

The correlation between biological activity and diffusion-weighted MR imaging and ADC value in cases with prostate cancer

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Summary *Purpose: Firstly, we aimed to investigate the correlation among dynamic contrasted magnetic resonance (MR) images, diffusion-weighted MR images, and apparent diffusion coefficient (ADC) values in patients with prostate cancer. Secondly, we aimed to investigate the roles of these variables on clinical risk classification and the biological behavior of the prostate cancer.*

Methods: A total of sixty with prostatic adenocarcinoma patients diagnosed between January 2011 and May 2013 were retrospectively included in the study. Risk classification of patients were evaluated as low-risk (Group 1) (n = 20) (Stage T1c-T2a, PSA < 10 ng/ml, Gleason Score < 7), moderate-risk (Group 2) (n = 18) (Stage T1b-T2c, PSA = 10-20 ng/ml, Gleason Score = 7) and high-risk (Group 3) (n = 22) (Stage > T3a, PSA > 20 ng/ml, Gleason Score > 7). Diffusion-weighted MR images, dynamic contrasted MR images, and ADC values of the prostates were correlated.

Results: ADC values of the cases in Group 3 were lower than those of the other groups (p < 0.001). ADC values of the areas without malignancy did not differ significantly between groups (p > 0.05). Biological activity of the tumor tissue was determined by GS, while a negative correlation was observed between GSs and ADC values of the patients, (p < 0.001).

Conclusion: In tumors with higher Gleason scores, lower ADC values were obtained. These measured values can play a role in the noninvasive determination of the cellularity of the tumoral mass.

KEY WORDS: Prostate cancer; Dynamic contrasted MRI; Diffusion-weighted MRI; Apparent diffusion coefficient value.

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INTRODUCTION

Prostate cancer is the most frequently diagnosed type of cancer among men in the *United States of America*, while it ranks after lung and colorectal cancer in *Europe* (1). However, it has the second most frequently seen cancer-related mortality among men (2, 3). Though the incidence of prostate cancer increases, it affects 15 and 4% of the male population in developed and developing countries, respectively (4). Prostate cancer has a wide spectrum ranging from slowly progressing course and higher aggressivity. Diagnosis of the prostate cancer and

determination of its location have been realized and evaluated using serum *prostate-specific antigen* (PSA) tests, digital rectal examination and *transrectal ultrasound* (TRUS) guided-biopsy which has a diagnostic accuracy of 36.8 percent (5, 6).

Imaging modalities, which provide individualized prognostic foresight are important for us. Currently applied functional *magnetic resonance* (MR) modalities including conventional MR and *diffusion-weighted imaging* (DWI) provide more detailed information about location, size and activity, of the tumor and also a noninvasive identification method (7). Since DWI is a technique used to demonstrate molecular diffusion due to Brownian movements in biological tissues, diffusion is restricted in tumor cells because of increased cellularity. Various studies based on lower *apparent diffusion coefficient* (ADC) demonstrated that DWI could discriminate between benign and malignant prostatic tissue in comparison with normal prostatic tissue (8, 9).

In our study, we aimed to investigate if determination of the biological behavior of the prostate cancer and the roles played by dynamic contrasted MRI and DWI in clinical risk classification of prostate cancer is possible by correlating dynamic contrasted MRI, DWI, ADC values and histopathological diagnosis.

In our study, firstly we aimed to investigate the correlation among dynamic contrasted MR images, diffusion-weighted MR images, and ADC values in patients with prostate cancer. Secondly, we aimed to investigate the roles of these variables on clinical risk classification and the biological behavior of the prostate cancer.

MATERIALS AND METHODS

Study design

The study has been conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board (25/11/2015, no:33). Written informed consent was obtained from all subjects.

A total of sixty patients with suspected prostate cancer

based on clinical examination and PSA measurements, and diagnosed as prostatic adenocarcinoma histopathologically between January 2011 and May 2013 were evaluated retrospectively.

Risk classification of 60 clinically localized prostate cancer patients who underwent radical prostatectomies were evaluated as low-risk (Group 1) (n = 20) (Stage T1c-T2a, PSA < 10 ng/ml, Gleason Score < 7), moderate-risk (Group 2) (n = 18) (Stage T1b-T2c, PSA = 10-20 ng/ml, Gleason Score = 7) and high-risk (Group 3) (n = 22) (Stage > T3a, PSA > 20 ng/ml, Gleason Score > 7).

Outcome parameters

T1-T2 axial, coronal section, axial diffusion-weighted MR images and dynamic contrasted MR images of the prostates of all cases were reviewed. In the present study “body” coil was used to obtain single shot images. Diffusion-weighted sequences were obtained on axial plane at 3 gradients with different b values (b: 0 sec/mm², b: 500 sec/mm², b: 1000 sec/mm²). ADC maps were constructed using automated devices. ADC values and histopathological diagnoses of 60 cases were comparatively evaluated. Patients with bleeding demonstrated on post-TRUS-Bx MR images and inoperable advanced stage and metastatic cases were excluded from the study. In our study Siemens Avanto (Erlangen Germany) 1.5 Tesla MR device of our radiology clinic was used.

Histopathological evaluations of radical prostatectomized cases were reported in consideration of prostate zone, tumor percentage, surgical margin, Gleason score (GS), locations with/without malignancy. Cases with low, moderate and high risk were classified as Groups 1, 2, and 3, respectively (Figures 1-3). ADC values obtained individually using DWI techniques for regions of malignancy detected in pathology specimens and also for regions reported as benign lesions were determined. These values were compared with histopathological results and GSs of patients who underwent radical prostatectomy.

Using this method, the correlation (if any) between biological activity detected by histopathological evaluation and DWI in prostate cancer patients was investigated.

Statistical Analysis: All statistical analyses were realized using Windows for SPSS v.13.0 (Statistical Package for Social Sciences) (SPSS Inc. Chicago, ABD). ADC values were expressed as mean ± standard deviation. Student’s t test was used to compare ADC values. For intergroup comparisons of age, PSA values, GS One Way ANOVA (Tukey) Test was used. p < 0.05 was accepted as the level of statistical significance.

RESULTS

Median age of 60 patients who underwent conventional MRI and DWI was 60.95 (range, 45 to 73) years without any significant intergroup difference regarding age of the patients (p > 0.05). Median PSA value of the cases was 10.81 (range, 3.10 to 43.35) ng/ml. As a matter of fact, PSA values were significantly higher in Group 3 (p < 0.001). GS of 7 points was detected in Groups 1 (n = 20) and 2 (n = 22). In Group 3, GSs of 8 (n = 7), 9 (n = 3) and 10 (n = 1) points were detected in respective num-

ber of cases (Table 1). To calculate ADC values of the cases circumscribed regions of interest (ROI) of the cases were determined based on anatomical location of histopathologically detected adenocarcinoma foci in radical prostatectomy specimens of each patient. Therefore, for each patient diagnosed as prostate cancer, foci of adenocarcinoma were on different locations. They were on peripheral zone (n = 51 foci), central zone (n = 5) and both central and peripheral zone (n = 4). A median ROI of the prostatic area of 25 mm² containing adenocarcinoma foci based on histopathological examination of the

Table 1.
Prostate-specific antigen values and Gleason scores according to groups.

	Group 1 (n = 20)	Group 2 (n = 22)	Group 3 (n = 18)
Mean age (years)	58.45	61.59	62.94
Mean PSA (ng/ml)	6.79	8.80	18.08
Gleason 6 (n)	20	5	2
Gleason 7 (n)	-	17	5
Gleason 8 (n)	-	-	7
Gleason 9 (n)	-	-	3
Gleason 10 (n)	-	-	1

Table 2.
Apparent diffusion coefficient values of malign lesions according to groups.

	n (%)	ADC (×10 ⁻⁶ mm ² /sec) mean (min-max)	P value
Group 1	20 (33.3%)	1130.30 ± 110.77 (931-1305)	p < 0.001
Group 2	22 (36.6%)	988.05 ± 141.54 (618-1241)	
Group 3	18 (30%)	822.33 ± 141.11 (445-1034)	
Total	60 (100%)	985.75 ± 179.03 (445-1305)	

Table 3.
Apparent diffusion coefficient values of benign lesions according to groups.

	n (%)	ADC (×10 ⁻⁶ mm ² /sec) mean (min-max)	P value
Group 1	20 (33.3%)	1541.50 ± 190.76 (1244-2002)	p > 0.05
Group 2	22 (36.6%)	1513.32 ± 132.64 (1337-1782)	
Group 3	18 (30%)	1431.94 ± 163.87 (1196-1773)	
Total	60 (100%)	1498.30 ± 166.67 (1196-2002)	

Table 4.
Apparent diffusion coefficient values of malign lesions according to Gleason scores.

	n (%)	ADC (×10 ⁻⁶ mm ² /sec) mean (min-max)	P value
Gleason 6	27 (45%)	1105.78 ± 112.70 (898-1305)	p < 0.001
Gleason 7	22 (36.66%)	940.00 ± 139.19 (618-1241)	
Gleason 8	7 (11.66%)	863.43 ± 114.75 (670-1034)	
Gleason 9	3 (5%)	706.67 ± 67.26 (646-779)	
Gleason 10	1 (1.66%)	445 (445-445)	
Total	60 (100%)	985.75 ± 179.03 (445-1305)	

prostate specimens of each patient was measured and average value of these measurements were taken into consideration as the basic reference value. Therefore, ADC values were determined based on the histopathology reports of the cases with prostate cancer. Accordingly ADC values of the cases in Group 3 were lower than those of the other groups ($p < 0.001$) (Table 2).

ADC values were determined based on ROIs of 25 mm² of prostates without malignancy as detected by histopathological evaluation. Accordingly, ADC values of the areas without malignancy (ie. benign areas) did not differ significantly between groups ($p > 0.05$) (Table 3). Biological activity of the tumor tissue was determined by GS, while a negative correlation was observed between GSs and ADC values of the patients, ($p < 0.001$) (Table 4).

DISCUSSION

Gleason score is the most widely used and accepted scoring system in the evaluation of the aggressivity of the prostate cancer D'Amico classification of clinical risk has been developed by combining PSA value and GS in order to evaluate tumor aggressivity more accurately (10, 11). Using conventional imaging modalities, it is quiet difficult to make a diagnosis of locally advanced prostate cancer. Besides because of the presence of benign diseases as BPH and chronic prostatitis it is more difficult discriminate among these entities (12). Magnetic resonance imaging can delineate the contours of the prostate and anatomical details of the internal zone can be disclosed. In addition, DWI, MR Spectroscopy (MRS) and dynamic contrasted MRI can also provide functional data. All of these data can determine the location of cancer, tumor volume and aggressivity more accurately when compared with other imaging modalities. In cases with suspect clinical prostate cancer patients with higher PSA values, but negative recurrent negative biopsy results, MRI demonstrates anatomic location of the tumor and functions as a road map for biopsies and surgery to be perform and also paves the way for focal radiotherapeutic approach (13, 14).

Many studies have been performed on the discrimination between normal and malignant prostate tissue using DWI technique. ADC values reported in the literature for peripheral zone of the normal prostate (1.60-1.97 $\times 10^{-3}$ mm²/s), transitional zone (1.27-1.79 $\times 10^{-3}$ mm²/s) and prostate cancer (0.98-1.38 $\times 10^{-3}$ mm²/s) vary considerably. This variability may stem from the power of the diffusion gradient (300-1000 s/mm²) and magnetic area (1.5-3 T) (15-17).

Yagci *et al.* performed a study on 43 patients and reported that pre-biopsy DWI was valuable in the detection, localization and staging of the tumor in the peripheral zone and ADC values would be a

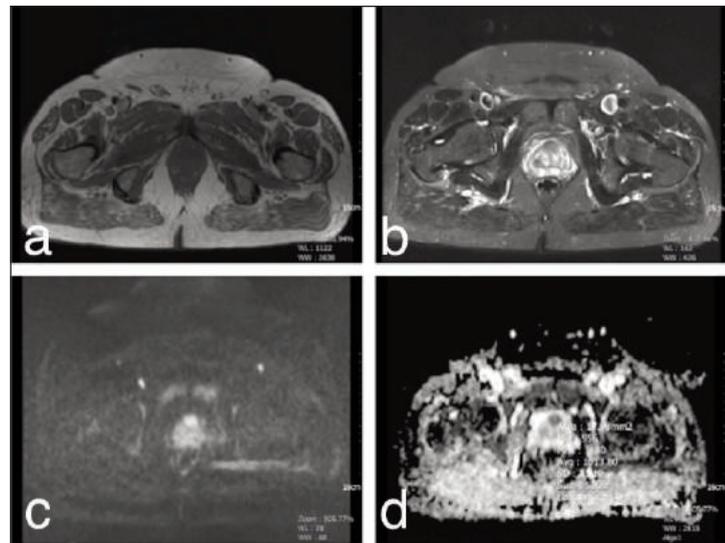


Figure 1.

A low-risk patient with PSA = 8.3 ng/ml and Gleason score of 6. T1A and T2 fat sat sequences showing hypointense central zone of the prostate (a, b, e). Restricted DWI MRI showing a malignant focus with ADC value measured as 1013 \times 106 mm²/sec which demonstrated marked contrast uptake during contrast-enhanced examination (c, d).

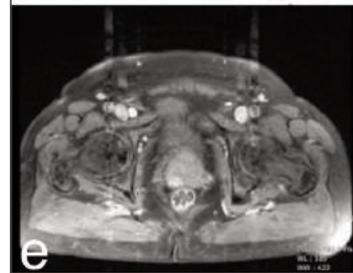
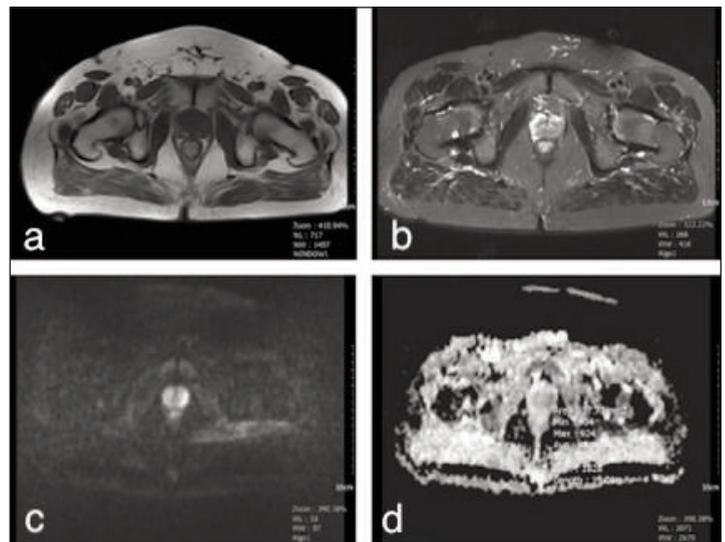
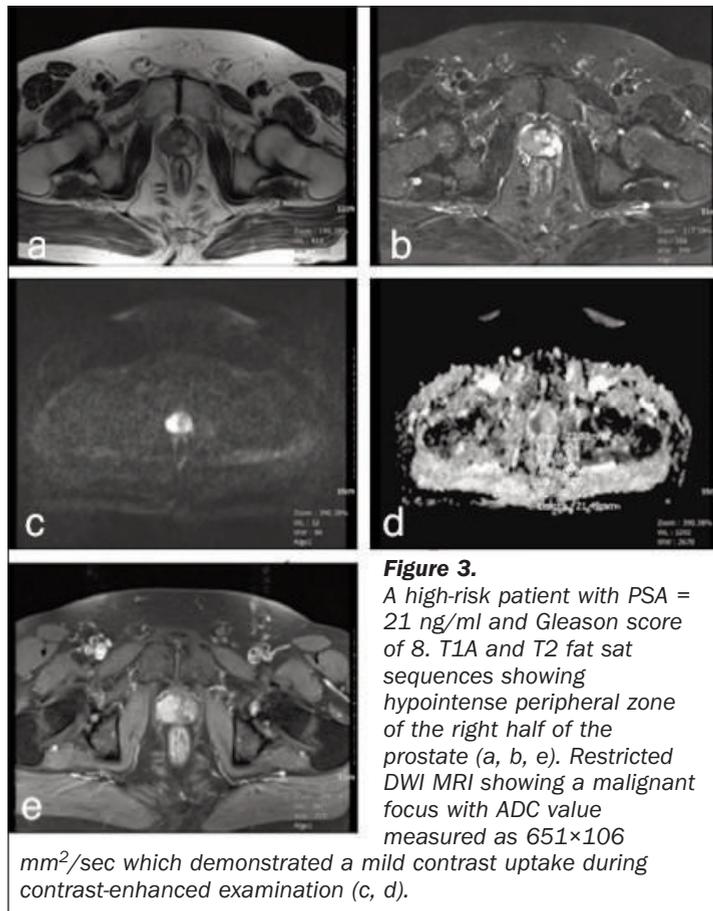


Figure 2.

A moderate-risk patient with PSA = 15 ng/ml and Gleason score of 7. T1A and T2 fat sat sequences showing hypointense peripheral zone of the left half of the prostate (a, b, e). Restricted DWI MRI showing a malignant focus with ADC value measured as 914 \times 106 mm²/sec which demonstrated a mild contrast uptake during contrast-enhanced examination (c, d).



demonstrated a mild contrast uptake during contrast-enhanced examination (c, d).



guiding tool for biopsy. In parallel with GSs, they found ADC values as $1.18 \pm 0.44 \times 10^{-3}$ mm²/s (GS 6); $1.05 \pm 0.15 \times 10^{-3}$ mm²/s (GS7) and $0.84 \pm 0.16 \times 10^{-3}$ mm²/s (GS \geq 8) (18). Differently from our study, they accepted a b value of 800 s/mm² as a base value and used endorectal coil. Tamada *et al.* used 1.5 T MR in their study group consisting of 90 prostate cancer patients and indicated the presence of a negative correlation between ADC values and GSs (19). Similarly, Mazaheri *et al.* and deSouza *et al.* compared ADC levels in cases with low and high-risk prostate cancer and found significant intergroup differences (20, 21). van As *et al.* followed up 86 patients for an average of 29 months and then evaluated PSA, clinical stage and results of recurrent biopsy outcomes with the intention of detecting localized prostate cancer with a favorable prognosis. The Authors revealed that ADC value is an important prognostic factor demonstrating progression of the disease (22).

Gibbs *et al.* prospectively correlated 3T MRI, T2 relaxation time and ADC values in patients scheduled for radical prostatectomy and compared cellular density measurements in prostate cancer tissue in prostatectomy materials and ADC values calculated for normal peripheral zone and cancer tissue. In conclusion, a negative correlation between cellular density, more markedly between GSs and ADC values was observed. In the light of the data obtained, it was concluded that via determination of cellular density, which is potentially related to GS, MRI can have a prognostic role in the

prediction of metastatic activity and aggressivity of the tumor tissue (23).

In a study by Türkbey *et al.*, performed in the year 2011, the authors demonstrated a negative correlation between D'Amico risk classification using 3T MR and endorectal coil GS of the tumor and ADC values and indicated that ADC values would help the clinicians in the evaluation of tumor aggressivity (24). In our study, a negative correlation was detected between ADC values and Gleason risk classification. In tumors with increased GSs, a drop in ADC values was observed due to altered structure of the tumor tissue in its location in the prostate gland because of tumoral cellularity and also restricted movement of water molecules in this location. Besides, an important difference was detected in ADC values of the tumors included in low, moderate and high clinical risk classification. Treatment protocol effects the determination of biological aggressivity in prostate cancer. In some clinics, active surveillance is the most optimal follow-up strategy in the determination of biological aggressivity. It will be appropriate to evaluate aggressivity of prostate cancer and use it with the intention to follow-up the patients who will be included in the active surveillance protocol with ADC mapping.

This approach can provide us a noninvasive method of monitorization of the patients when compared with recurrent biopsies (25).

CONCLUSIONS

Since all regions of the prostate gland can be visualized and ADC mapping can be obtained using diffusion-weighted MR, it can provide more advantageous evaluation when compared with TRUS biopsy. Foci of malignancies, which can not be detected in TRUS biopsy, can be determined with attentive and detailed examination for the purpose of ADC mapping. At the same time, in the patient group with persistently higher PSA levels but without any detected adenocarcinoma foci in recurrent prostate biopsies, ADC mapping with diffusion-weighted MR imaging of the prostate detects locations with lower ADC values which can contribute significantly to the determination of targeted biopsy locations for recurrent biopsies to be performed in the future with resultant decrease in the number of unnecessary biopsies. In our study, the correlation between Gleason scoring system and D'Amico clinical risk classification which determines biological activity of the tumor, and ADC values were revealed. In tumors with higher GSs, lower ADC values were obtained. These measured values can play a role in the noninvasive determination of the cellularity of the tumoral mass. Discrimination between low and high GSs using ADC values may allow noninvasive specification of the disease prognosis. As the number of prospective studies performed with ADC increase in the years to come, ADC may have a guiding role in the selection of treatment for the cases with locally advanced stage and metastatic prostate cancer, in the monitorization of treatment response and also in determination of the disease-free survival.

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