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Apparent Diffusion Coefficient of Variation (ADC_{cv}): A New Biomarker for Aggressiveness in Prostate Cancer?

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

Apparent diffusion coefficient (ADC_{cv}) could be benefical in improving future prostate cancer imaging. The validation of ADC_{cv} 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_{mean}, $ADC_{coefficient\ of\ variation}$ (ADC_{cv}), 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_{mean} values for the two groups were not significantly different (p=0.218). ADC_{cv} 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_{cv} 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_{cv} 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 (MpMRI). MpMRI 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

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over a tissue area per second (mm^2/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_{ratio} 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 (Acıbadem Mehmet Ali Aydınlar 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 imagesand 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 fuzed 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/mm^2 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_{mean} and standard deviation.This ROI, known as $ADC_{mean,}$ 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_{cv} was computed using the formula Standard Deviation/ADC_{mean} on the ADC map, according to a previous study (11). The measurements of ADC_{mean} and ADC_{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_{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.

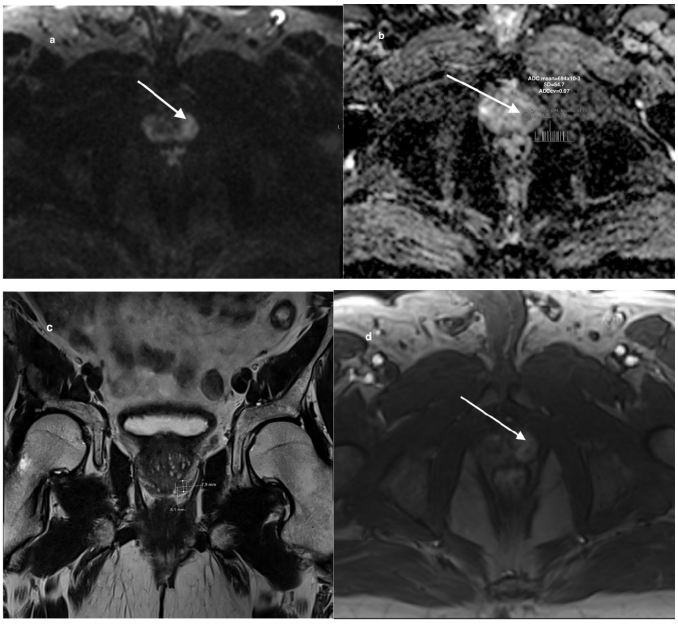

Figure 1. A 65-year-old patient with ISUP Grade Group 2 (Gleason Score 3+4) prostate cancer. On diffusion-weighted image (a) the tumour has hyperintensity signal. The apparent diffusion coefficient (ADC) map (b) demonstrates ADC_{mean} ($694x10^{-6}$) ADC_{cv} (54,7/694= 0.07) (white arrows). T2-weighted coronal (c) and post-contrast T1-weighted axial (d) images (white arrow) depict 8 mm diameter tumour

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_{mean} inverse correlation with ISUP (p=0.218) while ADC_{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_{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_{cv} value of low grade group and high-grade groups were 0.099 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

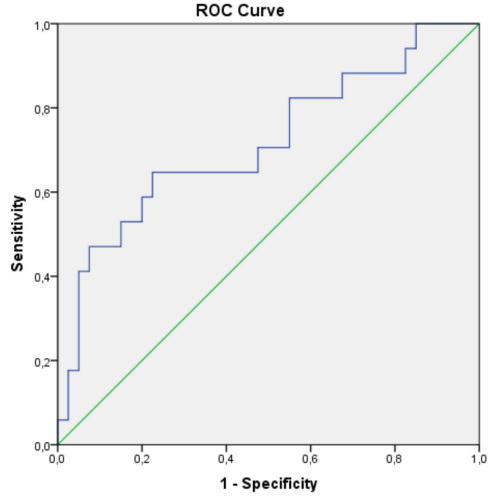

Figure 2. Receiver operating characteristic (ROC) analysis curve of high-risk prostate cancer detection with ADC_{cv}, AUC: 0.716 (p<0.010)

Group 3. ADC_{mean} value of low grade group and high grade group was 760.6±201.8×10^{-6} mm^2/s and 633.4±182.3×10^{-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_{mean} and ADC_{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_{min}, ADC_{mean}, and ADC_{ratios} 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.

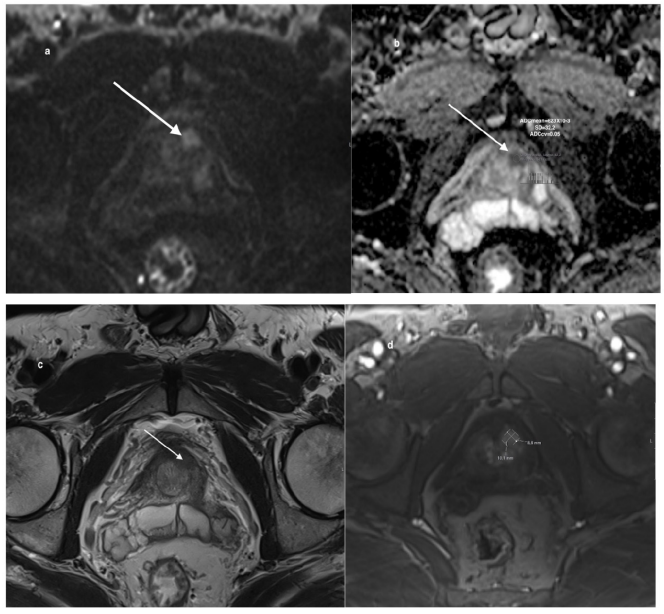

Figure 3. Prostate cancer ISUP Grade Group (Gleason score 4+3). The diffusion-weighted image (a) and ADC map (b) reveal an ADC_{mean} of 623 X 10^{-6} and an ADC_{cv} of 32/623 = 0.05 (white arrow). T2-weighted axial (c) and post-contrast T1-weighted axial (d) images depict a tumour with a 10 mm diameter

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

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

*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

ADC parameters	ISUP 1-2 n=40	ISUP 3-4-5 n=17	P*	P**
ADC_{cv}	0.099±0.06	0.174±0.12	**0.010**	**0.041**
ADC_{mean}	760.6±201.8	633.4±182.3	**0.009**	0.218
SD	72.02±43.44	101.56±56.48	0.052	

ADC_{cv}: Apparent diffusion coefficient of variation, SD: Standard deviation

Recent publications have compared conventional ADC parameters with ADC_{ratios}. Many new studies have shown that ADC_{ratios}, particularly the ADC_{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 $ADC_{minimum}$ ($ADC_{min)}$ and ADC_{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. ADC_{min} and ADC_{ratio} (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 ADC_{cv} as an imaging biomarker.

The ADC_{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 ADC_{cv} is a simple-to-calculate statistical parameter that indicates related variation. They evaluated the ADC_{cv} and maximum standardized uptake value (SUV_{max}) values using positron emission tomography MRI of liver metastases. As the outcome of this investigation, it was discovered that the SUV_{max} value and the ADC_{cv} value have a positive link. Overall, the study findings suggest that the ADC_{cv} value obtained from diffusion-weighted MRI can serve as a usef 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 ADC_{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 ADC_{cv} parameter effectively predicts tumor aggressiveness. According to our findings, the ADC_{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 ADC_{cv} measurements into routine practice did not significantly increase the workload of radiologists. Throughout our investigation, ADC_{cv} demonstrated the highest efficacy in predicting tumor aggressiveness. Considering the ADC_{cv} cut-off value, it should be noted that prostate cancer may be highly aggressive with ADC_{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 ADC_{cv} could be advantageous in enhancing future prostate cancer screening methods. The validation of ADC_{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 ADC_{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 Aydınlar 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

Surgical and Medical Practices: A.A.K., B.Ç., A.T., Concept: A.A.K., Design: A.A.K., B.Ç., A.T., Data Collection or Processing: A.A.K., B.Ç., A.T., Analysis or Interpretation: A.A.K., B.Ç., Literature Search: A.A.K., Writing: A.A.K., B.Ç.

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

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References

1. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The Epidemiology of Prostate Cancer. Cold Spring Harb Perspect Med 2018;8:a030361.
2. Kim CK, Park BK, Kim B. Diffusion-weighted MRI at 3 T for the evaluation of prostate cancer. AJR Am J Roentgenol 2010;194:1461-1469.
3. Turkbey B, Pinto PA, Mani H, Bernardo M, Pang Y, McKinney YL, Khurana K, Ravizzini GC, Albert PS, Merino MJ, Choyke PL. Prostate cancer: value of multiparametric MR imaging at 3 T for detection--histopathologic correlation. Radiology 2010;255:89-99.
4. Saito S, Koyama Y, Ueda J, Hashido T. Relationship between Apparent Diffusion Coefficient Distribution and Cancer Grade in Prostate Cancer and Benign Prostatic Hyperplasia. Diagnostics (Basel) 2022;12:525.
5. Wu X, Reinikainen P, Vanhanen A, Kapanen M, Vierikko T, Ryymin P, Hyödynmaa S, Kellokumpu-Lehtinen PL. Correlation between apparent diffusion coefficient value on diffusion-weighted MR imaging and Gleason score in prostate cancer. Diagn Interv Imaging 2017;98:63-71.
6. Manetta R, Palumbo P, Gianneramo C, Bruno F, Arrigoni F, Natella R, Maggialetti N, Agostini A, Giovagnoni A, Di Cesare E, Splendiani A, Masciocchi C, Barile A. Correlation between ADC values and Gleason score in evaluation of prostate cancer: multicentre experience and review of the literature. Gland Surg 2019;8(Suppl 3):S216-S222.
7. Ingole SM, Mehta RU, Kazi ZN, Bhuyar RV. Multiparametric Magnetic Resonance Imaging in Evaluation of Clinically Significant Prostate Cancer. Indian J Radiol Imaging 2021;31:65-77.
8. Felker ER, Margolis DJ, Nassiri N, Marks LS. Prostate cancer risk stratification with magnetic resonance imaging. Urol Oncol 2016;34:311-319.
9. Bengtsson J, Thimansson E, Baubeta E, Zackrisson S, Sundgren PC, Bjartell A, Flondell-Sité D. Correlation between ADC, ADC ratio, and Gleason Grade group in prostate cancer patients undergoing radical prostatectomy: Retrospective multicenter study with different MRI scanners. Front Oncol 2023;13:1079040.
10. Hötker AM, Mazaheri Y, Aras Ö, Zheng J, Moskowitz CS, Gondo T, Matsumoto K, Hricak H, Akin O. Assessment of prostate cancer aggressiveness by use of the combination of quantitative DWI and dynamic contrast-enhanced MRI. Am J Roentgenol 2016;206:756-763.
11. Stein D, Goldberg N, Domachevsky L, Bernstine H, Nidam M, Abadi-Korek I, Guindy M, Sosna J, Groshar D. Quantitative biomarkers for liver metastases: comparison of MRI diffusion-weighted imaging heterogeneity index and fluorine-18-fluoro-deoxyglucose standardised uptake value in hybrid PET/MR. Clin Radiol 2018;73:832.e17-832.e22.
12. Raczeck P, Frenzel F, Woerner T, Graeber S, Bohle RM, Ziegler G, Buecker A, Schneider GK. Noninferiority of Monoparametric MRI Versus Multiparametric MRI for the Detection of Prostate Cancer: Diagnostic Accuracy of ADC Ratios Based on Advanced "Zoomed" Diffusion-Weighted Imaging. Invest Radiol 2022;57:233-241.
13. Onal C, Erbay G, Guler OC, Oymak E. The prognostic value of mean apparent diffusion coefficient measured with diffusion-weighted magnetic resonance image in patients with prostate cancer treated with definitive radiotherapy. Radiother Oncol 2022;173:285-291.
14. Bajgiran AM, Mirak SA, Sung K, Sisk AE, Reiter RE, Raman SS. Apparent Diffusion Coefficient (ADC) Ratio Versus Conventional ADC for Detecting Clinically Significant Prostate Cancer With 3-T MRI. AJR Am J Roentgenol 2019;213:W134-W142.
15. Alic L, Niessen WJ, Veenland JF. Quantification of heterogeneity as a biomarker in tumor imaging: a systematic review. PLoS One 2014;9:e110300.
16. Sokmen BK, Sokmen D, Comez Yİ, Eksi M. Prediction of Prostate Cancer Aggressiveness Using a Novel Multiparametric Magnetic Resonance Imaging Parameter: Tumor Heterogeneity Index. Urol Int 2022;106:946-953.