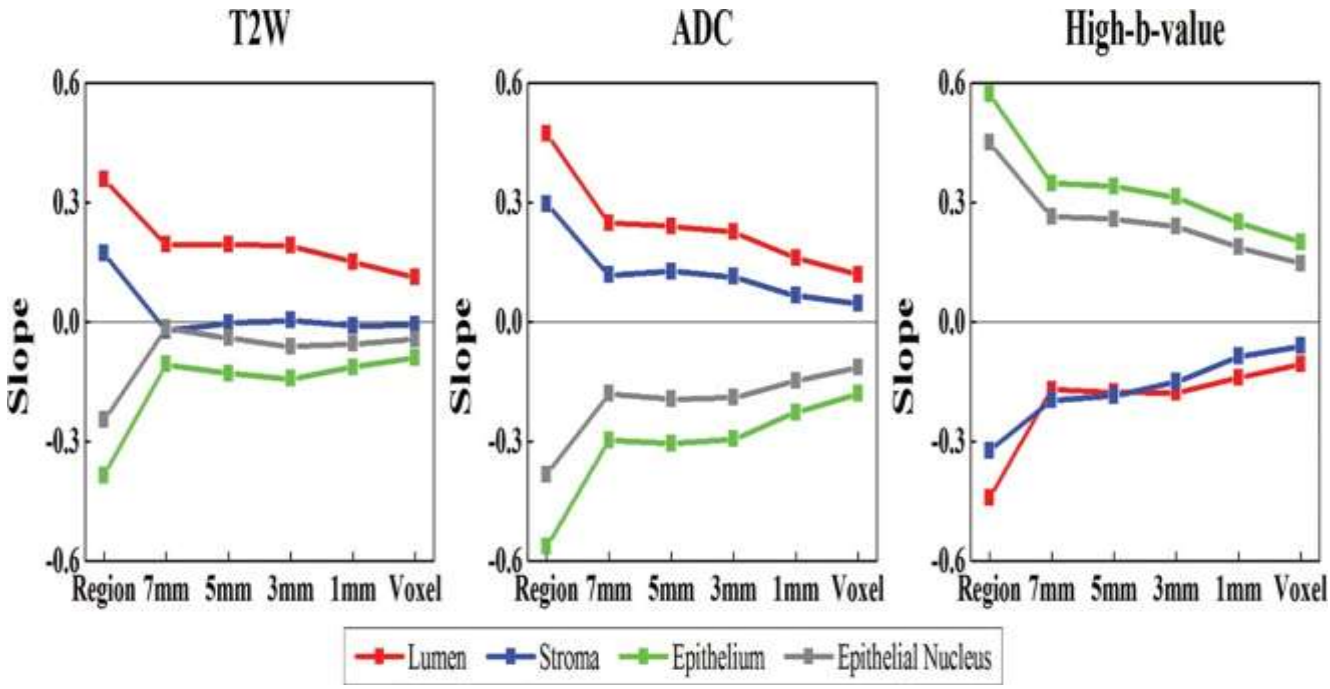


Figure 2-A 60-year-old man with prostate cancer. A, Axial T2W MR image (T3a, gleason score (GS): 7); B, Corresponding apparent diffusion coefficient (ADC) map calculated from diffusion weighted imaging (DWI). Arrows show prostate cancer in the left peripheral zone.

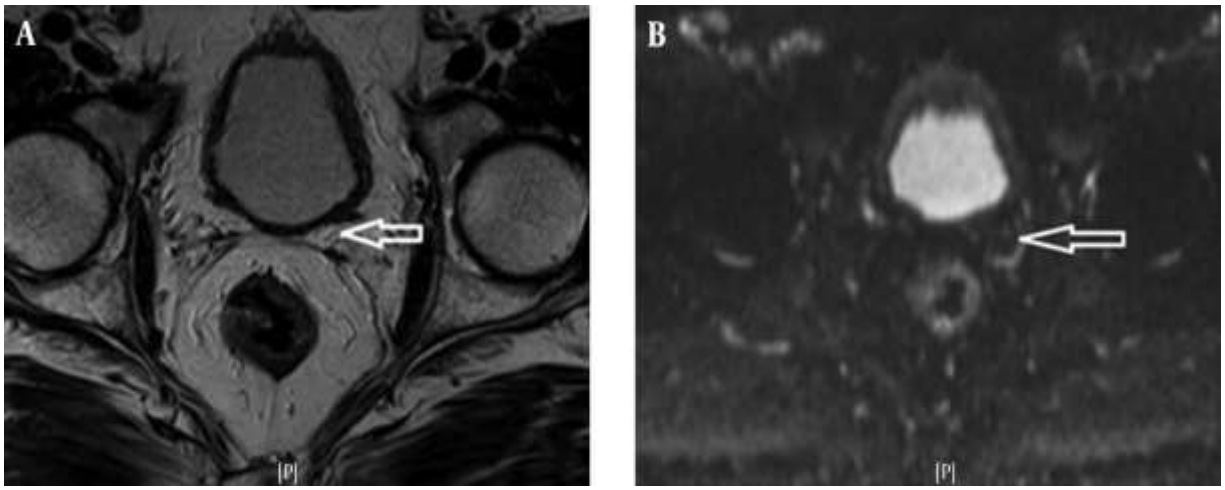
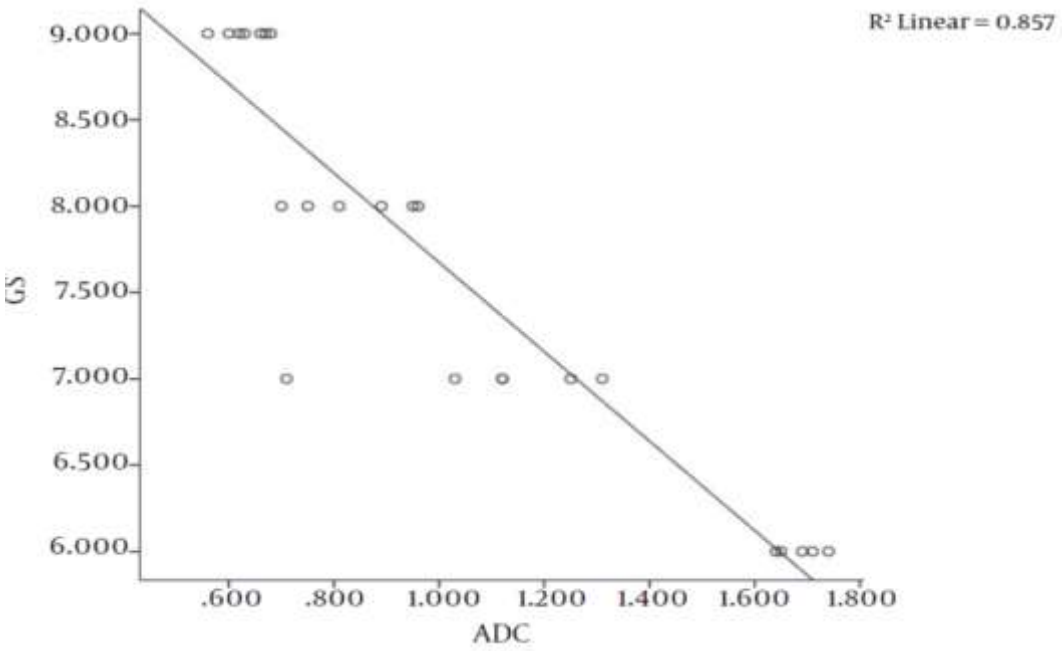


Figure 3- Correlation of ADC Values with Gleason Scores



As per figure 3 the Pearson correlation analysis revealed a strong significant negative correlation between Gleason scores and ADC measurements (r = -0.717, P = 0.01).

Discussion:

Prostate cancer has caused a significant decrease in the diffusion properties of water protons, which has resulted in a decrease in the measured ADC value of prostate cancer. There is a well-documented comparison between normal prostatic tissue.so it is supported our investigation [9,10]

A tissue's architecture can be altered, such as an increase in the ratio of intracellular to extracellular water proton, A more restricted movement of water proton is caused by the replacement of less cellular normal prostate tissue with more highly cellular neoplastic tissue. The reduced extracellular space and more viscous and complex intracellular environment are the reasons for this more restricted movement.[11]

The definitive preoperative diagnosis of PCa is currently obtained by acquiring pathological results through needle biopsy, which is a benchmark procedure. However, the detection rate for this invasive method is only 62.2%.It is useful for measuring biological activity, invasiveness, guiding treatment strategies, and conducting prognostic evaluations. Additionally, it seems to be a dependable indicator of postoperative progress and survival.[12]

In our analysis of the connection between prostate cancer aggressiveness and its diffusion properties we that higher Gleason scores were linked to lower ADC values, and that ADC values may aid in distinguishing between low-risk (Gleason score,6) If the tumor is apparent on DW pictures and ADC maps, the prostate cancer is classified as intermediate risk (Gleason score, 7) and between low-risk (Gleason score, 6) and high-risk (Gleason score, > 7) Because poorly differentiated tumors have larger cellular densities, which hinder the passage of water protons, the more aggressive tumors in our study may have lower mean ADC values.[13]

Our study analyzed a total of 256 ROIs from 128 tissue sections, with a specific focus on differentiating cancerous from benign areas in both the PZ and TZ. Our findings, particularly

the differences in ADC values between malignant and benign ROIs, reinforce the role of diffusion-weighted imaging in prostate cancer assessment. The correlation between Gleason scores and MRI findings was another critical aspect of our study. Higher Gleason scores were associated with more pronounced changes in MRI signal characteristics, particularly in ADC and high-b-value DW imaging. Our study's findings contribute to the growing body of evidence that MRI can be a valuable non-invasive tool for assessing tumor aggressiveness and guiding clinical decisions.[14]

Our analysis revealed that lumen and stroma density were positively correlated with normalized T2-weighted MRI signal intensity and Apparent Diffusion Coefficient (ADC) values ($P < .01$). This suggests that regions with higher lumen and stroma density exhibit brighter T2-weighted signals and higher ADC values, typically indicative of benign prostatic tissues.

Negative Correlation of Epithelium and Epithelial Nucleus Density with T2-Weighted Imaging and ADC. Conversely, we found a negative correlation between the density of epithelial and epithelial nucleus components and both normalized T2-weighted MRI signal intensity and ADC values ($P < .01$). Regions with higher epithelial and nuclear density, typically associated with malignant tissues, exhibited lower T2 signal intensity and reduced ADC values.

Our study found that normalized T2-weighted MRI signal intensity and Apparent Diffusion Coefficient (ADC) were not significantly correlated with the Gleason score when all ROIs, including both PZ and TZ tumor ROIs, were considered together ($P > 0.05$). This lack of significant correlation suggests that these MRI parameters alone may not reliably reflect the histopathological aggressiveness of prostate cancer across different regions of the prostate.

A noteworthy finding in our study was the geographical variation in the correlation between MRI parameters and Gleason score. Specifically, in the TZ, the Gleason score was positively correlated with ADC and normalized T2-weighted MRI signal intensity, whereas in the PZ, the Gleason score showed a negative correlation with these measures. This suggests that the relationship between MRI characteristics and histopathological aggressiveness may differ significantly depending on the anatomical location of the tumor.

Conclusion-

The strong negative correlation between Gleason scores and ADC measurements in our study supports the integration of ADC values into the diagnostic pathway for prostate cancer. This correlation can aid clinicians in identifying patients with more aggressive disease, potentially guiding the decision-making process regarding biopsy, treatment planning, and prognosis. The ability to predict Gleason score non-invasively through mpMRI, particularly using ADC, could reduce the need for repeated biopsies and improve patient outcomes by enabling earlier and more accurate detection of high-grade tumors.

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