Evaluation of the Diagnostic Efficacy of Normalized Apparent Diffusion Coefficient (nADC) in Differentiating Benign and Malignant Prostatic Lesions

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ABSTRACT

Introduction: Current prospective observational study evaluates the diagnostic efficacy of normalized apparent diffusion coefficient (nADC) in differentiating benign and malignant prostatic lesions in peripheral prostatic zone using normal peripheral zone as a reference organ.

Material and methods: This study included 64 patients with increased serum PSA level (>4 ng/ml) and who were scheduled to undergo a TRUS-guided biopsy. Conventional sequences and DW-MRI were done and ADC values were calculated. The normalized ADC value were calculated by dividing the ADC of lesion by ADC of reference site. DWI-MRI results were compared to the results of biopsy.

Results: In 64 patients, total 47 patients were found to have suspected neoplastic lesions in peripheral zone. On biopsy, out of 47 lesions in peripheral zone, 33 were found to be malignant. On analysis by ROC curve, significant difference were found in benign and malignant cases by using both nADC and ADC values.

Conclusion: However on comparing the two parameters, no significant statistical difference were found.

Keywords: Apparent Diffusion Coefficient (nADC), Malignant Prostatic Lesions

INTRODUCTION

Prostate cancer is the most common non-cutaneous malignancy in men worldwide, and accounts for almost 20 percent of all newly diagnosed male cancers and sixth leading cause of cancer mortality in men[1]. Available screening methods for prostate cancer includes serum prostate-specific antigen PSA), TRUS-guided biopsy and MRI prostate, of which first two methods are limited by sampling error along with) low sensitivity and specificity, apart from invasiveness of TRUS Biopsy. [2,3]

Magnetic resonance (MR) imaging continues to evolve as a powerful non-invasive modality for diagnosis and staging of prostatic malignancy, in that process, some focus also have been made on diagnostic efficiency of diffusion weighted MR and ADC values.

Diffusion-weighted MRI depends on motion of water molecules, which is restricted in cancerous tissues, and this can be quantified by apparent diffusion coefficient (ADC) value[4,5,6] , however reported absolute ADC values to diagnose the malignant lesions, differs between studies, mainly due to lack of standard DWI parameters, mainly varying b values[4,5,6]. To solve this variability, normalized value of ADC, using a reference organ like renal cortex, psoas muscle and spleen, is being studied, showing promising results[7,8,9,10].

Current prospective observational study focuses on evaluation of normalized ADC, using normal peripheral zone(PZ) of prostate as reference organ, in diagnosis of prostatic lesions.

MATERIAL AND METHODS

2.1 Patients

This study was conducted in Department of Radio-diagnosis & Imaging, S.S. Hospital, IMS, BHU in collaboration with Department of Urology during the period of September, 2016 to July, 2018 with approval of institutional review committee as well as patient's informed consent.

Study included total 64 cases (mean age, 68.15 years; range, 50–90 years), who were sent for mpMRI of prostate due to elevated serum PSA (>4 nm/ml) and underwent subsequent TRUS guided biopsy. Mean PSA level was 21.8 ng/mL (median, 10.5 ng/mL; range, 5.40–142.0 ng/mL). The mean interval between biopsy and MRI was 28 days (range, 1–77 days). None of the patients was diagnosed with prostate cancer before MRI.

2.2 MR imaging protocol

Prostate MP-MRI was performed in all patients under fasting conditions. MP-MRI was performed with a 1.5-T MRI scanner (Signa Excite High speed, GE Healthcare) with a maximum gradient amplitude of 33 mT/m and a maximum slew rate of 77 mT/m/s.

MP-MRI protocols included axial and coronal T2- weighted fast spin-echo (FSE) imaging, axial T2- weighted echo-planar imaging (EPI), axial DWI, axial DCE-MRI, and axial unenhanced and contrast- enhanced T1-weighted FSE imaging. DCE-MRI was performed using an FSE sequence or a 3D T1-weighted gradient echo liver acquisition with volume acceleration (LAVA) sequence. Data acquisition for DCE-MRI began simultaneously with initiation of IV injection of gadopentetate dimeglumine (Magnevist, Bayer

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Schering Pharma).

Axial DWI was performed using a multi-section spin echo single-shot EPI sequence. ADC maps were reconstructed by calculating the ADC in each pixel of each slice. ADC values in dominant prostatic lesions were taken as the average of 3 ADC values. The ADC values in normal peripheral zone (reference site) were calculated as the average of ADC in 3 different normal sites. ROI was placed as a circle or oval, with an area of 6 mm^2. (Figure 1) The mean normalized ADC value was calculated by dividing the ADC value of lesion by ADC of reference peripheral zone.

2.3 Image Interpretation and Data Analysis

Image interpretation was done according to Prostate imaging - reporting and data system, version 2 (PIRADS v2). PI-RADS™ v2 assessment uses a 5-point scale based on the likelihood (probability) that a combination of mpMRI findings on T2W, DWI, and DCE correlates with the presence of a clinically significant cancer for each lesion in the prostate gland.

2.4 Transrectal ultrasound guided prostate biopsy:\

Patients underwent TRUS guided prostate biopsy within 3 month after MRI was done. A 10 core biopsy strategy was performed to sample tissue from the prostate gland. Six were from peripheral zone at the base, mid-gland and apex on both side. Another four cores were taken from upper and lower central gland from both side.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS software (version 16.0, SPSS). ROC curve were drawn to examine the diagnostic ability of nADC. Comparison of the areas under curve for the ADCs and nADCs was done through DeLong's test. All statistical tests were two sided, and p values of 0.05 or less were considered indicative of a significant difference.

RESULT

Of 64 patients included in current study, 17 patients did not show any definite lesion in peripheral zone, so were assigned PIRADS 2 category on MRI, and were not included for ADC evaluation. Rest 47 patients showed presence of definite lesion in peripheral zone on MRI, which were assigned either PIRADS 3, PIRADS 4 or PIRADS 5, based on ACR PI-RADS v2. On histopathological examination, 33 out of 47 cases were found to have malignant lesion in peripheral zone.

Interpretation of ADC and nADC values

The ADC values in both benign and malignant cases were not normally distributed so Wilcoxon-mann-whitney U test was used to compare the benign and malignant groups.

Mean ADC value in benign group was 633.55 and in malignant group, it was 529.41.

Significant difference was found between two groups with W Score being 334 and p Value as 0.017.

Strength of association (point-biserial correlation) was 0.37 (large effect size) (Table 1)

Similarly, nADC values in both benign and malignant cases also, were not normally distributed so Wilcoxon-mann-whitney U test was used.

Mean nADC value in benign group was 0.41 and in malignant group, it was 0.35.

Again, significant difference was found between two groups with W Score being 388 and p Value as 0.001.

Strength of association (point-biserial correlation) was 0.55 (large effect size) (Table 2)

Density plots of ADC and nADC values are shown in figure 2 and 3.

On ROC curve analysis, at cut off mean ADC value of 651.33, sensitivity and specificity were found to be 91 and 57.1 percent respectively, whereas at cut off nADC value of 0.38, they were 86 and 92 percent respectively. So best parameter for sensitivity was ADC value, and for specificity, it was nADC value. (figure 2, 3,4)

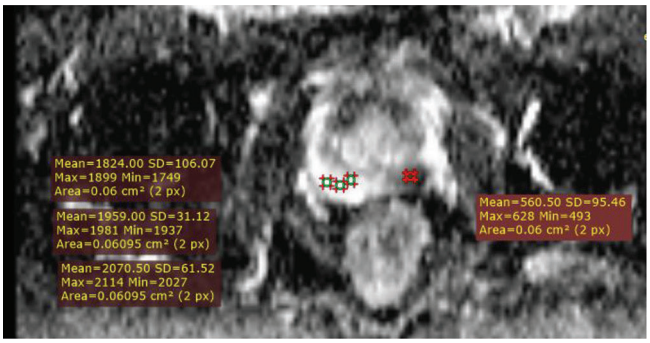

Figure-1: Axial section of ADC map of prostate, at the level of lesion, showing method of calculation of ADC values.

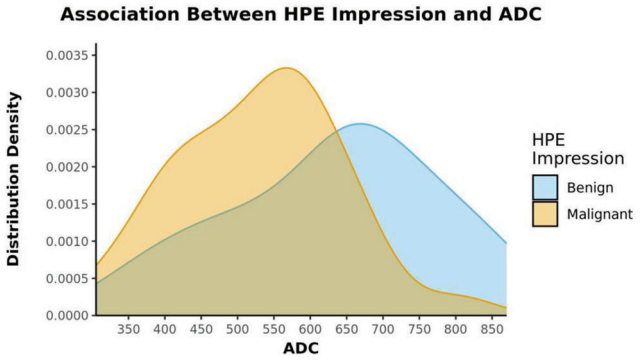

Figure-2: Distribution of ADC values in benign and malignant groups.

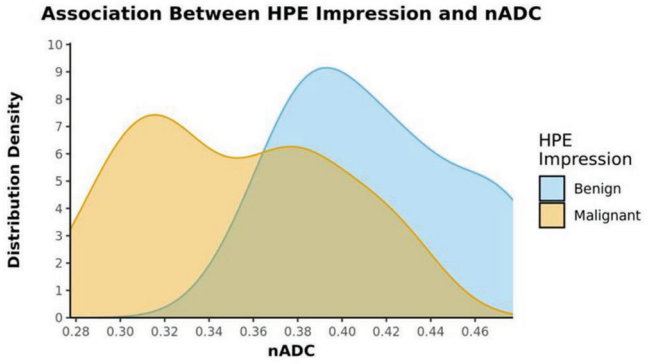

Figure-3: Distribution of nADC values in benign and malignant groups.

Predictor	AUROC	95% CI	P	Sn	Sp	PPV	NPV	DA
ADC	0.724	0.541-0.907	0.017	91%	57%	83%	73%	81%
nADC	0.840	0.727-0.953	<0.001	73%	86%	92%	57%	77%

AUROC: Area under ROC curve; CI: Confidence interval; P: P value; Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; DA: Diagnostic Accuracy.

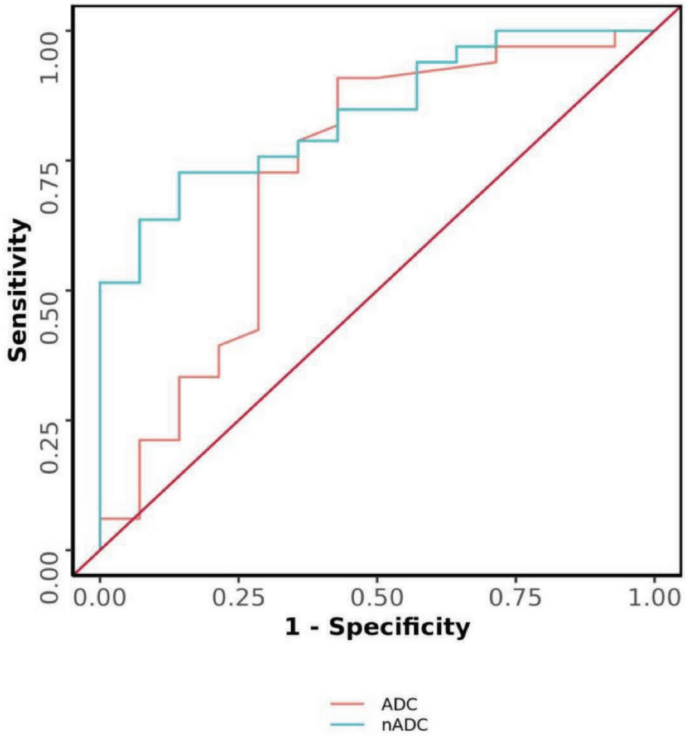

Figure-4: Comparison of diagnostic performances of ADC and nADC values in predicting the malignant lesions.

ADC	HPE Impression		Wilcoxon-Mann-Whitney U Test	
	Benign	Malignant	W	p value
Mean (SD)	633.55 (147.28)	529.41 (111.12)	334.500	0.017
Median (IQR)	666 (532.67-717.25)	541 (445.33-595)		
Range	357 - 870	305.33 - 804.67		

Table 1. Comparison on ADC values in benign and malignant groups.

nADC	HPE Impression		Wilcoxon-Mann-Whitney U Test	
	Benign	Malignant	W	p value
Mean (SD)	0.41 (0.04)	0.35 (0.05)	388.000	<0.001
Median (IQR)	0.41 (0.38-0.44)	0.35 (0.31-0.38)		
Range	0.36 - 0.48	0.28 - 0.43		

Table 2. Comparison on nADC values in benign and malignant groups.

Best parameter in terms of positive predictive value was nADC, but for negative predictive value, it was ADC.

However, overall, no significant difference was found between the two parameters (DeLong's Test p = 0.248)

DISCUSSION

Multiparametric MRI (mpMRI) represents a growing modality for the non-invasive evaluation of prostate cancer and is increasingly being used for patients with persistently elevated PSA and prior negative biopsies. In the current method of multi-parametric MRI evaluation of localized prostate cancer, PI-RADS version 2 recommendations for DWI assessment mainly rely on the radiologist's subjective interpretation of qualitative lesion intensity characteristics.

There is no consensus on quantitative ADC value cut off to diagnose a malignant lesion, leaving it on interpreters discretion, hence affecting the diagnostic efficacy of multi-parametric MRI.

At present, many studies are being done to establish a cut off value for absolute and normalized ADC to enhance diagnostic accuracy of MRI.

Multiple previous studies on ADC have shown significantly lower ADC value for malignant prostatic lesion in comparison to normal tissue [11,12]

Gauhar GK et al, showed that the mean ADC as 1.0 ± 0.22×10−3 mm^2/sec for tumor tissue versus 1.44 ± 0.28×10−3 mm^2/sec for non-tumor tissue with sensitivity and specificity of 81% and 84% respectively in prostatic cancer detection[11].

In study of, Sato C et al, in the 23 patients with cancer, the mean ADC value of all cancer ROIs and that of all non-cancer ROIs, respectively, were 1.11 +/- 0.41 x 10^{-3} and 1.68 +/- 0.40 x 10^{-3} mm^2/second (values are mean +/- SD) ($P < 0.01$)[5].

Another study done by Klaas N A Nagel et al, which included, 116 biopsy specimens, median ADCs of normal prostate tissue, prostatitis and prostate cancer were 1.22 x 10^{-3} mm^2/sec, 1.08 x 10^{-3} mm^2/ sec, and 0.88 x 10^{-3} mm^2/sec, respectively[13].

Similarly, in our study, mean ADC value of biopsy proven peripheral zone prostate cancer is 0.53 x 10^{-3} and of normal peripheral zone is 1.52 x 10^{-3} mm^2/sec with p value being <0.05, indicating presence of significant difference.

However, Despite multiple studies showing significant difference in mean ADC value of malignant and normal prostate tissue, no consensus have reached on a single cut-off value that can differentiate the two. Reasons may be, varying patient's age, body temperature during scan and technical causes such as b- value used and sampling Location. That is why previous related studies have shown a wide variability in the mean ADC of cancer prostate (ranged from 0.77 ± 0.19×10−3 mm2/sec to 1.38 ± 0.52×10−3 mm2/sec[5,11].

So we have examined the diagnostic efficacy of normalized ADC (nADC) i.e. ratio of ADC values of suspected prostatic lesion in peripheral zone and normal prostatic tissue in opposite side of peripheral zone. At nADC cut off value of 0.38, our study shows sensitivity and specificity of 73 and 86 percent respectively.

We have some limitation in our study –(1) small number of patients (2) dependence on TRUS guided biopsy, which itself has less sensitivity and specificity (3) absence of intra and inter observer correlation (4) fixed use of b value

CONCLUSION

Quantitative ADC evaluation can be proved to be a better screening method and can avoid significantly painful and invasive procedure like TRUS guided biopsies and transperineal biopsies. More studies are required to validate nADC as screening/diagnostic procedure in prostatic malignancy cases, preferably with standardized DWI protocol along with varying levels of b values.

REFERENCES.

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017 Jan;67(1):7-30.
2. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320-8.
3. Kirkham AP, Haslam P, Keanie JY, et al. Prostate MRI: Who, when, and how? Report from a UK consensus meeting. Clin Radiol 2013;68:1016-23.
4. Hosseinzadeh K, Schwarz SD. Endorectal diffusion-weighted imaging in prostate cancer to differentiate malignant and benign peripheral zone tissue. J Magn Reson Imaging 2004;20:654–61.
5. Sato C, Naganawa S, Nakamura T, Kumada H, Miura S, Takizawa O, et al. Differentiation of noncancerous tissue and cancer lesions by apparent diffusion coefficient values in transition and peripheral zones of the prostate. J Magn Reson Imaging 2005;21:258–62.
6. Gibbs P, Pickles MD, Turnbull LW. Diffusion imaging of the prostate at 3.0 tesla. Invest Radiol 2006;41:185–8.
7. Vargas HA, Akin O, Franiel T, Mazaheri Y, Zheng J, Moskowitz C, et al. Diffusion weighted endorectal MR imaging at 3 T for prostate cancer: tumor detection and assessment of aggressiveness. Radiology 2011;259:775–84.
8. Litjens GJ, Hambrock T, Hulsbergen-van de Kaa C, Barentsz JO, Huisman HJ. Interpatient variation in normal peripheral zone apparent diffusion coefficient: effect on the prediction of prostate cancer aggressiveness. Radiology 2012;265:260–6.
9. Thörmer G, Otto J, Horn LC, Busse H. Non-invasive estimation of prostate cancer aggressiveness using diffusion-weighted MRI and 3D proton MR spectroscopy at 3.0 T. Acta Radiol 2015;56:121–8.
10. Barrett T, Priest AN, Lawrence EM, Goldman DA, Warren AY, Gnanapragasam VJ, et al. Ratio of tumor to normal prostate tissue apparent diffusion coefficient as a method for quantifying DWI of the prostate. Am J Roentgenol 2015;205:W585–93.
11. Gouhar GK, Taha TF, Allam MA. Detection of prostate cancer: Utility of diffusion weighted MR imaging and 3D MR spectroscopic imaging. EJRNM 2010;41:429–39.
12. Hosseinzadeh K, Schwarz SD. Endorectal diffusion-weighted imaging in prostate cancer to differentiate malignant and benign peripheral zone tissue. J Magn Reson Imaging 2004;20:654–61.
13. Nagel KN, Schouten MG, Hambrock T, Litjens GJ, Hoeks CM, ten Haken B, Barentsz JO, Fütterer JJ. Differentiation of prostatitis and prostate cancer by using diffusion-weighted MR imaging and MR-guided biopsy at 3 T. Radiology. 2013 Apr;267(1):164-72

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