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Role of ADC Map MR Imaging in Prediction of Local Aggressiveness of Prostate Cancer

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ABSTRACT

Objective: of this study is to evaluate the relationship between ADC map values of MR imaging and local aggressiveness of the prostate Cancer via comparing the ADC values and Gleason score in prostate Cancer.

Methodology: this study carried out in Radiology Department of Ain Shams University Hospitals. 21 patients with pathologically proven prostate cancer underwent pelvic MRI examination including diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC).

Result: The mean ADC value is inversely related to Gleason Score.

Keywords: prostate cancer (PCA), Gleason score (GS), apparent diffusion coefficient (ADC), transrectal ultrasound (TRUS).

INTRODUCTION

Prostate cancer is the most commonly diagnosed solid malignant tumor among men. The morbidity and mortality directly attributable to this common malignancy are significant. However, in a non-negligible proportion of patients, the disease may be considered relatively indolent [1].

The diagnosis of prostate cancer is based on a digital rectal examination (DRE) and assessment of serum prostate specific antigen (PSA) followed by transrectal ultrasound (TRUS)-guided biopsy [2].

T2-weighted MRI has been commonly used to detect prostate cancer. Recently, diffusion-weighted MRI (DW-MRI) has been widely introduced in the clinical setting. It is beneficial as it offers increased diagnostic accuracy due to the clear delineation between normal and prostate cancer, namely the high signal of cancerous lesions. DW-MRI is a non-invasive imaging technique that quantifies the diffusion of water molecules in tissues without any contrast agents, tracers, or exposure to radiation. DW-MRI may also provide qualitative information regarding the pathophysiological character of prostate cancer [3].

The assessment of local aggressiveness of prostate cancer (PCa) is of key importance for appropriate management of this disease. The increase in life expectancy of the general population combined with efficient screening methods will lead to an increase in the number of new PCa cases. These cases will tend to be more localized and at an earlier stage [4].

The Gleason scoring (GS) system has been accepted internationally as a reference grading system for prostate cancer with respect to tumor aggressiveness, tumors are classified as low risk (Gleason score, ≤6), intermediate risk(Gleason score, 7) or high risk (Gleason score, ≥ 8) [5].

To establish the ADC as a strong biomarker for predicting prostate cancer Gleason scores, standardization of quantitative ADC metrics is of crucial importance [6].

AIM OF WORK

The objective of this study is to evaluate the relationship between ADC map values of MR imaging and local aggressiveness of the prostate cancer via comparing the ADC values and Gleason score in prostate cancer.

PATIENTS AND METHODS

Patients

During a period of 6 months duration from August 2017, twenty-one patients were enrolled in the study. All patients with elevated prostatic specific antigen (PSA) values greater than 4 ng/ml underwent sextant TRUS guided biopsies. MRI examination was done either prior to the TRUS biopsy or at least 3 weeks after the TRUS biopsy.

The study was approved by the Ethics Board of Ain Shams University.

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Inclusion criteria

- Histopathologically (biopsy) proven prostate cancer.
- No age predilection.

Exclusion criteria

- Patients having contraindication to MRI.
- Histopathologically proven cases of benign lesions.
- Patients with pathologically proven prostate cancer and the lesion is not detected by MRI.

Histopathological Analysis

The histology was reviewed by an experienced pathologist.

MRI imaging

Conventional MRI and DWIs were performed using Philips achieva XR 1.5-T system using a torso XL 16 channels phased array coil.

Diffusion study

DW images were acquired in the axial plane using the single-shot echo-planar imaging technique. Diffusion-encoding gradients were applied using three b values of 0,600 and 800 s/mm^2 along the three orthogonal directions of motion-probing gradients. ADC maps were automatically constructed on a pixel by-pixel basis.

MRI data analysis

Region of interest (ROI) was drawn on the ADC maps on the visualized tumor, and if multiple tumors were present the average ADC value was recorded for each lesion.

When the ROI was drawn, attention was paid to the exclusion of the neurovascular bundle and urethra to minimize any error in the Calculation of the ADC.

Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 23. Data were summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of ADC for detection of the grade of cancer prostate. P-values less than 0.05 were considered as statistically significant.

RESULTS

The 21 patients enrolled in this study were ranging from 64 to 85 years with mean age of 73.4 years. The total PSA was elevated ranging from 7.6 to 905.5 in all patients.

Table (1) Demonstrating the PSA and age of the patients

	Mean	Standard Deviation	Median	Minimum	Maximum
PSA	***100.1***	***168.05***	***35.70***	***7.6***	***905.50***
Age	***73.4***	***7.14***	***75.00***	***64.00***	***85.00***

Regarding the histopathological type of the diagnosed prostate cancer patients, all had adenocarcinoma. 90.47 % of the lesions were located in the peripheral zone, 14.3 % were located in the central zone and 4.76 % were located in the transitional zone (9.5% of the lesions were located in both the peripheral and central zones).

90.5% of the lesions were localized by theT2WIs. In about 9.5% the lesions were not well identified by the T2WI.

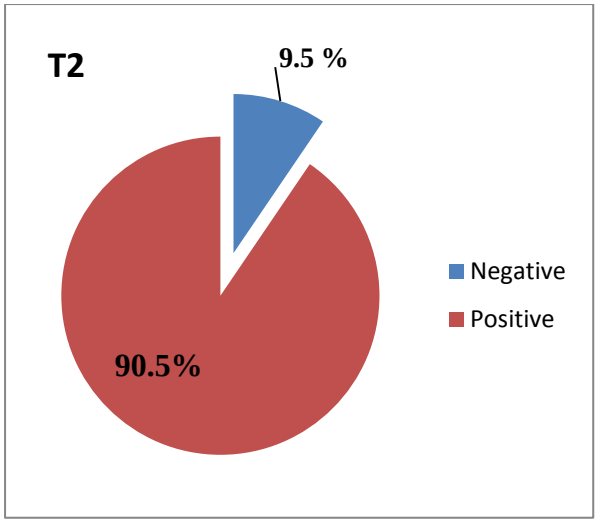


Figure (1): Pie chart demonstrating percentage of positive T2 in localization of prostate cancer

Localization of the lesions was then confirmed by the DWI where the lesions appeared bright in 95.2% of them. In only 4.8% restriction was not clear among the rest of the prostatic tissue and the lesions were identified by the dark signal in the ADC map.

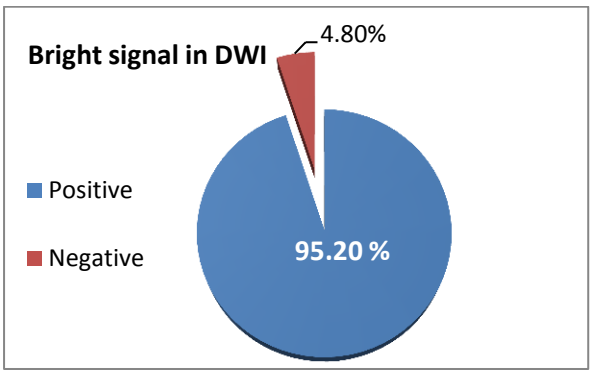


Figure (2): Pie chart demonstrating

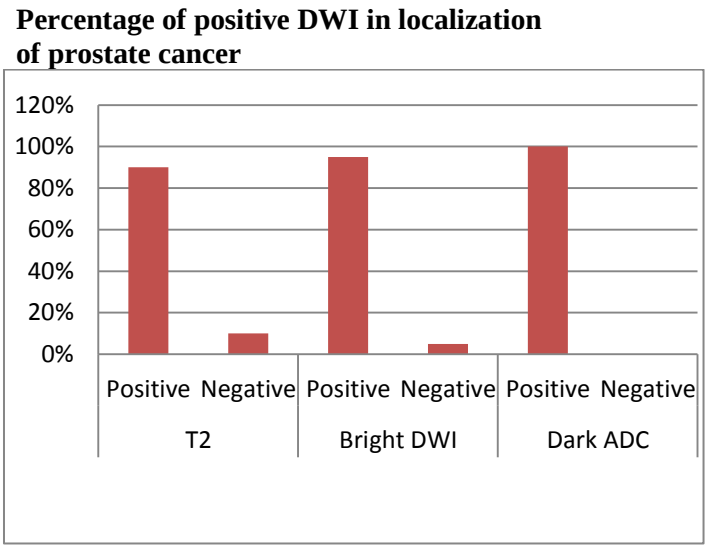


Figure (3): Chart demonstrating the difference between T2, DWI and ADC map images in localization of the lesions.

Regarding the Gleason scores;2 of the cases had Gleason score (3+3),5 had Gleason score (3+4),4 had Gleason score (4+3), 5had Gleason score (4+4),2had Gleason score (4+5), 2had Gleason score (5+4) and 1 had Gleason score (5+5).

The mean ADC and standard deviation is calculated for each different group.

Table (2) Demonstrating the mean ADC value and the standard deviation of each Gleason score

		Gleason Score							P value
		3+3	3+4	4+3	4+4	4+5	5+4	5+5	
MEAN ADC	Mean	*0.926*	*0.814*	*0.782*	*0.765*	*0.709*	*0.680*	*0.630*	<0.001
	SD	*±0.005*	*±0.006*	*±0.001*	*±0.004*	*±0.001*	*±0.002*		

The mean ADC decreases as the Gleason score increases with a significant p value <0.001

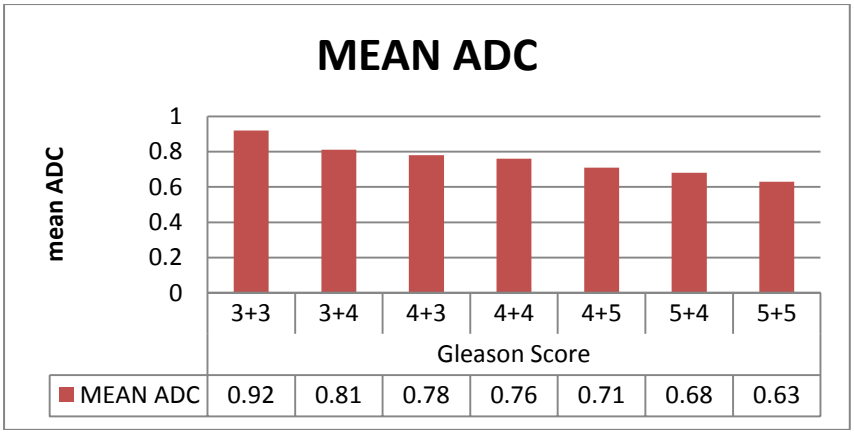
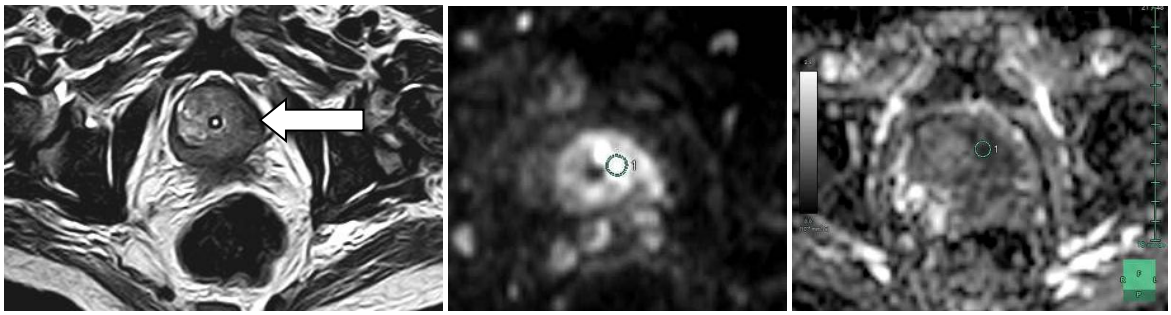


Figure (4) demonstrating the relationship between the mean ADC value and the Gleason score



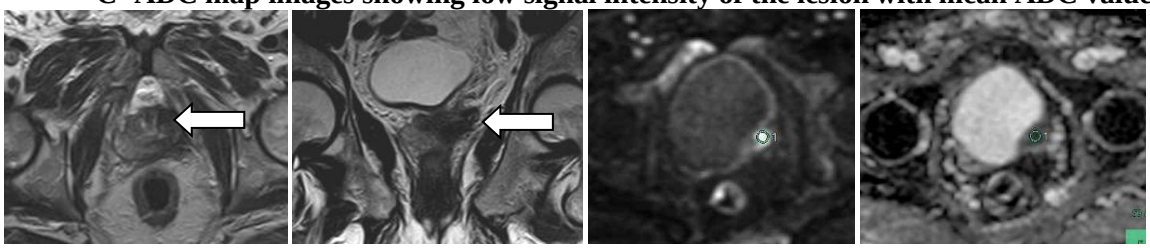
A B C

Figure (5) cancer prostate in a 73 year old male patient with total PSA 12.4 ng/ml and Gleason score 3+4

A- Axial T2 weighted images showing low signal intensity lesion seen in central zone and left part of peripheral zone.

B- DWI (at b value 600) showing bright signal intensity of the lesion.

C- ADC map images showing low signal intensity of the lesion with mean ADC value 0.810



A B C D

Figure (6) cancer prostate in a 79 year old male patient with total PSA 50.6 ng/ml and Gleason score 4+4

A and B Axial and coronal T2 weighted images showing left peripheral zone low signal intensity lesion with extra capsular extension.

C- DWI (at b value 600) showing bright signal intensity of the lesion.

D- ADC map image showing low signal intensity of the lesion with mean ADC value 0.77.

Tumors were then classified as low risk (Gleason score, ≤6), intermediate risk(Gleason score, 7) or high risk (Gleason score, ≥ 8) and the mean ADC value and the standard deviation were calculated for each group.

Table (3) Demonstrating the mean ADC value and the standard deviation of different grades of the tumor.

		GS		
		6	**7**	**8-10**
MEAN ADC	**Mean**	***0.926***	***0.799***	***0.724***
	Standard Deviation	***±0.006***	***±0.017***	***±0.049***

We found that the mean ADC decreases as the Gleason score increase which helps as to discriminate between low grade (Gleason score 6), intermediate grade (Gleason score 7) and high grade (Gleason score 8-10) prostate cancer with a significant p value < 0.001

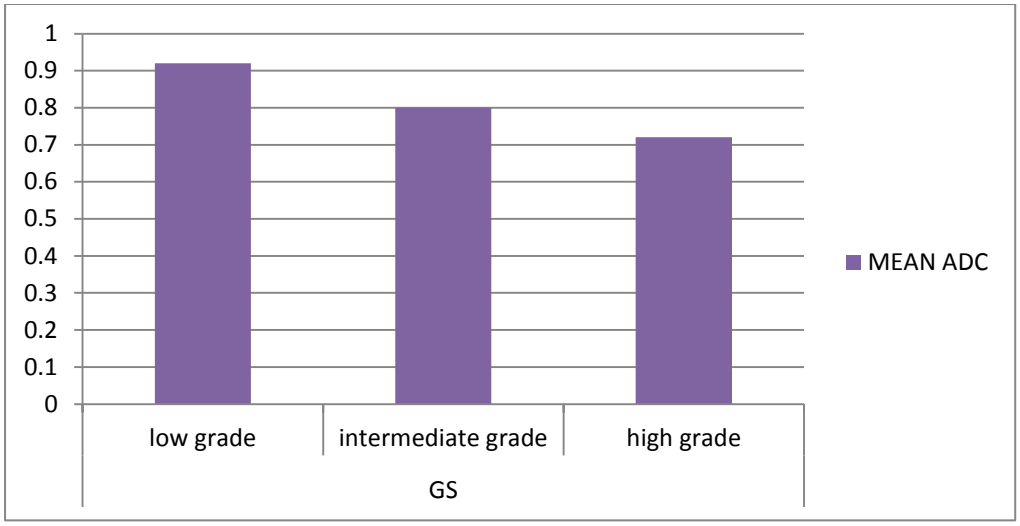


Figure (7) Demonstrating the relationship between the mean ADC value and the grade of the tumor.

But we found that the mean ADC of Gleason score (4+3) was lower than that of Gleason score (3+4) which means that tumors with Gleason score (4+3) was more aggressive than that of Gleason score (3+4).

Table (4) Demonstrating the difference between the mean ADC value and the standard deviation of Gleason score 3+4 and Gleason score 4+3

		Gleason Score		P value
		3+4	**4+3**	
MEAN ADC	**Mean**	***0.814***	***0.782***	***0.001***
	Standard Deviation	***±0.006***	***±0.001***	

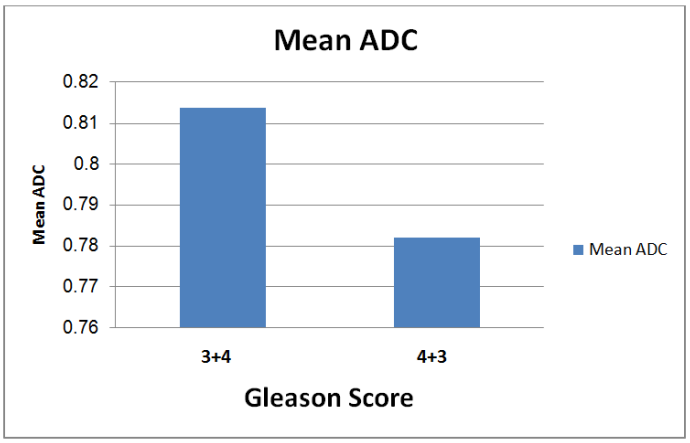


Figure (8) Chart demonstrating the relation chip between the mean ADC value and Gleason scores 3+4 and 4+3

ROC analysis was done for ADC cut off value as a marker for identification of high and low grade tumors and showed a significant p value < 0.001.

The cut off value for GS >7 was < 0.7725 and for GS < 7 was > 0.8620 with AUC (area under the curve) in both 100% and with sensitivity and specificity of 100%

Table (5) Demonstrating the results of the ROC for Gleason score >7

Area under curve	P value	95% Confidence Interval		Cutoff value	Sensitivity (%)	Specificity (%)
		Lower Bound	Upper Bound			
1.000	*<0.001*	*1.000*	*1.000*	*0.7725*	*100*	*100*

Table (6) Demonstrating the results of the ROC for Gleason score <7

Area under curve	P value	95% Confidence Interval		Cutoff value	Sensitivity (%)	Specificity (%)
		Lower Bound	Upper Bound			
1.000	*<0.001*	*1.000*	*1.000*	*0.8620*	*100*	*100*

DISCUSSION

Within the prostate, the predominant contribution of DW MR imaging signal is from the extracellular component (from tubular structures and their fluid content), with a lesser contribution from the extracellular stromal space and the intracellular components (epithelial and stromal cells). Because of the abundant self-diffusion of water molecules within the predominant tubular components within the peripheral zone, their contents provide a high signal on ADC maps [7].

With increasing Gleason grade, the change in tissue organization to a more solid and compact architecture (with higher cellular density) should be reflected in restrictions in the distances of free water motion within the tissue. Well-differentiated prostate carcinomas display tubular formation with a concomitant higher contribution of unrestricted water motion to ADCs. Lower-grade tumors are also known to have a remarkable heterogeneity in glandular size and the ability to grow between pre-existing ducts. Conversely, poorly differentiated adenocarcinomas show more expansile masses of small, tightly packed cell groups with small-to-absent lumina [8].

In our study there are about 9.5 % of the cases the lesions are not well identified by T2 and in about 4.8 % the lesions are not well identified by DWI. We agreed with the previous results obtained by **Tan *et al.*[9](2011)**in the limitation of T2 in TZ tumors and limitation of DWI in both TZ tumors and prostatic base tumors.

On T2WI, the peripheral zone (PZ) is distinctly separate from the transitional zone (TZ), which would theoretically include the anatomic central zone as well. It is accepted that tumor detection by T2WI in the transitional zone (TZ) is inferior to that in the PZ. The PZ is predominantly composed of glandular tissue that is hyperintense on T2WI and contrasts well with tumor. In comparison, the TZ contains more stromal tissue, giving rise to lower T2 signal which may overlap with tumor. Diffusion-weighted imaging may improve MRI detection of TZ tumors. However, as with T2WI, DWI sensitivity for tumor in the TZ remains less than in the PZ.

Evaluation of tumors in prostatic base by DWI can be limited by increased cellularity in the normal prostatic base**[9].**

The results of this study showed that mean ADC values are negatively correlated with GS with a significant p value <0.001.

The relationship between the mean ADC values and the GS in the previous studies was summarized by **Caivano *et al.*[10]** in Table 7.

(Table 7) Published data on Gleason Score (GS) and ADC Values (Caivano *et al*.). [10]

	ADC value [mean + SD (mm2/s)] and GS				Field strength (T)
Studies	**N**	**4+4**	**3+4**	**3+3**	
Kagebayashi et al.	30	0.77± 0.2	0.77± 0.2	1.14± 0.4	1.5
Oto et al.	70	1.3±/	none	1.7±/	1.5
Ibrahiem et al.	68	none	1.045± 0.336	none	1.5
Woodfield et al.	57	0.672 ± 0.057	0.702± 0.03	0.86± 0.036	1.5
Nagarajan et al.	44	0.831± 0.087	0.976± 0.103	1.135± 0.119	1.5
Hambrock et al.	51	0.68 ± 0.13	0.97± 0.22	1.36± 0.26	3
Doo et al.	51	0.779 ± 0.171	0.779 ±0.171	0.875± 0.131	3
Somford et al.	23	0.86 ± 0.21	none	1.16 ± 0.19	3
Caivano etal.	40	0.916 ± 0.072	1.104 ± 0.122	1.193 ±0.094	3

Substantial agreement has been found among our results and all these findings.

In our study ROC analysis for ADC cut off value as a marker for identification of high and low grade tumors showed a significant p value < 0.001. The cut off value for GS > 7 was < 0.7725 and for GS < 7 was > 0.8620 with AUC in both 100% (may be due to limited sample size)and with sensitivity and specificity of 100% (may be due to limited sample size).

Nowak *et al.*[11] who performed their study in 104 cancers calculated ADC cutoff values for different criteria for maximum values of both sensitivity(90.5%) and specificity (62.5%), ADC values lower than 1.005 x $10^{-3}mm^2/s$ indicated a GS ≥7, for high sensitivity (95.2%) and specificity of50%, the cutoff ADC value for GS>7 was $1.052x10^{-3}mm^2/s$ and ADC of >0.762 $X10^{-3}mm^2/s$ indicated rather a 3+4 type Gleason grade with an AUC of 69.6%, corresponding to a sensitivity and specificity of 77.5% and 64.7% respectively.

Our results also showed that the mean ADC value might be able to separate PCA with a GS of 7 into the subgroups of 3+4=7 and 4+3=7 cancers. There was a statistically significant difference between ADC values in patients with GS4+3 and those with GS 3+4 prostate cancers. Patients with GS 4+3 had lower ADC values when compared to those with GS 3+4 and there were statistically significant differences between the ADC values of the two groups (P<0.001).This is consistent with the studies of **Itou *et al.*,Verma *et al.* , Caivano *et al.* and Nowak *et al.* [10-13],** who agreed that the mean values of Gleason grade 3+4 cancers were significantly

different from those of the reference category of 4+3 cancers.

SUMMARY AND CONCLUSION

Carcinoma of the prostate is an important health problem. It is the most frequently diagnosed solid malignant tumor among men.

DW MRI in the prostate is a relative new and increasingly used imaging technique. It has the advantage that it can be obtained during a single breath-hold, as well as lack of use of contrast media.

The ADC maps can provide quantitative measurements of tissue water diffusivity through ADC values, which can be used for many applications including assessment of prostate cancer aggressiveness.

This study suggests that ADC values may allow the non invasive assessment of biological aggressiveness of prostate cancer, which may contribute in planning initial treatment strategies.

In conclusion, quantitative DW MR imaging may be a noninvasive biomarker that is well suited for determining prostate cancer aggressiveness. The mean ADC value is inversely related to Gleason Score.

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