

# Correlative Study between ADC Value and Grading of Bladder Carcinoma

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## Abstract

**Background:** Studying urinary bladder carcinoma is of great importance as it is one of the most common urological malignancies. Accurate pre-operative assessment of disease characteristics and prognosis would be of great help in the diagnosis and treatment planning of bladder cancer.

**Aim of Study:** The aim of this study is to evaluate the role of the Apparent Diffusion Coefficient (ADC) value in detecting the grading of urinary bladder cancer prior to management.

**Patients and Methods:** Prospective study of 108 patients with mean age of  $60.81 \pm 12.24$ , diagnosed with proven bladder carcinoma. Two radiologists prospectively assessed the morphological and qualitative descriptors of the included carcinomas (restricted diffusion) and quantitative analysis of the ADC maps. The mean ADC value of the bladder lesions was calculated and correlated with the pathological grade according which was established by means of an open or a core needle biopsy (considered as the standard reference).

**Results:** There was significant difference between the mean ADC value of tumors of grade I and III ( $p=0.000$ ); and between grade I and II ( $p=0.00$ ) with slight less significant difference between grade II and III ( $p=0.022$ ). High ADC values were associated with low grade tumors.

**Conclusion:** DWI is a contrast-free modality that allows for both morphological and quantitative analysis. ADC value is a good discriminator between low and high grade tumors and hence predictor of the histological grade of bladder tumors and prognosis.

**Key Words:** Diffusion – ADC value – Urinary bladder cancer – Grade and magnetic resonance imaging.

## Introduction

**URINARY** bladder cancer is the 9<sup>th</sup> most frequent tumor and 13<sup>th</sup> cause of cancer related death all over the world. It has been noted that urinary bladder cancer detection is three to four times more common in males than in females [1].

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Recently, Magnetic Resonance Imaging (MRI) is considered the technique of choice in the preoperative assessment of many tumors by providing multi-planar images, the new addition of functional techniques, higher soft tissue characterization, higher accuracy of staging estimation and accurate detection of the extent of a disease, avoiding the possible effects of radiation associated with the use of CT [2].

In addition diffusion weighted MRI doesn't require contrast media with short exam duration yet it gives valuable information about the biologic characteristics of tissue giving unique data regarding the cellularity and the status of molecular content of water [3].

The ADC is a q value that can be quantified measuring signal attenuation being influenced by microscopic motion, including molecular diffusion of water as well as blood microcirculation [4].

Qualitative and quantitative assessment by DW-MRI can detect the nature of the tissues (benign or malignant) and to determine the grade of malignancy and divide bladder tumors into low and high grade tumors [5].

In the current study we evaluated the impact of interpreting Apparent Diffusion Coefficient (ADC) value as a prognostic factor that can predict the grading of invasive urinary bladder cancer before deciding the options of management.

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### List of abbreviations:

ADC : Apparent Diffusion Coefficient.  
DWI : Diffusion Weighted Images.  
MRI : Magnetic Resonance Imaging.  
PPV : Positive Predictive Value.  
NPV : Negative Predictive Value.  
UB : Urinary Bladder.

## Patients and Methods

This study is a prospective analysis, approved by the Ethics Committee at Kasr El-Aini Hospital, the cases were referred from the Urology/ Urosurgery Clinic in Kasr El-Aini Hospital in the period from March 2015 till May 2018. Tumor grading was established by means of transurethral cystoscopic biopsy (considered as the standard reference).

### Patients:

It included 108 patients who underwent non contrast MRI scanning including diffusion weighted sequences.

### Inclusion criteria:

Patients proved to have urinary bladder cancers that require further advanced pathological analysis for grading.

### Exclusion criteria:

- Cases that received neoadjuvant chemotherapy.
- Cases that lacked pathological confirmation.
- Cases proved to be benign.
- Solid masses less than 1cm (The ADC value could not be evaluated).

### Methods:

#### MR imaging:

MRI was performed using a 1.5T magnet scanner (GyrosanIntera; Philips Medical Systems, Best, the Netherlands) equipped with a radiofrequency coil (Quadrature Body Coil; Philips Medical Systems). All the patients were imaged in the supine position, Total study time ranged from 30 to 45 minutes. No sedation was used.

#### Patient preparations:

Patients were instructed to start drinking water and prohibit urination 1 hour before the MRI examination to moderately distend the bladder. In patients with a urethral catheter, 250-400ml of sterile saline was used to distend the bladder.

#### MRI imaging protocol:

A- Cases were examined first by non contrast sequences: Axial T1 weighted turbo spin echo images, axial, sagittal and coronal T2 weighted turbo spin echo images were obtained (repetition time/echo time, 2250-3500/90-100; bandwidth, 20-83kHz; matrix, 256 X 256; section thickness, 4-6mm; intersection gap, 1-2mm; field of view, 2cm).

B- Diffusion-weighted images: They were performed using a "Echo-Planar Imaging" (EPI) sequence with following parameters: TR/TE= 5000/77msec; slice thickness=5mm and 1mm interslice gap; matrix=256 X 256, b-values (0, 850, 1000, 1500s/mm<sup>2</sup>); and the diffusion image was supplied from "Spectral Adiabatic Inversion Recovery" (SPAIR) MR sequence. Respiratory triggering was used for better resolution.

#### Post processing and image analysis:

Qualitative and quantitative analysis of the examined lesions were done as follows:

I- *Qualitative analysis:* Restricted diffusion was determined by visualization of abnormal bright signal intensity that became enhanced with increasing b values (0 → 850 → 1000 → 1500) at "Diffusion Weighted" (DW) images. The ADC map presented intermediate/low Signal Intensity (SI) that corresponded to the abnormality.

II- *Quantitative analysis:* The ADC values were measured manually by applying ROI at areas of bright SI on DW images and intermediate/low SI on ADC maps, aiming to cover as much as possible of the lesion, avoiding cystic/necrotic areas.

#### Statistical analysis:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data was 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 chi-square and Fisher's exact tests (6). ROC curve was constructed with area under curve analysis performed to detect best cutoff value of ADC for detection of high grade tumors.

p-values less than 0.05 were considered as statistically significant.

## Results

One hundred and eight patients were included in this study, 81 (75%) males and 27 (25%) females, their age ranged from 17 to 79 years (mean age 60.81 ± 12.24).

The histopathological diagnosis of the patients was: 51 (47.2%) had urothelial UB cancer, 27 (25%) urothelial + squamous cell carcinoma, 15 (13.9%) squamous cell carcinoma, 9 (8.3%) adenocarcinoma and 6 (5.6%) rare forms (rhabdomyosarcoma and leiomyosarcoma).

The number of lesions was single in 87 (80.6%), double in 15 (13.9%) and multiple in 6 (5.6%) with circumferential thickening in 60 (55.6), endophytic mass in 21 (19.4%), exophytic mass in 18 (16.7%) and mixed in 9 (8.3%). 9 lesions (8.3%) were grade I, 54 lesions (50%) were grade II and 45 (41.7%) lesions were grade III (Table 1).

Analysis of the diffusion-weighted images and comparison of the mean ADC value with the pathological grade of the tumor was done.

All the included lesions (100%) showed persistent high signal on DWI with low to intermediate signal on ADC map denoting restricted diffusion Fig. (1).

ADC values ranged from 0.48 to  $1.21 \times 10^{-3} \text{ mm}^2/\text{s}$  (mean  $0.81 \pm 0.18 \times 10^{-3} \text{ mm}^2/\text{s}$ ) Fig. (2).

The mean ADC value of grade I, grade II and grade III was  $1.11 \pm 0.15 \times 10^{-3} \text{ mm}^2/\text{s}$ ,  $0.83 \pm 0.14 \times 10^{-3} \text{ mm}^2/\text{s}$  and  $0.72 \pm 0.14 \times 10^{-3} \text{ mm}^2/\text{s}$  respectively.

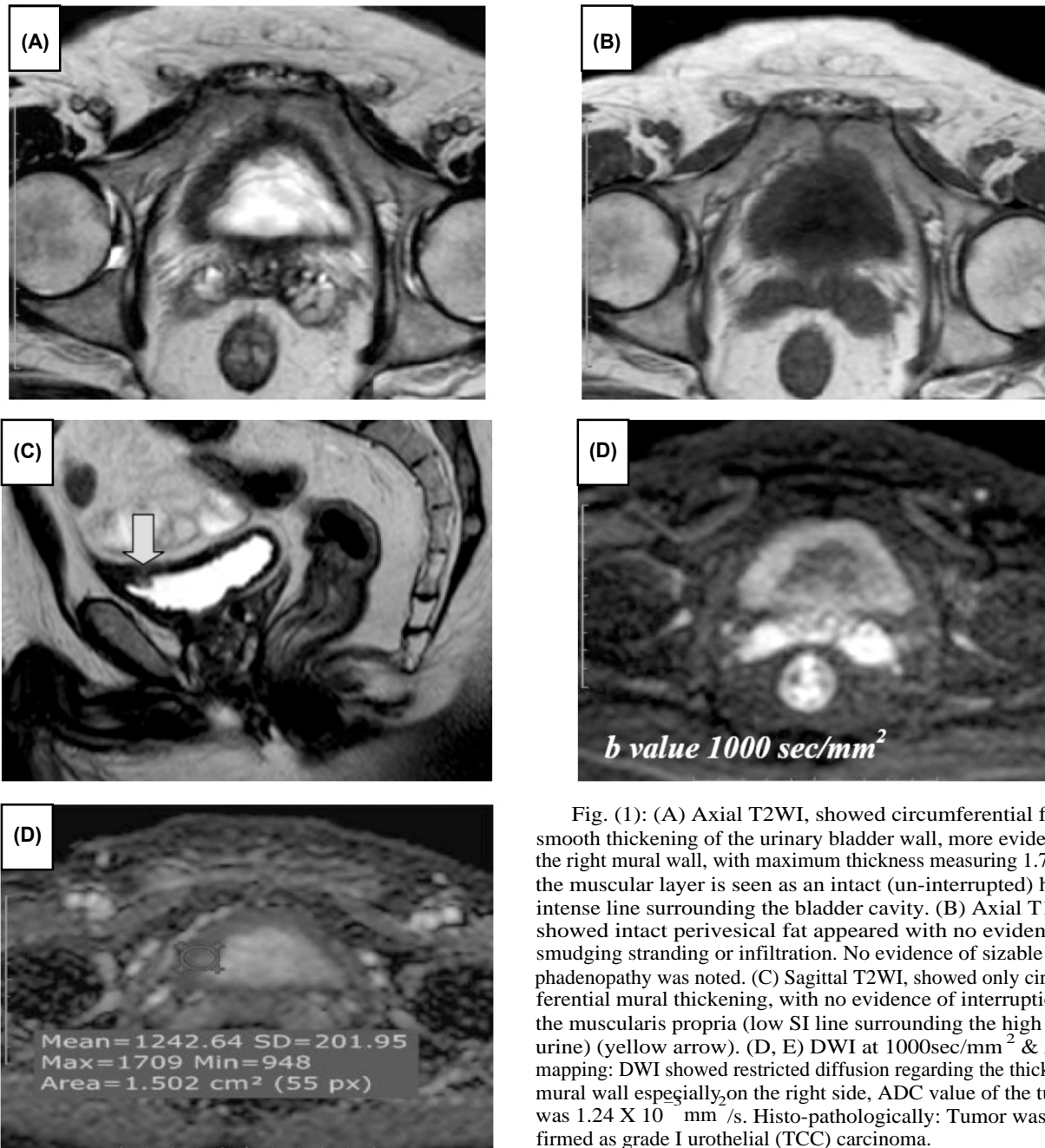


Fig. (1): (A) Axial T2WI, showed circumferential fairly smooth thickening of the urinary bladder wall, more evident on the right mural wall, with maximum thickness measuring 1.72cm, the muscular layer is seen as an intact (un-interrupted) hypo intense line surrounding the bladder cavity. (B) Axial T1WI, showed intact perivesical fat appeared with no evidence of smudging stranding or infiltration. No evidence of sizable lymphadenopathy was noted. (C) Sagittal T2WI, showed only circumferential mural thickening, with no evidence of interruption of the muscularis propria (low SI line surrounding the high SI of urine) (yellow arrow). (D, E) DWI at  $1000 \text{ sec}/\text{mm}^2$  & ADC mapping: DWI showed restricted diffusion regarding the thickened mural wall especially on the right side, ADC value of the tumor was  $1.24 \times 10^{-3} \text{ mm}^2/\text{s}$ . Histo-pathologically: Tumor was confirmed as grade I urothelial (TCC) carcinoma.

There was significant difference between the mean ADC value of tumors of grade I and III ( $p=0.000$ ); and between grade I and II ( $p=0.000$ ) there was slightly less significant difference between grade II and III ( $p=0.022$ ).

Moreover, statistical analysis of the data revealed that using the ADC value of  $0.77 \times 10^{-3} \text{ mm}^2/\text{s}$  as a cutoff value between high grade tumors (grades II & III) and low grade tumors (grade I),

has a sensitivity, specificity, PPV, NPV and accuracy of 60%, 71.4%, 60%, 71.4% and 66.7% respectively the mean ADC value of  $0.91 \times 10^{-3} \text{ mm}^2/\text{s}$  showed better statistical indices (sensitivity 93.7%, specificity 100%, PPV 100%, NPV 60% and accuracy 94.4%) and enhanced the performance of the ADC value in the assessment of the tumor cellularity of the bladder carcinoma. Figs. (3,4), (Tables 2,3).

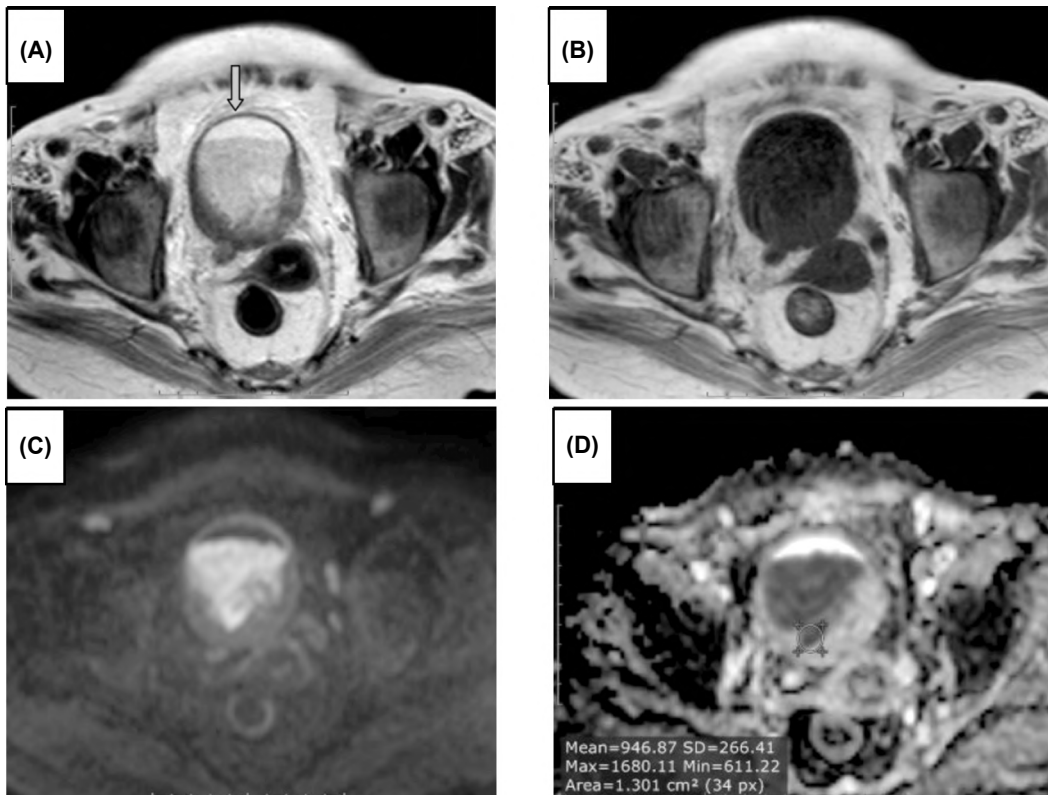


Fig. (2): (A, B) Axial T2WI & T1WI showing; right and left postero-lateral mural wall thickening involving the whole thickness of the muscularis propria (between 3 O'clock and 9 O'clock), it is seen involving both uretro-vesical junctions as well. The anterior bladder wall is seen spared (where the muscularis propria appears as an uninterrupted low SI line (yellow arrow) on T2WI). On T1WI the perivesical fat planes can be clearly seen to be spared and devoid of any signs of invasion by the tumor. (C, D) DWI at b value of  $1000 \text{ sec}/\text{mm}^2$  and ADC mapping showing; mild restriction of the SI of the mural wall lesion, however the ADC value for the lesion measured  $0.9 \times 10^{-3} \text{ mm}^2/\text{sec}$ . Histo-pathologically, the tumor was confirmed as grade II invasive adenocarcinoma of the urinary bladder.

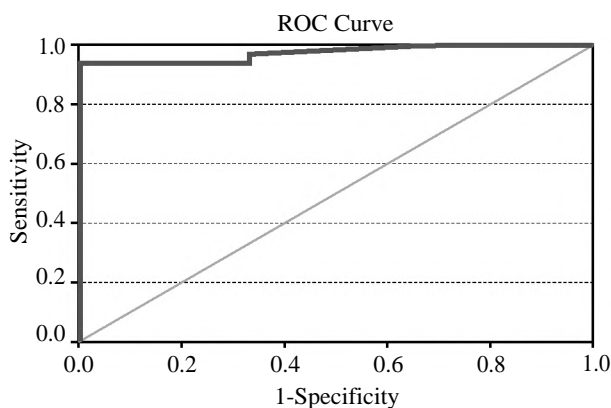


Fig. (3): ROC curve analysis to explore the discriminant ability of mean dADC value to differentiate high grade (Grade II & III) from low grade (Grades I) tumors.

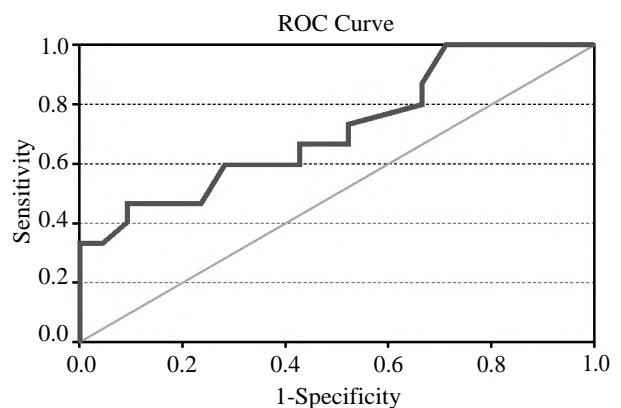


Fig. (4): ROC curve analysis to explore the discriminant ability of mean dADC value to differentiate high grade (Grade III) from low grade (Grades I & II) tumors.

Table (1): Description of study variables.

	Description (n=108)
<b>Age:</b>	
Range	17-79
Mean ± SD	60.81 ± 12.24
Median (IQR)	60.5 (57.5-69)
<b>Sex:</b>	
Male	81 (75)
Female	27 (25)
<b>Number of lesions:</b>	
Single	87 (80.6)
Double	15 (13.9)
Multiple	6 (5.6)
<b>Shape:</b>	
Circumferential thickening	60 (55.6)
Exophytic mass	18 (16.7)
Endophytic mass	21 (19.4)
Mixed	9 (8.3)
<b>Maximum thickness:</b>	
<1 cm	15 (13.9)
1-3cm	39 (36.1)
>3 cm	54 (50)
<b>Site:</b>	
Diffuse	45 (41.7)
Dome	21 (19.4)
Anterior wall	33 (30.6)
Posterior wall	45 (41.7)
Right lateral wall	39 (36.1)
Left lateral wall	24 (22.2)
Inferior	30 (27.8)

Table (2): Explore the discriminant ability of mean dADC value to differentiate high grade (Grade II & III) from low grade (Grades I) tumors

AUC	95% CI	p-value	Cut-off	Sen	Spec	PPV	NPV	Accuracy
0.975	0.947-1.000	0.000	≤0.91	93.9%	100%	100%	60%	94.4%

AUC : Area Under the Curve. Spec. : Specificity.  
 CI : Confidence Interval. PPV : Positive Predictive Value.  
 Sen. : Sensitivity. NPV : Negative Predictive Value.

Table (3): Explore the discriminant ability of mean dADC value to differentiate high grade (Grade III) from low grade (Grades I & II) tumors.

AUC	95% CI	p-value	Cut-off	Sen	Spec	PPV	NPV	Accuracy
0.714	0.616-0.813	0.000	≤0.77	60%	71.4%	60%	71.4%	66.7%

AUC : Area Under the Curve. Spec. : Specificity.  
 CI : Confidence Interval. PPV : Positive Predictive Value.  
 Sen. : Sensitivity. NPV : Negative Predictive Value.

### Discussion

Urinary bladder cancer is one of the commonest urological malignancies, causing remarkable morbidity and mortality all over the world [7] clinico/histo-pathological classification and staging of a

tumor, are valuable information for the appropriate choice of the course of management which noticeably affects the tumor's final prognosis [8].

DW-MRI is an extremely valuable imaging modality for the radiological assessment of the urinary bladder carcinoma, due to high tissue contrast, with absence of radiation exposure, multi-planar imaging capabilities, and short examination time; moreover there is no need for contrast media. Therefore it's incorporation in pre-operative assessment of urinary bladder tumors was reported in many studies. It also gives accurate information on cellular density, tissue compactness and membrane integrity by measuring the diffusion of water molecule in vivo, with lower loss of signal indicating low water diffusion and higher loss of signal indicating high water diffusion [9].

In this study, we found that the mean ADC value of the studied urinary bladder lesions was  $0.81 \pm 0.18 \times 10^{-3} \text{ mm}^2/\text{s}$ .

This is similar to the mean ADC values reported by other previous studies; Kobayashi et al., [10] reported that the mean ADC value in their study<sub>3</sub> was  $0.86 \times 10^{-3} \text{ mm}^2/\text{s}$ , while it was  $0.88 \times 10^{-3} \text{ mm}^2/\text{s}$  in Dagulli et al., [11] and  $0.63 \times 10^{-3} \text{ mm}^2/\text{s}$  in Yoshida et al., study [12].

However; Lista et al., [2] and Li et al., [7] reported a slightly higher mean ADC value measuring  $1.06 \times 10^{-3} \text{ mm}^2/\text{s}$  and  $1.22 \pm 0.22 \times 10^{-3} \text{ mm}^2/\text{s}$ , respectively.

In our study, ADC values ranged from 0.48 to  $1.21 \times 10^{-3} \text{ mm}^2/\text{s}$ , using the ADC value of  $0.77 \times 10^{-3} \text{ mm}^2/\text{s}$  as a cutoff value between high grade tumors (grades II & III) and low grade tumors (grade I), has a sensitivity, specificity, PPV, NPV and accuracy of 60%, 71.4%, 60%, 71.4% and 66.7%, respectively the mean ADC value of  $0.91 \times 10^{-3} \text{ mm}^2/\text{s}$  showed better statistical indices (sensitivity 93.7%, specificity 100%, PPV 100%, NPV 60% and accuracy 94.4%) and enhanced the performance of the ADC value in the assessment of the tumor cellularity of the bladder carcinoma.

And so, our result did not exceed the cut off value between low grade and high grade UB tumors set by previous studies, such as Wang et al., [13] who estimated a cutoff ADC<sub>3</sub> value, sensitivity and specificity of  $0.899 \times 10^{-3} \text{ mm}^2/\text{sec}$ , 100%, and 95%, respectively.

Similarly Kobayashi et al., [10] study showed a cut off ADC<sub>2</sub> value, sensitivity and specificity  $0.86 \times 10^{-3} \text{ mm}^2/\text{sec}$ , 88%, and 85%, respectively.

This was consistent with Al Johi et al., [14] who stated that the ADC cutoff  $<0.9 \times 10^{-3} \text{ mm}^2/\text{s}$  identified high-grade from low grade tumors with 91.7% sensitivity and 60% specificity.

The relation between the mean ADC value and the histological grade of the detected urinary bladder cancer was studied in the current work. We found that there was a significant inverse relation between them, meaning that tumors with higher grade (grade II & and grade III) showed lower ADC values when compared with those of lower grade (grade I) ( $p=0.000$ ).

Our results showed the Mean ADC value for grade I tumors were  $1.11 \pm 0.15 \times 10^{-3} \text{ mm}^2/\text{sec}$ , of grade II were  $0.83 \pm 0.14 \times 10^{-3} \text{ mm}^2/\text{sec}$  and of grade III were  $0.72 \pm 0.14 \times 10^{-3} \text{ mm}^2/\text{sec}$ .

This is consistent with the previous studies of Wang et al., [13] whose results were ADC of  $(1.141 \pm 0.164 \times 10^{-3} \text{ mm}^2/\text{sec})$  for low grade tumors and  $(0.766 \pm 0.091 \times 10^{-3} \text{ mm}^2/\text{sec})$  for high grade tumors ( $p < 0.05$ ).

We found a significant difference between the mean ADC value of tumors of grade I and III ( $p=0.000$ ); and between grade I and II ( $p=0.000$ ). However, there was less significant difference between grades II and III ( $p=0.022$ ).

Going on the same path both Barsoum et al., [15], and Takeuchi et al., [16] found that the mean ADC value of grade I tumors was significantly higher than that of grade II and grade III tumors. They found the Mean ADC value for all grade III tumors was  $<1.25 \times 10^{-3} \text{ mm}^2/\text{sec}$ , and  $<1.0 \times 10^{-3} \text{ mm}^2/\text{sec}$ , respectively.

Unlikely was Yamada et al., [8], results which showed slightly higher than our study, the author found that the ADC value for the low grade tumors was  $1.58 \pm 0.21 \times 10^{-3} \text{ mm}^2/\text{sec}$  and for the high grade tumors was  $(1.20 \pm 0.27 \times 10^{-3} \text{ mm}^2/\text{sec})$  ( $p < 0.001$ ).

This was different from the results of Al Johi et al., [14] who reported that significant difference in ADC values was found between grade I and grade III ( $p < 0.001$ ), grade II and grade III ( $p=0.045$ ) but not between grade I and grade II ( $p=0.066$ ). According to the WHO grading system (2004), high-grade tumors [No=84 (89.4%)] showed significantly lower ADC than low-grade tumors [No=10 (10.6%)] ( $p=0.0460$ , AUC: 0.74, 95% confidence interval=0.641-0.825).

### Conclusion:

ADC value could be a good discriminator between low and high grade tumors and hence predictor of cancer cells that would respond to therapy

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## دراسة ارتباطية بين قيمة ظاهرة معامل الانتشار وتصنيف أنواع سرطان المثانة

المقدمة: تعتبر دراسة سرطان المثانة البولية ذات أهمية كبيرة لأنها واحدة من أكثر الأورام الخبيثة شيوعاً. التقييم الدقيق قبل الجراحة لخصائص المرض والتكهن سيكون عوناً كبيراً في تشخيص وتخطيط علاج سرطان المثانة.

الهدف من الدراسة: الهدف من هذه الدراسة هو تقييم دور قيمة معامل الانتشار الظاهري (ADC) في إكتشاف تصنيف سرطان المثانة البولية قبل العلاج.

الوسائل والمرضى: دراسة مستقبلية لـ ١٠٨ مريض مع متوسط عمر  $60.81 \pm 12.24$ ، تم تشخيصهم بسرطان المثانة المثبت. قام إثنان من أخصائي الأشعة بتقييم مستقبلي للأوصاف المورفولوجية والنوعية للسرطانات المشمولة (الانتشار المقيد) والتحليل الكمي لخرائط ADC. تم حساب قيمة ADC المتوسطة لأفات المثانة وإرتبطت مع الدرجة المرضية التي تم تحديدها عن طريق خزعة إبرة مفتوحة أو أساسية (والتي تعتبر مرجعاً قياسيماً).

النتائج: كان هناك فرق كبير بين متوسط قيمة معامل الانتشار الظاهري من أورام الصف الأول والثالث ( $P=0.000$ )، وبين الصف الأول والثاني ( $P=0.000$ ) مع إختلاف طفيف أقل أهمية بين الصف الثاني والثالث ( $P=0.022$ ). إرتبطت قيم ADC عالية مع أورام درجة منخفضة.

الإستنتاج: معامل الانتشار الظاهري هي طريقة خالية من التباين تسمح بالتحليل المورفولوجي والكمي. تعد قيمة ADC تمييزاً جيداً بين أورام الدرجة المنخفضة والعالية ومن ثم تنبئ بالصف النسيجي لأورام المثانة والتشخيص.