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Correlation of Apparent Diffusion Coefficient with Gleason Score, TNM Staging, and PI-RADSv2 of Prostate Cancer at 3 Tesla

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Abstract

Background: Prostate tumors are one of the most common diseases in the contemporary world, with high mortality rates among oncology patients. This is in both developing and developed countries alike.

Aim of Study: To correlate apparent diffusion coefficient (ADC) with Gleason score (GS), TNM staging, and PI-RADSv 2.1 of prostate cancer at 3 Tesla.

Patients and Methods: Prospective study has been performed on 53 male patients (mean age 66 years) with prostate cancer at Mansoura Urology & Nephrology Centre. All patients underwent pre and post-contrast MR and DWI of the prostatic gland by single-shot echo planar imaging at 3 Tesla scanner. PI-RADSv2.1 of the prostate was achieved. The ADC of prostate cancer was calculated and correlated with GS, TNM staging, and PI-RADSv2.1 of prostate cancer.

Results: The mean ADC of prostate cancer was 0.612±0.12 $x10^{-3}$ mm^2/s. There was a significant difference in ADC of GS ≤6 versus ≥7 (p=0.001), T1-2 versus T3-4 (p=0.001), N0 versus N1 (p=0.002), M0 versus M1 (p=0.001) and PI-RADSv2 category 3-4 versus category 5 (p=0.001). The cut-off ADC value used to predict higher GS, higher T stage, presence of nodal spread, distant metastasis, and higher PI-RADSv2 were 0.71, 0.61, 0.63, 0.63, and 0.61 $x10^{-3}$ mm^2/s with an area under the curve of 0.96, 0.85, 0.78, 0.74 and 0.84 and accuracy of 90.9%, 81.8%, 73.6, 64.2 and 73.6% respectively.

Conclusion: ADC is correlated with GS, TNM staging, and PI-RADSv2 of prostate cancer. Lower ADC is linked to higher GS, higher T stage, presence of nodal and distant metastasis, and higher PI-RADSv2. So, the ADC might be recognized as a hopeful prognostic parameter of prostate cancer.

Key Words: *Magnetic resonance imaging – Prostate cancer – PI-RADSv2 – Apparent diffusion coefficient.*

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Introduction

PROSTATE cancer is the second most common cause of cancer affecting men in the USA, and it causes about 8% of cancer-related deaths **[1-3]**. Prognostic factors including Gleason's score (GS), and TNM staging. These parameters are essential for the treatment strategy and prognosis of patients with prostate cancer **[4-6]**. PI-RADS v2 is considered a qualitative MR imaging and reporting system that aims to standardize acquisition, interpretation, and reporting to propose a stratification of the risk of harboring prostate cancer. PI-RADSv2 utilizes the signal of T2-weighted imaging, diffusion-weighted imaging (DWI), and pattern of enhancement at dynamic contrast MR imaging with the creation of 5 points grade scale to diagnose prostate cancer **[7-9]**. Our group study previously reported that PI-RADS-v2 is reliable and reproducible imaging for detection of prostate cancer with an excellent overall inter observer agreement (k= 0.81) for both zones **[7]**.

Objectives: To correlate ADC values with GS, TNM staging, and PI-RADSv2 of prostate cancer at 3 Tesla.

Patients and Methods

Study population:

Approval for this study from the University Ethics Committee has been acquired and every patient has been given written informed consent before underwent the MR examination. A prospective observational study was carried out on 56 patients. Patients referred to Mansoura Urology & Nephrology Centre, During July 2018 to December 2020.

Inclusion criteria:

Were untreated male patients with pathology-proven prostate cancer that underwent trans-rectal ultrasound (TRUS) guided biopsy. Three patients with low-quality MR imaging due to motion artifacts were excluded.

Exclusion criteria:

The final patients in this study were 53 male patients; mean age of 66 years (range; 53-84 years). The mean PSA value was 8.7mg/mL (range: 6.2-14.0mg/mL). The TNM staging of prostate cancer [3] depended upon pathological reports of true-cut biopsies from the prostate, MR imaging findings of the prostate, and presence of metastatic deposits at bone survey or isotope study. The time delay between the TRUS-guided biopsy and MR imaging was 6 weeks. The patients in this study were part of a previous study to analyze the inter-observer agreement of PI-RADS v2 [7].

MR imaging:

All MRI studies were performed at 3 Tesla (Ingenia 3.0T-TX, Phillips Healthcare, Best, Netherlands). An intravenous administration of 25mg of hyoscine-N-butyl bromide was given about 1 hour before the examination to limit the bowel peristalsis. Multi-parametric MR imaging protocol of the prostate followed the PI-RADSv2 guidelines was done [8]. The examination was done in the supine position by a phased-array multi-channel 32 pelvic phased-array surface coil. Every patient examination consisted of the routine T1-WI (TR/TE =600/14ms), T2-WI (TR/TE=4000-6000/85ms) in the high-resolution axial plane with a section thickness=5mm, inter-slice gap=1mm, a field of view (FOV)=38-42cm, acquisition matrix= 256 x192, and the number of excitation (NEX)=2. DWI of the prostate was done by a multi-slice, a single-shot, spin-echo, echo-planar sequence with the following parameters: TR/TE= 8000/74-104ms, FOV=26x30cm; matrix, 128 x128; section thickness=5mm; intersection gap=1mm and b factor of 0, 800, 1400s/mm^2. The ADC maps were reconstructed. Dynamic contrast MR imaging was obtained before and after intravenous administration of a contrast agent 0.05mmol/kg gadoteric acid (Dotarem 0.5mmol/mL; Guerbet, France) was done.

Image analysis:

The images have been examined by one expert uroradiologist (MA) for 10 years, who had no idea about the clinical data and histopathological results. The ADC value was measured by manually drawing a region of interest within the lesion boundaries using an electronic indicator (Fig. 1) on all sectors of the tumor, and the mean values of the tumor were considered. The radiologist used T2WI, DWI, and Dynamic MR to classify the prostate lesion according to PI-RADSv2 [7]. The MR images divided the prostate into 6 zones into both sides at the base, mid part, and apex of the gland to simulate the systematic TRUS biopsies taken from different regions of the prostate. The highest Gleason score from systematic or targeted biopsies taken from the area of the target lesion was used for analysis.

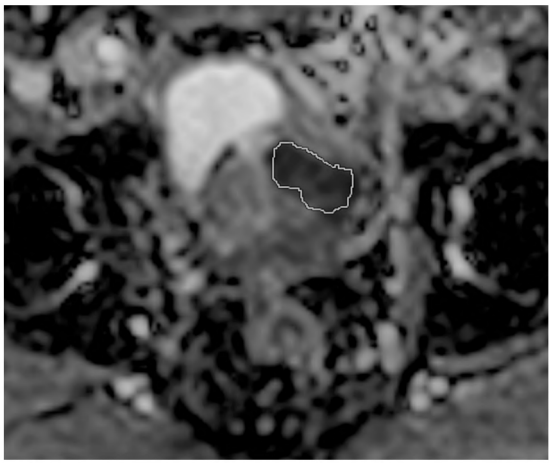

Fig. (1): R.O.I localization: ADC map in the axial plane R.O.I localization with restricted diffusion.

Pathologic analysis:

TRUS-guided biopsies, with 6 cores were obtained from all patients and put in numbered bottles. The prostatic biopsy was put in 4% buffered formaldehyde for nearly 2 days and then it has been organized according to the local clinical histopathologic routines. The hematoxyline eosin and saffron-stained slides were interpreted and categorized according to GS [2].

Statistical analysis:

Data analysis was performed by the SPSS program (Statistical package for social science version 22). The mean and standard deviation (SD) of the ADC value in relation to grading, staging, and PI-RADSv2 was calculated. The data analysis was done to measure a statistically significant difference. An independent sample (student *t*-test) was done to study the difference of the ADC between GS <6 versus ≥ 7, T staging T1-2 versus T3-4 stages, N staging N0 versus N1, M staging M0 versus M1 and PI-RADS v2 3-4 versus 5. The *p*-value was considered significant if ≤ 0.05 at a confidence interval of 95%. The cut-off ADC that was used to differentiate between T 1 -2 versus T3-4 stages, N staging N0 versus N1, M staging M0

versus M1 and PI-RADS v2 3-4 versus 5 was determined with the calculation of area under the curve (AUC), accuracy, sensitivity, and specificity.

Results

In this prospective study which included 53 males, The mean ADC value of prostate cancer was $0.61 \pm 0.12 \times 10^{-3}$ mm^2/s. Table (1) shows the ADC in relation to GS, TNM staging, and PI-RADSv2 of prostate cancer. Table (2) displays the ROC curve results of ADC in relation to GS, TNM staging, and PI-RADSv2 of prostate cancer.

Table (1): The mean, minimum and maximum ADC ($X10^{-3}$ mm^2/s) of cancer prostate in relation to grading, staging and PI-RADS v2.

Prognostic parameter	Mean ± SD	min	max	*p*-value
Cancer prostate	0.612±0.12	0.40	0.90	
Gleason Score:				
≤6 (n = 9)	0.78±0.07	0.70	0.90	0.001
≥7 (n = 44)	0.58±0.10	0.40	0.81	
T stage:				
T1-T2 (n = 22)	0.69±0.09	0.45	0.86	0.001
T3 -T4 (n = 31)	0.56±0.11	0.40	0.90	
N stage:				
No (n = 21)	0.67±0.1	0.45	0.86	0.002
N1 (n = 32)	0.57±0.12	0.40	0.90	
M stage:				
M0 (n = 32)	0.66±0.12	0.45	0.9	0.001
M1 (n = 21)	0.54±0.09	0.40	0.73	
PI-RADS v2:				
3,4 (n = 14)	0.71±0.11	0.45	0.86	0.001
5 (n = 39)	0.58±0.11	0.40	0.90	

Table (2): ROC curve results of ADC ($X10^{-3}$ mm^2/s) of cancer prostate cancer in relation to grading, staging and PI-RADS v2.

	AUC	Cut off	Sensitivity (%)	Specificity (%)	Accuracy (%)
GS ≤6 Vs. ≥7	0.96	0.72	77.8	93.2	90.6
T1-2 Vs. T 3-4	0.85	0.61	80.6	81.8	81.1
N0 vs. N1	0.78	0.63	78.1	66.7	73.6
M0 Vs. M1	0.74	0.63	81.0	53.1	64.2
PI-RADSv2 3-4 Vs. 5	0.84	0.61	85.7	69.2	73.6

The mean ADC of prostate cancer with GS ≤6 (n=9) was $0.78 \pm 0.07 \times 10^{-3}$ mm^2/s and prostate cancer with GS ≥7 (n=44) was $0.58 \pm 0.10 \times 10^{-3}$ mm^2/s with significant difference (p=0.001). When an ADC value of 0.71×10^{-3} mm^2/s was used as a cut point value for discriminating prostate cancer with GS ≤6 from ≥7, the greatest result was found with AUC of 0.96, an accuracy of 90.9%, sensitivity of 77.8% and specificity of 93.2% (Fig. 2A).

The mean ADC of prostate cancer with T 1, T2 stages (n=22) was $0.69 \pm 0.09 \times 10^{-3}$ mm^2/s and of T3, T4 stage cancer (n=31) was $0.56 \pm 0.11 \times 10^{-3}$ mm^2/s with significant difference (p=0.001). When the ADC value of 0.61×10^{-3} mm^2/s was used as a cut point value for differentiating T1, T2 from T3, T4 stages, the greatest result was found with an AUC of 0.85, an accuracy of 81.1%, the sensitivity of 80.6%, and specificity of 81.8% (Fig. 2B).

The mean ADC of prostate cancer with N0 stage (n=21) was $0.67 \pm 0.1 \times 10^{-3}$ mm^2/s and of N 1 stage (n=32) prostate cancer was $0.57 \pm 0.12 \times 10^{-3}$ mm^2/s with significant difference (p=0.002). When ADC of 0.63×10^{-3} mm^2/s was used as a cut point value for discriminating prostate cancer with N0 from N1, the greatest result was found with an AUC of 0.78, an accuracy of 73.6%, the sensitivity of 78.1%, and specificity of 66.7% (Fig. 2C).

The mean ADC of prostate cancer without distant metastasis M0 stage (n=32) was $0.66 \pm 0.12 \times 10^{-3}$ mm^2/s and of M1 stage (n=21) was $0.54 \pm 0.09 \times 10^{-3}$ mm^2/s with significant difference (p=0.001). When ADC of 0.63×10^{-3} mm^2/s was used as a cut point value for discriminating M1 from M0, the greatest result was found with an AUC of 0.74, the accuracy of 64.2%, the sensitivity of 81.0%, and specificity of 53.1% (Fig. 2D).

The mean ADC of prostate cancer with PI-RADSv2 category 3-4 (n=14) was $0.71 \pm 0.11 \times 10^{-3}$ mm^2/sec and of PI-RADSv2 category 5 (n=39) was $0.58 \pm 0.11 \times 10^{-3}$ mm^2/sec with significant difference (p=0.001). When ADC of 0.61×10^{-3} mm^2/s was used as a cut point value for discriminating two groups, the greatest result was found with an AUC of 0.84, an accuracy of 73.6%, and sensitivity of 85.7% and specificity of 69.2% (Fig. 2E).

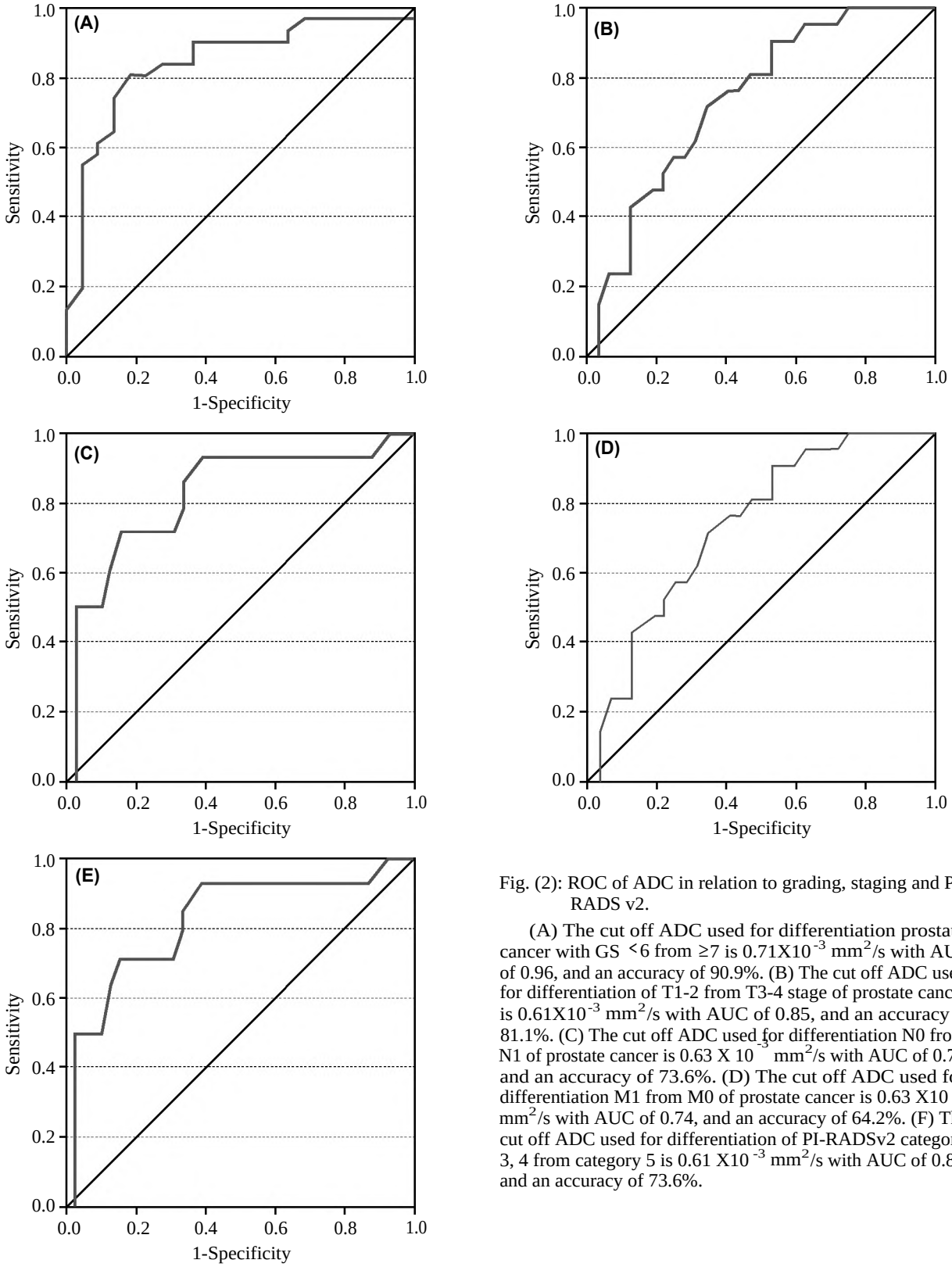

Fig. (2): ROC of ADC in relation to grading, staging and PI-RADS v2.

(A) The cut off ADC used for differentiation prostate cancer with GS <6 from ≥ 7 is $0.71X10^{-3}$ mm^2/s with AUC of 0.96, and an accuracy of 90.9%. (B) The cut off ADC used for differentiation of T1-2 from T3-4 stage of prostate cancer is $0.61X10^{-3}$ mm^2/s with AUC of 0.85, and an accuracy of 81.1%. (C) The cut off ADC used for differentiation N0 from N1 of prostate cancer is 0.63×10^{-3} mm^2/s with AUC of 0.78, and an accuracy of 73.6%. (D) The cut off ADC used for differentiation M1 from M0 of prostate cancer is 0.63×10^{-3} mm^2/s with AUC of 0.74, and an accuracy of 64.2%. (F) The cut off ADC used for differentiation of PI-RADSv2 category 3, 4 from category 5 is 0.61×10^{-3} mm^2/s with AUC of 0.84, and an accuracy of 73.6%.

Discussion

The corner-stone result in our study is there is a correlation between ADC of prostate cancer with GS, TNM staging, and PI-RADSv2. Lower ADC value of the prostate cancer correlated with a higher degree of malignancy differentiation, higher GS, higher T stage, presence of nodal and distant metastasis, and higher category of PI-RADSv2. The lower ADC value is denoting more aggressive

features of prostate cancer with higher TNM staging, larger nodal spread, and presence of distant metastasis. The low ADC of prostate cancer can be clarified by the abnormal biologic morphology of malignancy that featured by weakened Brownian motion of water particles because of the increased cellularity, abnormal or whole damage of normal tissue architecture in higher-grade malignancy tumors **[14,15]**.

The GS is one of the principal prognostic parameters of prostate cancer. There is an opposite correlation between GS and ADC of prostate cancer. ADC values are beneficial in distinguishing patients with high- or intermediate-risk prostate cancer from those with a low risk of prostate cancer. The ADC has the ability to guide the biopsy toward the most aggressive section of a prostate malignant lesion **[14]**. ADC maps derived DWI has shown a high correlation with GS, considering the importance of an accurate grading of the focal lesion, as the main predictor factor **[15]**. One study reported that DWI localizes the cancerous lesion of the prostate by mean, ratio, and 10th percentile of the ADC value that well correlated with pathological neoplasm cellular density **[21]**. Another study added that GS has a negative relationship with both ADC values and ADC_{ratio}. Furthermore, ADC_{ratio} (p=0.001) has a more solid association compared to the ADC value only (p=0.014) **[22]**. A recent study performed by Ragheb et al., 2020 added that DW metrics (ADC and ADC ratio) can assess the biological aggressiveness of prostate cancer and the PIRADSv2 scoring to determine clinically significant cancer **[18]**. Another study added that there was a correlation between the PSA level, tumor diameter, PIRADSv2 score, ADC min value, and GS in both central and peripheral zone of prostate cancer **[20]**.

Previous studies reported that the ADC value correlates with T-staging of head and neck cancer, salivary cancer, and urinary bladder cancer **[23-25]**. One study reported that ADC has superior diagnostic performance than routine pre and post-contrast MR imaging in forecasting muscle infiltration of patients with urinary bladder cancer **[24]**. Other studies added that greater T stages of the salivary gland cancerous lesions have lower ADC value **[23]** and there is a significant variance in the ADC value between different sizes of retinoblastoma (p=0.015) **[25]**.

In our work, the ADC value of prostate cancer seen with N1 is lower regarding ADC values with N0. The explanation might be related to that cancer with advanced N stage is commonly seen in the higher grade of malignancy. Nodal metastases of prostate cancer are seen in 10-15% of patients at presentation. The rank and features of local lymph nodes found to have an effect on the patient treatment plan and allover prognosis **[26]**. DWI is used for the evaluation of lymph nodes in different regions of the body **[27,28]**. One study concluded that the ADC value is significantly lower (p=0.003) in a patient with nasopharyngeal carcinoma in patients with metastatic cervical lymph nodes **[29]**.

In our work, the ADC of cancer M0 stage is significantly different (p=0.001) from patients with M 1 stage cancer prostate. The recognition of distant metastasis at the earliest diagnosis of prostate cancer establishes the treatment methodology and has a great prognostic value. The application of whole-body DWI helps in detection of distant metastasis of prostate cancer **[30]**. Metastasis Reporting and Data System for Prostate Cancer is a scoring system that recently applied in clinical practice **[31]**.

In our study, the lower ADC copes with a higher PI-RADSv2 category and there is a significant difference (p=0.001) in the ADC values for differentiating PI-RADSv2 category 3, 4 from PI-RADSv2 category 5. A recent study reported that the PI-RADSv2 is developed recently to assure uniform multi-parametric MRI protocol and method of reporting. One study reported that ADC value can aid discriminating clinically non-significant from clinically significant prostate cancer, helping pre-biopsy and pre-management risk stratification **[32]**. Another study added that ADC values and categories help to diagnose clinically significant prostate cancer when lesions are assigned a PI-RADS v2 category 4. The AUC of PI-RADSv2 alone and with ADC categories are significantly dissimilar in peripheral and transition zone lesions (p=0.026 and p=0.03, respectively) **[33]**. The third study reported that ADC values are inversely correlated with PI-RADSv2 and can help as quantitative metrics to assigning PI-RADSv2 categories 4 or 5 **[34]**. The Lexicon of PI-RADSv2 standardize the nomenclature and analysis of prostate cancer to facilitate reporting across institutions, better communication among clinicians and between clinicians and patients decrease inter-reader variability **[35-40]**.

In this study, DWI was done at a 3-tesla scanner using higher B values. Previous studies reported that DWI of the prostate used more b-values to suppress the background signals from the T2-hyperintense peripheral zone so it can raise the tumor depiction. Modern higher 3-Tesla MRI sym-

bolizes the most powerful diagnostic technique for prostate cancer and it is really recognized as the corner-stone imaging technology in identifying, localizing and staging of cancer prostate **[8,33]**.

Our study has a few limitations. First, the number of studied population is relatively small. Further studies applied a greater population number of patients are advised. Second, our study used DWI, further studies correlated multi-parametric imaging parameters using diffusion tensor imaging, arterial spin labeling or contrast perfusion MR imaging and susceptibility-weighted imaging will improve the results in the future. Third, the analysis of the ADC value was done by ROI localization. Further studies applied to machine learning will enhance the outcomes of the results in the future.

Conclusion:

Our study concluded that ADC is correlated with GS, TNM staging, and PI-RADSv2 of prostate cancer. The lower ADC is associated with higher GS, higher T stage, presence of nodal and distant metastasis, and higher PI-RADSv2. So, the ADC might be recognized as a hopeful prognostic parameter of prostate cancer.

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ارتباط معامل الانتشار الظاهرى بمقياس جليسون، ونظام تى ان ا م لتصنيف المراحل مع نظام تحليل بيانات تشخيص البروستاتا متعدد الأساليب فى تقييم حالات سرطان البروستاتا على جهاز رنين مغناطيسى عالى المجال (٣ تسلا)

المقدمة: تعد أورام البروستاتا من الأمراض الأكثر شيوعاً فى العالم المعاصر بنسب وفيات عالية بين مرضى الأورام وذلك فى الدول النامية والمتقدمة على السواء.

الهدف من الدراسة: دراسة ارتباط معامل الانتشار الظاهرى مع مقياس جليسون، وكذلك نظام تى ان ام لتصنيف مراحل الأورام مع نظام تحليل بيانات تشخيص البروستاتا متعدد الأساليب فى تقييم حالات سرطان البروستاتا على جهاز رنين مغناطيسى عالى المجال (٣ تسلا)

مكان الدراسة: أجريت الدراسة فى وحدة الرنين المغناطيسى بقسم الأشعة التشخيصية مركز أمراض الكلى والمسالك البولية جامعة المنصورة بالتعاون مع قسم جراحة المسالك البولية.

طريقة الدراسة: أجرى البحث كدراسة استباقية على ٥٣ مريض ذكر مصاباً بسرطان البروستاتا (متوسط أعمارهم ٦٦ عام) خضعوا جميعاً لفحص التصوير بالرنين المغناطيسى متعدد الطرائق وفقاً لأحدث البروتوكولات المتبعه عالمياً ويتضمن ذلك استخدام الصبغة وكذلك الانتشار الطيفى وحساب معامل الانتشار الظاهرى وذلك على جهاز رنين مغناطيسى عالى المجال (٣ تسلا) مع مقارنته بخصائص الورم المتعددة مع مقياس جليسون، وكذلك نظام تى ان ام لتصنيف مراحل الأورام.

النتائج: وتم استعراض الجوانب العلمية للموضوع ورصد نتائج الفحص وتحليلها ومقارنتها. و كانت حساسية الفحص عالية فى توقع عدائية الورم مثل وجود انتشار للأنسجة المحيطة أو الغدد الليمفاوية وهذه الحساسية والدقة كانت تتفق مع نتائج الباحثين الاخرين.

كان متوسط معامل الانتشار الظاهرى لسرطان البروستاتا (0.612±0.12)x ١٠-٣مم٢/ثانية وكان هناك اختلاف كبير فى معامل الانتشار الظاهرى مع مقياس جليسون (p=0.001) يميز بين المراحل المبكرة من المراحل المتأخرة وبين وجود غدد ليمفاوية من عدمه بالاضافة إلى وجود انتشار بعيد أم لا علاوة على درجة تصنيف نظام تحليل بيانات تشخيص البروستاتا متعدد الأساليب.

النقطة القاطعة لمتوسط معامل الانتشار الظاهرى التى من خلالها يمكن التنبؤ بمقياس جليسون، وكذلك نظام تى ان ام لتصنيف مراحل الأورام ووجود غدد ليمفاوية والانتشار إلى الأنسجة البعيدة ومستوى أعلى من نظام تحليل بيانات تشخيص البروستاتا متعدد الأساليب بينما المنطقة تحت المنحنى كانت (٠.٩٦ و٠.٨٥ و٠.٧٨ و٠.٧٤ و٠.٨٤) بدقة (٩٠.٩٪ و٨١.٨٪ و ٧٣.٦٪ و ٦٤.٢٪ و ٧٣.٦٪) على التوالى.

الاستنتاج: يتوافق معامل الانتشار الظاهرى مع مقياس جليسون وكذلك نظام تى ان ام لتصنيف مراحل الأورام وأيضاً نظام تحليل بيانات تشخيص البروستاتا متعدد الأساليب فى تقييم حالات سرطان الروستاتا. بحيث أن انخفاض معامل الانتشار الظاهرى يرتبط بشكل جيد مع درجة عدائية الورم ومرحلة تصنيف الورم مثل الامتداد للأنسجة المحيطة أو الغدد الليمفاوية وكذلك وجود انتشار للأنسجة البعيدة.