Apparent Diffusion Coefficient of Variation (ADC<sub>cv</sub>): A New Biomarker for Aggressiveness in Prostate Cancer?

Aylin Altan Kuş, Burak Çıtamak, Ali Tekin

1Acıbadem University Atakent Hospital, Department of Radiology, İstanbul, Türkiye
2Acıbadem University Atakent Hospital, Department of Urology, İstanbul, Türkiye

What’s known on the subject? and What does the study add?

Apparent diffusion coefficient (ADC<sub>cv</sub>) could be beneficial in improving future prostate cancer imaging. The validation of ADC<sub>cv</sub> as an imaging biomarker may have important consequences for the detection and assessment of aggressiveness of prostate cancer.

Abstract

Objective: The aim of the study was to evaluate which apparent diffusion coefficient (ADC) parameter can predict the aggressiveness of prostate cancer in patients confirmed by radical prostatectomy specimens.

Materials and Methods: Patients who underwent radical prostatectomy for prostate cancer between October 2019 and June 2023 were retrospectively reviewed. Patients were separated into two groups based on the International Society of Urological Pathology (ISUP) classification, and the correlation between ADC metrics and ADC parameters, including ADC<sub>mean</sub>, ADC<sub>coefficient of variation</sub> (ADC<sub>cv</sub>), and ISUP classification the aggressiveness of prostate cancer was studied.

Results: Fifty-seven patients were included in the study. Patients were evaluated as low-risk (group 1) (n=40), and high-risk (group) (n=17). ADC<sub>mean</sub> values for the two groups were not significantly different (p=0.218). ADC<sub>cv</sub> values that can demonstrate tumour heterogeneity index were higher in group 2 than in group 1 (p<0.001). Multivariate analysis revealed that extracapsular extension, positive surgical margin, and ADC<sub>cv</sub> values indicated tumour proliferation, whereas seminal vesicle invasion, prostate-specific antigen levels, and body mass index were not correlated with ISUP grade groups.

Conclusion: ADC<sub>cv</sub> is a promising new biomarker for tumour aggressiveness in prostate cancer.

Keywords: Diffusion weighted imaging, apparent diffusion coefficient, ISUP grade group, prostate cancer, prostatectomy

Introduction

Prostate cancer is a leading cause of disease and death among men, with 1.6 million men being diagnosed annually and 366.000 men dying from the disease (1). In recent years, imaging has taken on more significance in the detection, staging, posttreatment evaluation, and detection of prostate cancer recurrence. Magnetic resonance imaging (MRI) offers the most exact representation of zonal anatomy and the highest soft tissue resolution of any imaging technique to date, allowing for a thorough anatomic evaluation of the prostate. The most effective MRI approach is multiparametric MRI (MpmMRI). MpmMRI combines T1-weighted and multiplanar T2-weighted images and functional diffusion-weighted imaging with apparent diffusion coefficient (ADC) maps and dynamic contrast-enhanced imaging sequences that can provide information about anatomy and function. Diffusion-weighted imaging (DWI), which uses the random mobility of water molecules to construct ADC maps, allows for both qualitative and quantitative assessments of prostate cancer (2,3). ADC is the net movement of molecules...
over a tissue area per second (mm²/s) (4). In fact, the typical glandular morphology is changed in prostate cancer, with nests of cancer cells and fibrous stroma displacing the large interstitial gaps and glandular lumens, resulting in a decrease in unrestricted water circulation. Consequently, a high-signal-intensity zone on DWI pictures indicates clinically severe malignancy. In the monoexponential model, the ADC has a mean value that is connected to diffusion. The ADC value has proven to be an effective indicator of cancer aggressiveness, providing quantitative information on tumor characteristics (5).

Many studies in the current literature indicate that the mean value of ADC reflects the degree of aggressiveness of prostate cancer (6-8). In contrast, a study that examined the ADC_mean and ADC_cv values revealed no association with the aggressiveness of prostate cancer (9). However, there is still some uncertainty in this area, and no agreement has been achieved (6,10). This notion is related to some challenges. First, the ADC can differ greatly due to various factors. These are the b-values employed, MR scanner field strength, patient and coil geometry, temporal fluctuations in the magnetic field, and measurement differences between different readers. Furthermore, non-cancerous tumours, such as benign prostatic enlargement, may have lower ADC values. Consequently, various options beyond ADC_mean are needed to determine the aggressiveness of prostate cancer. Therefore, we intended to investigate the efficacy of ADC_coefficient of variation (ADC_cv) measurement, a new biomarker of tumour heterogeneity index, in prostate cancer and examine, in a cohort of consecutive patients, the correlation between absolute ADC_mean and ADC_cv and the International Society of Urological Pathology (ISUP) grade following robot-assisted laparoscopic prostatectomy (RALP).

Materials and Methods

Patient Selection

The local ethics committee accepted this single-center retrospective study conducted between October 2019 and June 2023 and waived the requirement for informed consent (Acibadem Mehmet Ali Aydinlar University Medical Research Evaluation Board - approval ID: 2023-13/466, date: 17.08.2023) because of the retrospective evaluation of anonymized medical data. The following were the criteria for inclusion: (1) prostate mpMRI collected on a 3.0 Tesla unit and (2) accessible serum prostate-specific antigen (PSA) levels at the time of prostate mpMRI. Patients with motion artifacts and inadequate images and a history of androgen deprivation therapy, radiation, or transurethral resection were also excluded. The cohort in our study was divided into two distinct groups based on the final whole prostate specimen obtained following radical prostatectomy. Group 1 was classified as the low-risk group, whereas Group 2 was categorized as the high-risk group. This classification was determined on the basis of the ISUP grading system related to the pathology findings of the excised prostate specimen.

- Grade Group 1: Very low-grade cancer with well-formed glands (corresponding to Gleason Score 6)
- Grade Group 2: Low-grade cancer with slightly irregular glands (corresponding to Gleason Score 3 + 4 = 7)
- Grade Group 3: Intermediate-grade cancer with irregular and fused glands (corresponding to Gleason Score 4 + 3 = 7)
- Grade Group 4: High-grade cancer with fused and poorly formed glands (corresponding to Gleason Score 8)
- Grade Group 5: Very high-grade cancer with no gland formation, characterized by sheets of tumor cells (corresponding to Gleason Score 9-10)

Specifically, Grade 1 and Grade 2 are considered low risk and assigned to Group 1, whereas Grade 3, Grade 4, and Grade 5 are categorized as high-risk and assigned to Group 2. This classification allows for the differentiation of prostate cancer cases based on their perceived risk levels according to the ISUP grading system. Table 1 shows patient distribution according to the ISUP grade.

MRI Protocol

All patients underwent prostate mpMRI using a Siemens Medical Systems Skyra 3.0 Tesla MRI scanner with an 18-channel phased-array coil (Skyra, Siemens Medical Systems, Erlangen, Germany). Butylscopolamine bromide (Buscopan, Boehringer Ingelheim) was administered before all exams to reduce bowel motions, which could cause motion artifacts. The index lesion was assessed using prostate mpMRI by an abdominal radiologist with 10 years of experience. Our institution's mpMRI protocol for prostate imaging included tri-planar T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging. Echo-planar imaging in axial planes with b-values of 50, 500, 1,000, and 1,400 s/mm² was used for DWI. This was accomplished by merging data from all accessible b-values and fitting them using a least-squares monoexponential fitting.

| Table 1. Patient distribution according to ISUP grade groups |
|-----------------|---------------|-----------|
| ISUP Grade groups | Number of patients | Percentage (%) |
| 1               | 16            | 28.1      |
| 2               | 24            | 42.1      |
| 3               | 10            | 17.5      |
| 4               | 2             | 3.5       |
| 5               | 5             | 8.8       |
technique. This approach represents the diffusion properties of prostate tissue.

**Image Analysis**

To accurately evaluate prostate cancer lesions with true-positive findings, a free-form region of interest (ROI) was constructed. The ADC maps were generated automatically using the software (Syngo Via, Siemens Medical Systems) used in our facility. The radiologist evaluated the ADC maps and manually delineated an ROI on the tumour visible on the ADC map. Where ROI was entered, the software automatically calculated ADC\text{mean} and standard deviation. This ROI, known as ADC\text{mean}, corresponded to the interior margin of the entire tumour outline. On the tumour segment with the greatest cross-sectional area, ROIs were carefully established. ADC\text{cv} was computed using the formula Standard Deviation/ADC\text{mean} on the ADC map, according to a previous study (11). The measurements of ADC\text{mean} and ADC\text{cv} are depicted in Figure 1. To ensure that only the tumor region was examined, normal tissue outside the borders of the lesion was excluded.

**Statistical Analysis**

To determine the normality of variable distribution, the Kolmogorov-Smirnov test was used. The chi-square test for categorical data was used to evaluate patient characteristics and postoperative pathological outcomes. For regularly distributed data, the Student’s t-test was employed, whereas for non-normally distributed data, the Mann-Whitney U test was used. Variables less than 0.05 in the univariate analysis were investigated further in a multivariate logistic regression analysis to identify high-grade prostate cancer. In addition, receiver operating characteristic curve (ROC) analysis was performed on ADC\text{cv} to determine its sensitivity, specificity, area under the curve (AUC), and cut-off value (Figure 2).

The data were analyzed using SPSS 22.0 (IBM SPSS Corp., USA). Variables less than 0.05 were accepted as statistically significant.

**Results**

Overall, 57 men with prostate cancer were enrolled in our dataset (age, 62.2±6.5; range, 51-76 years). The detailed patient distribution according to ISUP Grade Groups is shown in Table 2. ADC\text{mean} inverse correlation with ISUP (p=0.218) while ADC\text{cv} showed a strong positive correlation with ISUP grade groups (p=0.041). Detailed information regarding the ADC metrics of the study sample is shown in Table 3. When ROC analysis was performed by evaluating ADC\text{cv}, the threshold value was defined as 0.081 with 55% sensitivity and 82% specificity (p=0.010, AUC: 0.716).

However, bladder invasion, extracapsular extension (ECE), and positive surgical margin were correlated with ISUP grade groups, whereas seminal vesicle invasion, prostate-specific antigen (PSA) levels, and body mass index (BMI) were not correlated with ISUP grade groups. Table 2 demonstrates the laboratory and pathological findings of patients.

ADC\text{cv} value of low grade group and high-grade groups were 0.099±0.06 and 0.174±0.12 respectively (p=0.041***). Figure 3 depicts the ADC metrics of a patient categorized as ISUP Grade

---

**Figure 1.** A 65-year-old patient with ISUP Grade Group 2 (Gleason Score 3+4) prostate cancer. On diffusion-weighted image (a) the tumour has hyperintensity signal. The apparent diffusion coefficient (ADC) map (b) demonstrates ADC\text{mean} (694x10\textsuperscript{-6}) ADC\text{cv} (54.7/694= 0.07) (white arrows). T2-weighted coronal (c) and post-contrast T1-weighted axial (d) images (white arrow) depict 8 mm diameter tumour

**Figure 2.** Receiver operating characteristic (ROC) analysis curve of high-risk prostate cancer detection with ADC\text{cv}, AUC: 0.716 (p<0.010)
Group 3. ADC\textsubscript{cv} value of low grade group and high grade group was \(760.6\pm201.8\times10^{-6}\) mm\(^2\)/s and \(633.4\pm182.3\times10^{-6}\) mm\(^2\)/s, respectively (p=0.218). In 13 patients (22.8%), surgical margins were positive. Seminal vesicle invasion was detected in 16 patients (28.1%), whereas bladder neck invasion was observed in 8 patients (14%). Extraprostatic extension was in 22 patients (38.6%). The ADC results for the two groups are shown in Table 3.

**Discussion**

In the present study, we validated the utility of two ADC parameters (ADC\textsubscript{mean} and ADC\textsubscript{cv}) as imaging biomarkers in patients who underwent 3-T mpMRI and radical prostatectomy with WM histopathologic analysis correlation.

Indeed, multiple previous studies with different cohorts have compared ADC\textsubscript{min}, ADC\textsubscript{mean}, and ADC\textsubscript{risk} in prostate imaging and reported conflicting results with varying endpoints. These studies have evaluated different clinical outcomes or endpoints, such as tumor detection, differentiation of malignant and benign lesions, and prediction of tumor aggressiveness or treatment response (10,11-13). The inconsistency of these studies’ conclusions highlights the intricacy and diverse nature of prostate imaging, as well as the difficulties in establishing a clear superiority of one ADC parameter over another.

### Table 2. Laboratory and pathological findings of patients according to ISUP grade groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>ISUP 1-2 (n=40)</th>
<th>ISUP 3-4-5 (n=17)</th>
<th>P*</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.47±6.18</td>
<td>63.94±7.2</td>
<td>0.202</td>
<td></td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>8.31±5.83</td>
<td>13.72±15.84</td>
<td>0.120</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>28.2±3.9</td>
<td>29.55±5.3</td>
<td>0.543</td>
<td></td>
</tr>
<tr>
<td>Blood loss (cc)</td>
<td>318.7±178.1</td>
<td>288.2±182.4</td>
<td>0.539</td>
<td></td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
<td>9 (22.5%)</td>
<td>7 (41.2%)</td>
<td>0.201</td>
<td></td>
</tr>
<tr>
<td>Bladder neck invasion</td>
<td>1 (2.5%)</td>
<td>7 (41.2%)</td>
<td>&lt;0.001</td>
<td>0.237</td>
</tr>
<tr>
<td>Extraprostatic extension</td>
<td>8 (20%)</td>
<td>14 (82.4%)</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Positive surgical margin</td>
<td>3 (7.5%)</td>
<td>10 (58.8%)</td>
<td>&lt;0.001</td>
<td>0.019</td>
</tr>
</tbody>
</table>

*Univariate analyses  
**Multivariate analyses  
PSA: Prostate-specific antigen, BMI: Body mass index, ISUP: International Society of Urological Pathology

### Table 3. ADC parameters according to ISUP grade groups

<table>
<thead>
<tr>
<th>ADC parameters</th>
<th>ISUP 1-2 (n=40)</th>
<th>ISUP 3-4-5 (n=17)</th>
<th>P*</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC\textsubscript{cv}</td>
<td>0.099±0.06</td>
<td>0.174±0.12</td>
<td>0.010</td>
<td>0.041</td>
</tr>
<tr>
<td>ADC\textsubscript{mean}</td>
<td>760.6±201.8</td>
<td>633.4±182.3</td>
<td>0.009</td>
<td>0.218</td>
</tr>
<tr>
<td>SD</td>
<td>72.02±43.44</td>
<td>101.56±56.48</td>
<td>0.052</td>
<td></td>
</tr>
</tbody>
</table>

ADC\textsubscript{cv}: Apparent diffusion coefficient of variation, SD: Standard deviation
Recent publications have compared conventional ADC parameters with $\text{ADC}_{\text{ratio}}$. Many new studies have shown that $\text{ADC}_{\text{ratio}}$ particularly the $\text{ADC}_{\text{mean}}$ ratio concerning the conventional parameter, exhibit the strongest negative correlation with prostate cancer aggressiveness (14). Variability in study designs, patient populations, imaging protocols, and analysis methodologies may have contributed to the disparate findings. The inherent heterogeneity of prostate cancer, with its diverse histological subtypes and varying degrees of aggressiveness, further complicates the interpretation of ADC measurements.

Given the contradictory findings in the literature, additional research involving larger and more diverse cohorts is required to determine the clinical significance and optimal use of $\text{ADC}_{\text{minimum}}$, $\text{ADC}_{\text{max}}$, and $\text{ADC}_{\text{mean}}$ in prostate imaging applications.

These studies should aim to address the limitations of prior research and establish robust correlations between these ADC parameters and clinically relevant endpoints, with the goal of improving diagnostic accuracy and patient management in prostate cancer. $\text{ADC}_{\text{min}}$ and $\text{ADC}_{\text{mean}}$ (reported as the ratio of tumour and nontumour ADC values) are two of the metrics that have been investigated. According to studies, all of these variations have a substantial connection with the Gleason score; however, there are gaps in clinical relevance and aggressiveness. In the current study, we used 3-T mpMRI metrics and histopathological results acquired after radical prostatectomy to validate the usefulness of $\text{ADC}_{\text{cv}}$ as an imaging biomarker.

The $\text{ADC}_{\text{cv}}$ value represents a novel texture parameter that is utilized in cancer. Tissue heterogeneity has been proposed as a basis for a tumour biomarker in cancer investigations. Tissue heterogeneity is an emerging hallmark of tumour. Although numerous methods for measuring tissue heterogeneity using textural analysis tools have been described, they are frequently complicated and require sophisticated software (15). Stein et al. (11) reported that $\text{ADC}_{\text{cv}}$ is a simple-to-calculate statistical parameter that indicates related variation. They evaluated the $\text{ADC}_{\text{cv}}$ and maximum standardized uptake value ($\text{SUV}_{\text{max}}$) values using positron emission tomography MRI of liver metastases. As the outcome of this investigation, it was discovered that the $\text{SUV}_{\text{max}}$ value and the $\text{ADC}_{\text{cv}}$ value have a positive link. Overall, the study findings suggest that the $\text{ADC}_{\text{cv}}$ value obtained from diffusion-weighted MRI can serve as a useful biomarker for predicting tumor aggressiveness in liver metastases. This information could aid in cancer investigations and treatment planning for patients with liver metastases. Sokmen et al. (16) confirmed with MRI fusion prostatic biopsy that $\text{ADC}_{\text{cv}}$ is a tissue texture parameter in prostate cancer. However, our difference from their study is that our study was conducted after radical prostatectomy.

The multivariate analysis conducted in our study revealed that the $\text{ADC}_{\text{cv}}$ parameter effectively predicts tumor aggressiveness. According to our findings, the $\text{ADC}_{\text{cv}}$ parameter was suitable for regular inclusion in mpMRI reports. This parameter was considered easy to measure, facilitating its integration into radiology reports. Furthermore, integrating $\text{ADC}_{\text{cv}}$ measurements into routine practice did not significantly increase the workload of radiologists. Throughout our investigation, $\text{ADC}_{\text{cv}}$ demonstrated the highest efficacy in predicting tumor aggressiveness. Considering the $\text{ADC}_{\text{cv}}$, cut-off value, it should be noted that prostate cancer may be highly aggressive with $\text{ADC}_{\text{cv}}$ values higher than 0.081. Resection and lymph node dissection should be performed more carefully in these patients.

Nevertheless, it is important to note that other factors such as bladder invasion, extracapsular extension (ECE), and positive surgical margins were also correlated with ISUP grade groups.

**Study Limitations**

Our research has a few limitations. First, this is a retrospective study, and the data were collected from past medical records and imaging reports. This design has inherent limitations compared with prospective studies, where data are collected in real time. The study was conducted with a limited number of participants, which can impact the generalizability and statistical power of the findings. Due to the small sample size and retrospective nature of the study, there might be biases in the selection of participants, leading to a non-representative sample.

Overall, this study emphasizes the need for further research to enhance the understanding of ADC measurements in prostate cancer and their potential clinical applications. By addressing the study limitations and establishing stronger correlations, ADC values could be used more effectively for diagnostic accuracy and patient management in prostate cancer.

**Conclusion**

The statement suggests that the speed and accuracy of $\text{ADC}_{\text{cv}}$ could be advantageous in enhancing future prostate cancer screening methods. The validation of $\text{ADC}_{\text{cv}}$ as an imaging biomarker may have significant implications for the detection and assessment of prostate cancer aggressiveness, potentially aiding in more accurate diagnosis and treatment planning for patients. Our findings suggest that the $\text{ADC}_{\text{cv}}$ parameter holds promise as a valuable tool for characterizing prostate cancer aggressiveness. Its simplicity of use and potential to provide clinically meaningful information make it a compelling candidate for integration into routine clinical practice.

**Ethics**

**Ethics Committee Approval:** The local ethics committee accepted this single-center retrospective study conducted.
between October 2019 and June 2023 (Acıbadem Mehmet Ali Aydinlar University Medical Research Evaluation Board - approval ID: 2023-13/466, date: 17.08.2023).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

References