Discriminant Efficacy of mpMRI for Variant Pathology Associated with Prostate Adenocarcinoma

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Purpose: Implementation of multiparametric magnetic resonance imaging (mpMRI) for prostate adenocarcinoma's variant pathology requires awareness. The aim of this retrospective study was to investigate the discriminant efficacy of multiparametric magnetic resonance imaging modality for variant pathology associated with prostate adenocarcinoma.

Methods: Consecutive 247 prostate cancer patients who underwent radical prostatectomy in our university-based hospital between October 2014 and October 2019, were retrospectively reviewed. Data of mpMRI-associated contrast enhancements, T2 signals, apparent diffusion coefficients (ADC), ages, and PSA values were compared. Clinical and demographic data of patients were noted including associated variant pathologies and reports of preoperative mpMRI images.

Results: Among the patients, 63 (26%) had variant pathology and 14 (22%) had mpMRI before primary prostate biopsy. The group with variant pathology and the control group had similar perfusion curves and increased contrast when compared for mpMRI parameters, but different ADC values for each of the adjusted b-values for 400, 800 and 1400.

Conclusion: Our study demonstrates that mpMRI appears to have no role in distinguishing rare variant pathologies associated with prostate adenocarcinoma despite different ADC values.

Keywords: prostate adenocarcinoma; prostate cancer variants; mpMRI; apparent diffusion coefficient.

INTRODUCTION

Prostate cancer is the most common malignancy in men after lung cancer[1]. In recent years, prostate biopsy has been the first step to rule out malignancy, though it has low diagnostic efficiency of 30% for PSA ≥ 4ng/mL in older men[2]. Recently, multiparametric magnetic resonance imaging (mpMRI) has been introduced into the clinical practice to decrease those unnecessary prostate biopsies and their associated complications as well as to have better information about the location, grade, and extent of the tumor compared to other imaging modalities[3-5].

The ability of mpMRI to differentiate malignancy depends on its multiple sequences including T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), dynamic contrast imaging (DCE), and diffusion-weighted imaging (DWI). These two last sequences further provide functional information about tissues including diffusion reflected by the b-values (amount of diffusion weight) in DWI and perfusion in DCE. The apparent diffusion coefficient (ADC) map from multiple b-values is a quantitative measure of tissue diffusion[3]. Increasing the b-value, suppresses the signal of normal prostate tissue making tumoral tissue more prominent[5]. Likewise, in active surveillance patients prior to primary or secondary biopsy, the utility of ADC parameters in mpMRI has been shown to improve overall sensitivity while maintaining the specificity for the detection of prostate cancer[6].

Though adenocarcinoma is the most commonly encountered malignant histopathologic diagnosis of prostate, there are also substantial numbers of variant pathologies associated with primary adenocarcinoma[7]. However, variant pathologies are suggested to be associated with higher ISUP scores and worse prognoses including earlier biochemical recurrence and metastatic lesions at an earlier course of the disease[8,9].

Although many studies have been conducted on different b-values in the diagnosis of prostate cancer, there is no study in the literature on prostate cancer variants [10,11]. Nonetheless, if this accuracy can be determined in advance with mpMRI for variant pathologies related to prostate cancer, more accurate and faster planning for a treatment modality might be possible. Therefore, in this study, it was aimed to determine the role of mpMRI to differentiate rare variant pathologies related with prostate cancer.

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Table 1. The pathological prognostic factors compared according to the presence of associated variant pathology.

	Variant pathology absent	Variant pathology present	*p* value
Surgical Margin Negative	131 (73%)	28 (44%)	
Surgical Margin Positive	48 (27%)	35 (56%)	< 0.001
Extracapsular extension (ECE) absent	143 (80%)	38 (60%)	
Extracapsular extension (ECE) present	37 (20%)	25 (40%)	0.004
Lymphovascular Invasion Negative	162 (90%)	41 (65%)	
Lymphovascular Invasion Positive	18 (10%)	22 (35%)	< 0.001
Perineural Invasion Negative	56 (31%)	13 (21%)	
Perineural Invasion Positive	124 (69%)	50 (79%)	0.144
pN-	168 (93%)	49 (78%)	
pN+	12 (7%)	14 (22%)	0.001

MATERIALS AND METHODS

In this retrospective cohort study, we analyzed the pathology reports of all consecutive patients who underwent radical prostatectomy operation in our university-based hospital between October 2014 and October 2019.

In all MRI recordings similar protocol settings were utilized with the same software and scanner hardware which is 1.5T GE Signa voyager (General Electric, Milwaukee, WI). In supine position, anterior surface and posterior multiphase array coils were used in all imaging studies. Our mpMRI protocol included axial T1 (TR 595, TE 12), axial, sagittal and coronal T2-weighted (TE 107, TR 4400), diffusion-weighted (DW) (b-values of 400, 800 and 1400 mm/s^2), and dynamic contrast-enhanced (DCE) sequences. Dynamic contrast enhancement (DCE) technique: axial plan T1 GRE, injection: 0.1 mmol/kg at 3 mL/s. Field of view (FOV): 120-200 mm and slice thickness 3 mm for all images and no gap. ADC calculation of high b-value 1400 s/mm^2. Diffusion-weighted MRI apparent diffusion coefficient (ADC) and DCE subtract maps (SUB, computed as the difference between the phase corresponding to the contrast bolus arrival and the baseline phase) were computed using the scanner software. All patients' mpMRI records which are retrospective in nature were re-verified for their imaging findings by an expert radiologist (5 year-experience in prostate mpMRI interpretation). For each study, the diagnostic quality and that SUB was based upon subtraction of baseline pre-contrast images from first bolus arrival phase were confirmed. Regions of interest (ROI) were manually outlined on the T2 ax, ADC, and SUB series for the tumor-suspicious area, monitoring the matching slice in all other series for the given study. Overall, PI-RADS v2 was assessed for each study with automatically calculated mean ADC value for the ROI areas.

Clinical and demographic data of all patients who underwent radical prostatectomy during above dates were noted including associated variant pathologies and reports of preoperative mpMRI images, if performed, were noted. Patients with prostate cancer, mpMRI-associated contrast enhancement, T2 signals, apparent diffusion coefficients (ADC), and age and PSA values were compared with the control group patients.

Statistical analyses were performed with SPSS statistics software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Comparisons of groups were done with Chi-square test and Student's t test where appropriate. The mean values were presented with their 95% Confidence intervals. ROC curve was used to illustrate related sensivity and specificity of ADC values. Statistical significance was set at less than 0.05.

RESULTS

A total of 247 consecutive patients who underwent radical prostatectomy were included in the study. The mean age of all patients were 62.82 years (95% Confidence Interval (CI) 62.05-63.63). Mean body-mass index (BMI) of the patients was 26.79 kg/m2 (95% CI 26.31-27.27). Mean preoperative PSA value was 13.84 ng/ml (95% CI 11.46-16.22). Approximately two-thirds of the patients had one or more co-morbid diseases with the commonest ones as hypertension (41%), diabetes mellitus (20%) and cardio-vascular diseases (15%). The histopathological ISUP grade of prostate adenocarcinoma was ≤ 2 in 78% and ≥ 3 in the rest. Patients were followed up with a mean follow up time of 4.05 ± 1.73 years. Of the total patients, 70% received no further adjuvant therapy, whereas 28% received further radiotherapy with or without androgen deprivation therapy. The rest 2% received androgen deprivation therapy only. Four percent progressed clinically to necessitate chemotherapy. Sixty-three of all patients (26%) were associated with variant pathology and 14 (22%) had mpMRI prior to primary prostate biopsy. Associated variant prostate cancer pathologies were intraductal type adenocarcinoma (79%), foamy gland type adenocarcinoma (14%), and ductal type adenocarcinoma (7%). The mean age and BMI of the patients or rates of co-morbidities did not differ statistically between groups of prostate adenocarcinomas with or without as-

Table 2. PSA, PSA Density, and diffusion pattern values of all prostate cancer patients compared according to the presence of variant pathology.

	Variant pathology absent Mean [%95 CI]	Variant pathology present Mean [%95 CI]	*p* value
Preoperative PSA (ng/ml)	7.99 [6.07-9.91]	12.96 [8.49-17.43]	0.064
Preoperative PSA Density (ng/ml^2)	0.33 [0.26-0.41]	0.46 [0.33-0.59]	0.095
ADC (mm^2/sec) (b=400)	1136 [911.12-1360.88]	1124.64 [906.74-1342.54]	0.709
ADC (mm^2/sec) (b=800)	937.20 [740.18-1134.22]	919.57 [740.69-1098.45]	0.585
ADC (mm^2/sec) (b=1400)	702.30 [583.48-821.12]	661.86 [517.70-806.01]	0.666

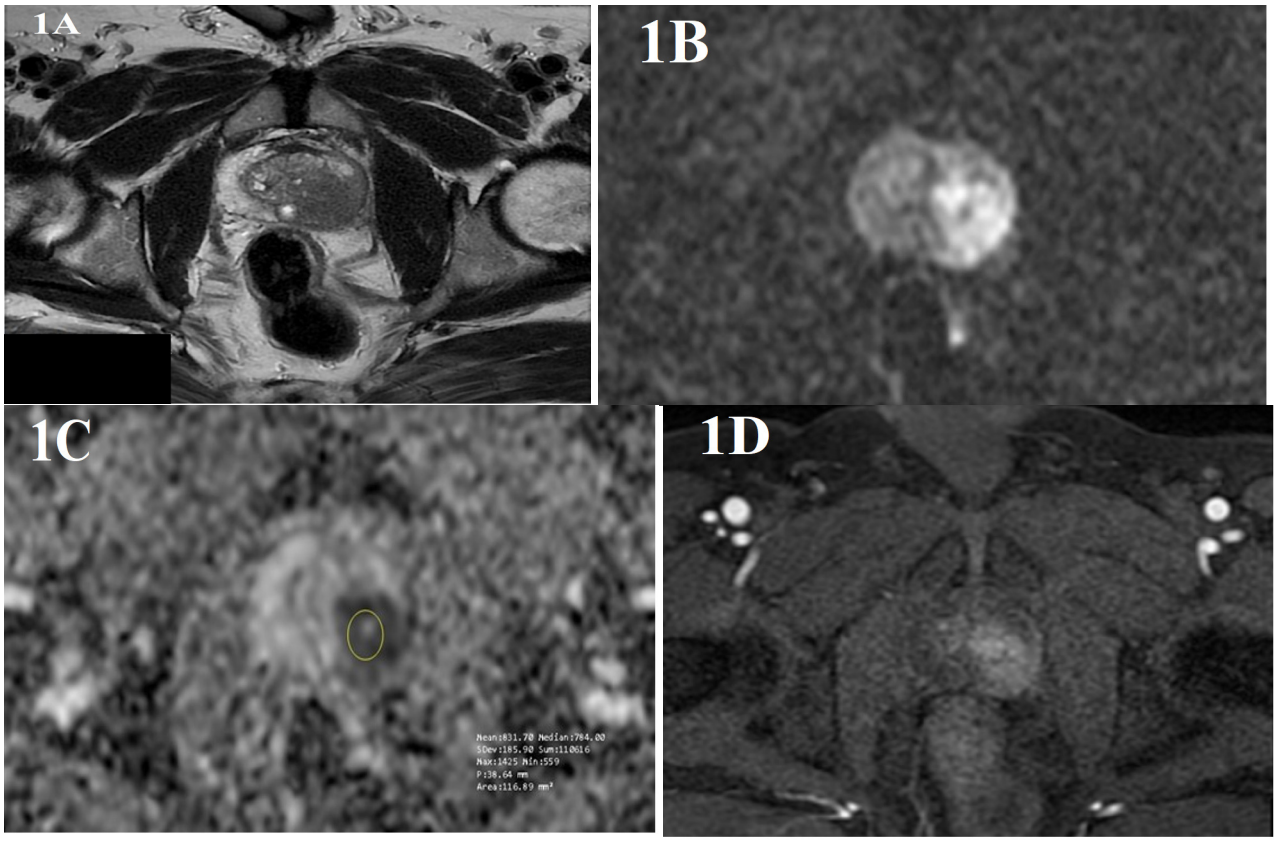

Figure 1. Variant focal point in the left peripheral zone with hypointensity on T2-weighted image **(a)**, hyperintensity on diffusion-weighted (b-1400) image **(b)**, decreased apparent diffusion coefficient (elips) **(c)**, and focal early enhancement on dynamic MRI **(d)**.

sociated variant pathology. The pathological prognostic factors related to the prostate specimen including surgical margin involvement, presence of extracapsular extension, lymphovascular invasion, perineural invasion and tumoral pelvic lymph nodal involvement (pN+) are compared according to the presence of associated variant pathology in **Table 1**. In both groups, perineural invasion was similarly higher but all other worse prognostic factors were significantly higher in the variant associated group.

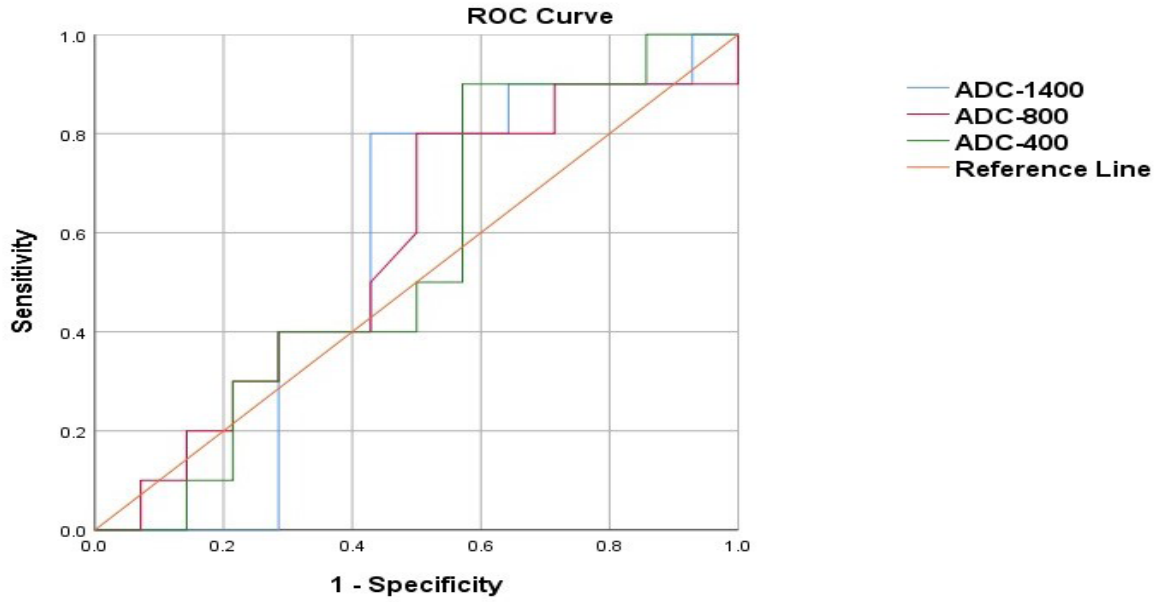

Figure 2. ROC curve analysis of all ADC values including b values for 400, 800, and 1400 to discriminate variant associated pathology.

PSA and PSA density values together with diffusion pattern values are shown in **Table 2**. A variant focal point in the left prostatic lobe which shows diffusion restriction (b: 1400) on the ADC map is shown in Figure 1. When compared in terms of mpMRI parameters, those with variant pathologies and the control group had similar perfusion curves and increased contrast values, but different ADC values for each of the adjusted b values for 400, 800, and 1400, however, this result was statistically insignificant. A ROC curve analysis of all ADC values including b values for 400, 800, and 1400 to discriminate variant associated pathology from acinar prostate carcinoma is shown in Figure 2. When ADC values were analyzed in subgroups of ISUP grades (≤ 2 versus ≥ 3) ADC values did not differ significantly in whole or subgroups of prostate cancer according to the presence of variant pathology.

DISCUSSION

For the management of prostate cancer, not only early diagnosis of prostate cancer but also identification of its associated prognostic factors like associated variant pathology is uttermost important due to its worse prognosis[8,9]. Multiparametric MRI has been proven to have better diagnostic ability with its included multiple various sequences, in prostate cancer and today it provides valuable information in the staging, risk assessment and diagnosis of clinically significant prostate cancer within the Prostate Imaging Reporting and Data System (PI-RADS) scoring which was created by the European Society of Urogenital Radiology (ESUR) first created this system in 2012 and further improved with the joint participation of ESUR, the American College of Radiology (ACR)[3,4].

In prostate cancer, the permeability of water molecules in the intracellular and extracellular environment is blocked by cell membranes, thereby inhibiting the diffusion of water molecules. This diffusion restriction is measured by the b-value and ADC. The b-value in DWI shows the strength and timings of magnetic field gradients applied to the patient therefore reflecting the diffusion. ADC in diffusion-weighted imaging is a quantitative measurement of the current and the distance that water molecules move. While the b-value in prostate cancer is found to be higher than that of in the normal tissue, the ADC value is found lower[3]. It is recommended to use at least two b-values which are 50–100 sec/mm^2, 800–1000 sec/ mm2 or if possible 1400 –2000 sec/ mm^2[3]. Therefore, in this study, we presented three different b values of 400, 800, and 1400 sec/ mm2 and compared results for each of them.

In general practice, after the patient is informed about the morbidity and mortality of the supposed treatments according to the patient's age, chronic diseases, sexual activity expectation, and anxiety status; (open, laparoscopic, or robotic) radical prostatectomy, radiotherapy, hormone therapy, active follow-up, watchful waiting, or their combination modalities are determined together with the patient. This delicate decision making might be harder with upgraded ISUP in radical prostatectomy specimen and associated variant pathologies[12]. The WHO classification has defined variant pathologies associated with prostate cancer[13]. Here in our patients the common associated variant pathologies were intraductal type, foamy gland type and ductal type in decreasing order. However, variant pathologies are not always detected even histopathologically as they were shown to be deceptively benign-appearing variants[14]. More care has to be taken during the management of prostate cancer with associated variant pathology as its prognosis worse compared to the acinar prostate adenocarcinoma[2,3]. Intraductal carcinoma of the prostate (IDC-P) has been suggested to show a strong association with aggressiveness of prostate cancer, with a significantly higher frequency in high-risk disease[15]. It was suggested that recognition and systematic reporting of IDC-P might improve patient risk stratification[15]. There is very scarce data related to ADC values in diagnosis of variant pathologies associated with prostate carcinoma. Therefore, our study provides a clinical data related to use of ADC values to identify this clinically important associated variant pathology.

In another recent study, ADC values of 15 patients with Gleason score 7 and intraductal component (IDC) prostate cancer was compared with two 15-patient non-IDC groups with Gleason score 7 and >7[16]. There was found no significant difference in mean ADC, which is the similar result in our study which included more patients and more variant subtypes[16]. In our study, the patients with the variant pathologies and the patients without associated variant pathologies had similar perfusion curves and increased contrast enhancements and those values were not statistically significant. However, the b values set for 400, 800, and 1400 each had different ADC values. The low number of sample groups in both studies prevents reaching a definitive conclusion.

CONCLUSIONS

In this small cohort, mpMRI appears to have no role in distinguishing rare variant pathologies associated with prostate adenocarcinoma despite different ADC values. Therefore, further studies with higher number of patients are needed to support or discard the possible diagnostic ability of mpMRI for identification variant pathology.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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