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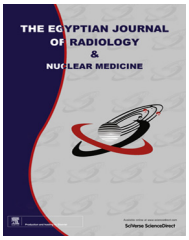

ORIGINAL ARTICLE

The role of diffusion-weighted magnetic resonance imaging in T staging and grading of urinary bladder cancer

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KEYWORDS

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Abstract *Purpose:* To evaluate the ability of diffusion-weighted imaging (DWI) in T staging of urinary bladder cancer and the correlation between the apparent diffusion coefficient (ADC) and tumor grading.
Patients and methods: This study included 40 patients with bladder mass diagnosed by ultrasonography. MR imaging sequences included, T2WI, DWI, ADC and T1 postcontrast MRI were done. The correlation between magnetic resonance findings and histopathological results was done.
Results: Of all forty patients, 14 patients (35%) were T1, 18 (45%) patients were T2, and 8 (20%) patients were T3. The overall accuracy of T2WI, DWI and postcontrast imaging sequences in differentiating superficial from invasive tumor was 60%, 85% and 75% respectively. The overall accuracy of T2WI, DWI and postcontrast imaging sequences in differentiating organ confined from non-organ confined tumor was 80%, 90% and 70% respectively. The mean ADC value was $0.95 \pm 0.13 \times 10^{-3}$ mm^2/s in low grade tumors and $0.69 \pm 0.12 \times 10^{-3}$ mm^2/s in high grade tumors.
Conclusion: DWI has a higher overall accuracy compared to both T2WI and postcontrast T1WI in T staging of bladder cancer, and also ADC value can predict the tumor grade. So, DWI can be recommended as promising MRI sequence in urinary bladder T staging and grading.

1. Introduction

Urinary bladder cancer is the second most common cancer of the genitourinary system (1), and bladder cancer in Egypt has significantly changed within the last three decades as transitional cell carcinoma (TCC) becomes the most common type (2).

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Clinical and imaging assessments are important for bladder cancer staging; however, imaging assessment forms a vital part of the management protocol (3). Cystoscopy with biopsy is still the gold standard tool for bladder cancer staging due to its high sensitivity in detecting lesions and the possibilities of tumor resections (4), invasiveness, limitation in detection of flat lesions, and lack of the assessment of extra-vesical tumor invasion represent the main drawbacks (5).

Proper staging and grading of bladder tumor are crucial for management (6). Under staging subjects patients to suboptimal treatment while over staging subjects patients to unwarranted treatment-related morbidity (7).

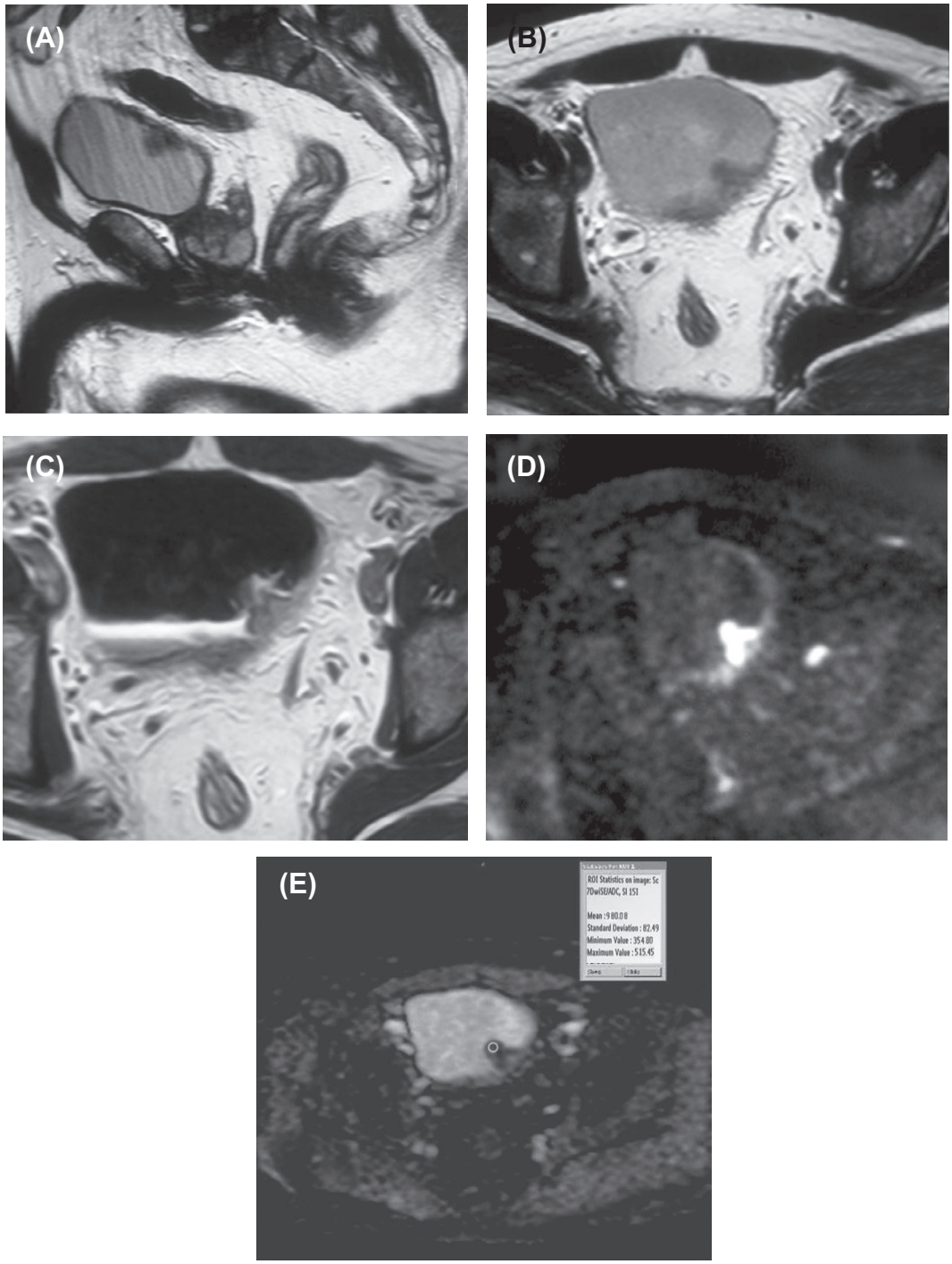

Fig. 1 56 old male histopathologically confirmed transitional cell carcinoma T1, G1 tumor. T2WI (A and B) shows small fungating mass lesion disrupting hypointense muscle layer at base of the mass, over staged as stage T2a. Post contrast T1 WI (C) the mass is showing heterogeneous contrast enhancement with almost indistinct urinary bladder wall, over staged as stage T2. DWI (D) the mass showed restricted diffusion evident by C-shaped high signal intensity with a low SI stalk connecting to left bladder wall ($b = 500$ and $b = 1000$) denoting stage T1 representing accurate staging. ADC value (E) measured within the ROI was 0.98×10^{-3} mm^2/s denoting low grade (G1) tumor.

Magnetic resonance imaging is the modality of choice in imaging bladder tumor and its accuracy ranges from 73% to 96%, and these values are 10–33% higher than CT staging of bladder cancer (3,8).

Diffusion weighted imaging (DWI) reveals micro-molecular diffusion. This can delineate pathologic lesions with high tissue contrast against generally suppressed background signal (9). DWI can provide useful information for T staging of bladder cancer (10).

Apparent diffusion coefficient (ADC) representing the degree of water molecular diffusion and the degree of restriction to water diffusion in biological tissues is inversely correlated to the tissue cellularity and the integrity of the cell membranes (11).

Several authors have already reported decreased ADC values among various malignant lesions due to dense cellularity and large cellular size (11,12).

ADC quantitatively differentiates benign from malignant lesions (9). In addition, the ADC can predict the histologic grade of bladder cancer (10).

The aim of this work was to evaluate the ability of diffusion-weighted imaging T-stage of bladder cancer and to find correlation between the apparent diffusion coefficient (ADC) and histologic grade.

2. Patients and methods

In this prospective study, 40 patients (28 males and 12 females) presented with bladder mass were diagnosed using ultrasound, in the period between October 2012 and April 2014. Their ages ranged from 52 to 70 years. A full history was obtained from all patients with special attention to hematuria, pain, passage of blood clots or necroturia, dysuria, frequency and urgency. A thorough clinical examination with special attention to

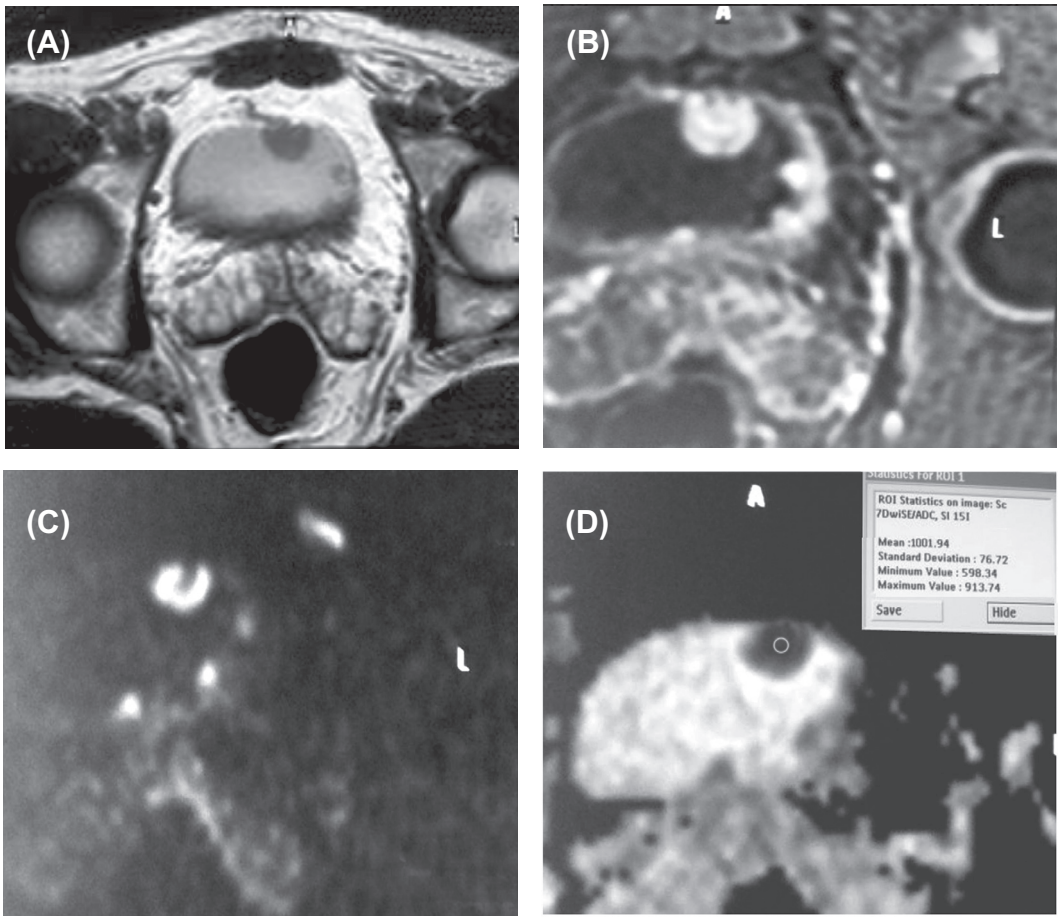

Fig. 2 68 old male histopathologically confirmed transitional cell carcinoma staged T1, low grade (G1). Axial T2-weighted image (A) showed 4 fungating soft tissue mass lesions seen involving the dome, left lateral wall and base of the urinary bladder, the large domal mass display intermediate signal intensity with irregular inner margin of hypointense line over staged as stage T2a. Other three masses showing intact hypointense line accurately staged as T1. Axial T1 post contrast image (B) showed homogenous enhanced soft tissue masses with intact muscle layer accurately staged as stage T1. DWI (C): The four bladder mass lesions are clearly detected, showing evidence of restricted diffusion. The domal lesions show intrinsic submucosal stalk while the others show submucosal thickening. The urinary bladder walls are seen clearly identified with no disruption accurately staged as stage T1. ADC values (D) of the domal mass was 0.71×10^{-3} mm^2/s over graded as high grade tumor. The mean ADC values of the other bladder lesions measure 1.02×10^{-3} mm^2/s, 0.99×10^{-3} mm^2/s and 1.1×10^{-3} mm^2/s. accurately graded as low grade tumor.

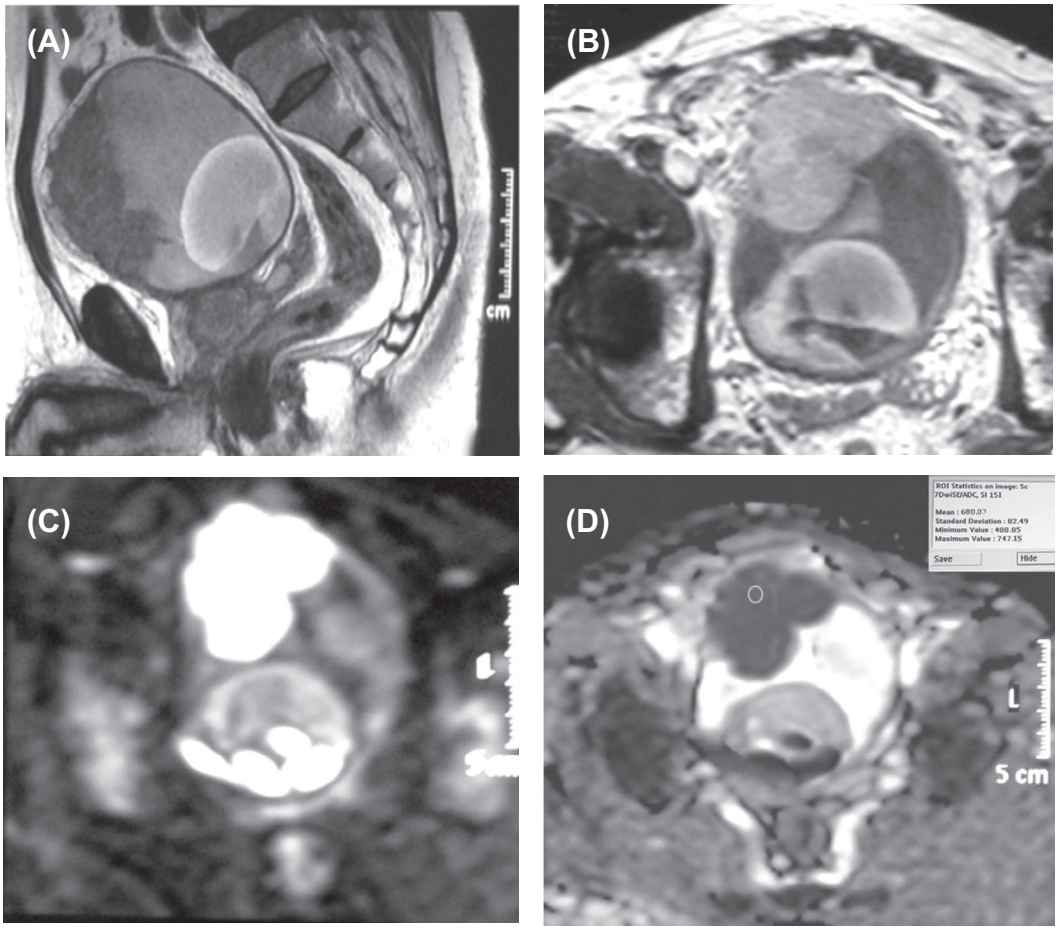

Fig. 3 64 old male histopathologically confirmed transitional cell carcinoma staged T2b, high grade (G3). Sagittal T2-weighted image (A) showed poorly defined endophytic fungating large soft tissue mass lesion in the dome and anterior wall of the bladder and high signal intensity blood clots seen in the lumen. Mass extending into perivesical fat with an irregular contour. Over staged as stage T3b. Axial T1 post contrast enhanced image (B) shows heterogeneous contrast enhancement of the mass with evidence of focal invasion into the perivesical fat planes over staged as stage T3. DWI (C) (b = 1000) showed evidence of restricted diffusion with a smooth bulging accurately staged as stage T2. ADC value (D) was 0.68×10^{-3} mm^2/s denoting high grade tumor (accurate grading).

digital rectal and bimanual examination and a full laboratory investigation were done for all cases.

Our patients were referred to radio-diagnosis department from Urology outpatient clinic, after obtaining institutional review board approval from our hospital and receiving informed consent from the patients before the study. The patients exclusion criteria were patients with impaired renal function (serum creatinine >2 mg/dl), claustrophobia and metallic implants (see Figs. 1–3).

3. Imaging assessment

Thirty minutes before the MRI study, all patients were asked for drinking water and presented by full bladder. In 5 patients with a urethral catheter, it was closed one hour before examination.

MR imaging was performed with a 1.5-T Philips Achieva system class II by using a pelvic phased-array coil with the patient in supine position. MR imaging examination included T2WI, DWI and T1WI postcontrast.

After localizer images, T2-weighted spin-echo MR images were obtained from the aortic bifurcation to the symphysis pubis with the following parameters: repetition time msec/echo time msec, 4400/120, section thickness, 4 mm; intersection gap, 0.4 mm; field of view, 23 cm; matrix, 256 × 190. T2-weighted images were done in the axial and sagittal planes.

Diffusion-weighted images were obtained by using single shot spin-echo echo-planar imaging with a pair of rectangular gradient pulses along three orthogonal axes. The imaging parameters were as follows: TR/TE = 2800/74; field of view 25 cm, section thickness, 3 mm; intersection gap, 1 mm. Images were zero-filled to a 256 × 256 matrix. The orientation and location of these images were prescribed identically to the axial T2-weighted images. The b values were 0, 500 and 1000 s/mm. To gain better signal-to-noise ratios, a larger field of view was used for DW imaging than for T2-weighted imaging, and a thicker section was used for T2-weighted and DW imaging than for T1-weighted fast field echo imaging. DW images were obtained in the axial and sagittal planes.

ADC maps were formed automatically by the device, circular regions of interest (ROIs) were set to be at least 20 mm^2 in order to minimize the influence of potential motion artifacts ranging from 10 to 40 mm^2 according to the size of the mass,

Table 1 T2WI, DWI and postcontrast T1WI criteria of T-staging.

	T2WI (13)	DWI (10)	Postcontrast T1WI (14)
⩽T1	Intact low SI muscle-layer at the base of the tumor	A thin, flat, high SI tumor or a high SI tumor with a low SI submucosal stalk or a thickened submucosa	Intact submucosal linear enhancement (SLE) adjacent to the tumor
T2	A lesion with focally disrupted muscle-layer without perivesical infiltration	A high SI tumor without a submucosal stalk and with a smooth tumor margin	SLE was disrupted by a tumor but there was no infiltration into the perivesical fat
T3	A lesion extending into the perivesical fat	Extension into the perivesical fat with an irregular margin	Tumors invading the perivesical fat
T4	A lesion extending into the adjacent organs	Extension into adjacent organs	Tumor extended to the adjacent organs

and it was placed in the center of the lesion in cases of large masses. ADC value was obtained with *b* values 500 and 1000 s/mm^2. The ADC values are expressed in square millimeters per second.

T1-weighted fast field-echo images with and without fat suppression technique; TR/TE = 500/20; matrix, 224 × 214; section thickness, 3 mm; gapless; field of view, 35 cm; were obtained before and after administration of 0.2 mL per/Kilogram of body weight gadopentetate dimeglumine (postcontrast study was done 20 s after injection of contrast medium).

The patients were referred again to Urology department. Diagnostic cystoscopy and transurethral resection of bladder tumor (TURBT), examination under anesthesia before and after TURBT were done for all patients and radical cystectomy was done for 28 patients.

4. Image interpretation

Imaging sequence sets (T2-weighted images, DW images and T1 postcontrast-enhanced images) were randomly reviewed by two radiologists (H M and I M with 10 years of experience) who were blinded to cystoscopic and histopathological results.

T-staging depends on criteria shown in Table 1.

Correlation between MR findings and histopathological results (after TURBT or radical cystectomy) was done.

Data were checked, entered and analyzed using SPSS version 13 for data processing and statistics. Mann–Whitney *U*-test was used to compare the mean ADC value of patients with low grade tumor (G1) and patients with high grade tumor (G2 or G3). Receiver operating characteristic (ROC) curve was used to select an optimal cutoff value of ADC. For all statistical tests were done, the threshold of significance was fixed at 5% level (*P*-value).

Table 2 T2WI staging results on a stage-by-stage basis compared with histopathological staging.

T2 weighted imaging stage	Histopathology stage				
	⩽T1	T2	T3	T4	Total
⩽T1	4	6	0	0	10
T2	8	10	4	0	22
T3	2	2	4	0	8
T4	0	0	0	0	0
Total	14	18	8	0	40

Table 3 DWI staging results on a stage-by-stage basis compared with histopathological staging.

DW imaging stage	Histopathology stage				
	⩽T1	T2	T3	T4	Total
⩽T1	12	4	0	0	16
T2	2	14	4	0	20
T3	0	0	4	0	4
T4	0	0	0	0	0
Total	14	18	8	0	40

Table 4 Postcontrast T1WI staging results on a stage-by-stage basis compared with histopathological staging.

Postcontrast T1WI stage	Histopathology stage				
	⩽T1	T2	T3	T4	Total
⩽T1	6	2	0	0	8
T2	8	10	6	0	24
T3	0	6	2	0	8
T4	0	0	0	0	0
Total	14	18	8	0	40

Table 5 Sensitivity, specificity and accuracy for differentiating superficial tumors (⩽T1) from invasive tumors (>T1).

Image	Sensitivity		Specificity		Accuracy	
	No.	%	No.	%	No.	%
T2WI	20/26	76.92	4/14	28.57	24/40	60
DWI	22/26	84.62	12/14	85.71	34/40	85
Postcontrast T1WI	24/26	92.31	6/14	42.86	30/40	75

Table 6 Sensitivity, specificity and accuracy for differentiating organ confined tumors (⩽T2) from non-organ confined tumors (>T2).

Image	Sensitivity		Specificity		Accuracy	
	No.	%	No.	%	No.	%
T2WI	4/8	50	28/32	87.5	32/40	80
DWI	4/8	50	32/32	100	36/40	90
Postcontrast T1WI	2/8	25	26/32	81.25	28/40	70

Table 7 Comparison between ADC values and histopathological grades.

	Low grade (G1) tumors	High grade (G2 and G3) tumors	*P* value
Mean × 10^{-3} mm^2/s ± SD	0.95 ± 0.13	0.69 ± 0.12	0.0001*

* < 0.05 significant.

Table 8 Cutoff value between low grade (G1) and high grade (G2 and G3) tumor by *b* value 1000 s/mm^2.

	Cutoff value (*b* = 1000 s/mm^2)	Sensitivity	Specificity	*P* value
Low grade versus high grade	0.82	100.0	100.0	0.001*

* < 0.05 significant.

5. Results

This study included 40 patients with bladder mass. They were 28 males (70%) and 12 females (30%). Their ages ranged from 52 to 70 years. The most common clinical symptom was painless hematuria presented in 36 patients (90%).

One case had diffuse wall thickening, and DWI predicts the site of tumor, while T2WI and T1 postcontrast cannot predict the site of tumor.

Regarding to histopathological results, transitional cell carcinoma was found in 34 (85%) patients, squamous cell carcinoma was found in 4 patients (10%) and adenocarcinoma was found in 2 patients (5%). Concerning MR staging, 14 patients (35%) were staged as T1, 18 patients (45%) staged as T2, 8 patients (20%) staged as T3 and we have no patient staged as T4.

Tables 2–4 showed that T2WI staging was correct in 18 patients (45%), under staging occurred in 10 patients (25%) and over staging occurred in 12 patients (30%). DWI staging was correct in 30 patients (75%), under staging occurred in 8 patients (20%) and over staging occurred in 2 patients (5%). Postcontrast enhanced T1WI staging was correct in 18 patients (45%), under staging occurred in 8 patients (20%) and over staging occurred in 14 patients (35%).

Accuracy of T2WI for proper tumor staging was 28.6%, 55.6% and 50% for stages T1, T2 and T3 respectively. Accuracy of DWI for proper tumor staging was 85.7%, 77.8% and 50% for stages T1, T2 and T3 respectively. Accuracy of postcontrast enhanced T1WI for proper tumor staging was 42.9%, 55.6% and 25% for stages T1, T2 and T3 respectively.

Table 5 showed sensitivity, specificity and accuracy for differentiating superficial tumors (⩽T1) from invasive tumors (> T1).

Table 6 showed that the specificity and accuracy of DWI are higher than that of T2WI and postcontrast imaging sequences in differentiating organ confined from non-organ confined tumor.

Table 7 showed that mean ADC value is high in low grade tumors and low in high grade tumors.

Table 8 showed cutoff value between low grade (G1) and high grade (G2, and G3) tumors by *b* value 1000 s/mm^2.

6. Discussion

As known, MRI has multiple advantages such as, no ionizing radiation, high spatial resolution and high soft tissue contrast (15), DWI was first applied in the brain and became the 'gold standard' imaging for the diagnosis of acute stroke (16). After technical advances such as fast sequences, DWI has been applied in the abdomen and pelvis including urinary tract tumors (10,17).

DWI has a high level of diagnostic performance in detecting bladder cancer and is comparable to T2WI but with better inter-observer agreement, this may be due to the clear contrast visible in DWI; signals of bladder cancer are very bright while images of surrounding tissues appear muted (18).

Recently, quantification of tissue by ADC has been more commonly used to assess the pathophysiological characteristics of bladder cancer. ADC was shown to be able to differentiate malignant tissues from normal bladder wall or benign tissues (19). In tumor grading, ADC values were reported to be significantly lower in high grade than in low grade (18).

The feasibility of using DWI in the detection of a urinary bladder carcinoma was reported by Matsuki et al. (20), and in their study the sensitivity in detecting the carcinomas was 100%. The same findings were also reported by El-Assmy et al. (8), and in their study the sensitivity of DWI was 100% in terms of correctly detecting the carcinomas.

However the previous studies did not compare the sensitivity of DWI with T2-WI. In our study the sensitivity of DWI was 100% regarding the carcinomas; however, the sensitivity of T2WI and postcontrast T1WI was 97.5%. In one patient, T2-WI and postcontrast T1WI only showed diffuse bladder wall thickening without any mass lesion; however, DWI revealed malignant mass lesion inside the diffuse wall thickening which helps urologist to take a biopsy at cystoscopy from suspected lesion which confirmed histopathologically to be squamous cell carcinoma.

In the current study, postcontrast T1WI has sensitivity and specificity of 25% and 81.25% respectively for distinguishing T2 stage or below (organ confined tumor) from T3 stage or higher (non-organ confined tumor). Our results are in agreement with the results of Tekes et al. (21) concerning specificity; however, our results showed lower sensitivity, as they reported sensitivity and specificity of 86% and 84% respectively for distinguishing T2 stage or below from T3 stage or higher.

In this study the DWI staging accuracy in differentiating superficial from invasive tumor and organ confined from non-organ confined tumors was 85% and 90% respectively and this is higher than the results of El-Assmy's et al. (22), who reported that DWI staging accuracy was 63.6% and 69.6% in differentiating superficial from invasive tumors and organ-confined from non-organ-confined tumors, respectively.

A retrospective study published by Watanabe et al. (23) compared DWI with T2 weighted and gadolinium enhanced techniques for determining tumor invasion into the bladder wall, and comparing the findings with histopathology. Tumor T-stage was correct in 68% of patients with DWI, 58% with contrast enhanced and 53% with T2 weighted imaging. Our study was in line with their results as tumor T stage

was correct in 75% of patients with DWI, 45% with T2 weighted imaging and 45% with contrast enhanced T1WI.

El-Assmy et al. (22) have reported the accuracy of DWI for individual tumor stages. They found that the accuracy of DWI for correctly identifying tumor stage was 63.6%, 75.7% and 93.7% for stages T1, T2 and T3 respectively. Our study was comparable to these results as accuracy of DWI for correctly identifying tumor stage was 85.7%, 77.8%, 50% respectively. The low percent in T3 in our study could be explained by small number of cases.

In our study the mean ADC values were $(0.95) \times 10^{-3}$ mm^2/s, $(0.69) \times 10^{-3}$ mm^2/s for low grade tumor (G1) and high grade tumor (G2 or G3), respectively. This is in agreement with Takeuchi et al. and Kobayashi et al. (10,18). Both studies demonstrate that ADC values in the tumors of higher grade were found to be significantly lower than those in tumors of lower grade.

7. Conclusions

DWI has a higher overall accuracy compared to both T2WI and postcontrast T1WI in T staging of bladder cancer, and also ADC map can predict the tumor grade. So DWI can be recommended as promising MRI sequence in urinary bladder T staging and grading.

Conflict of interest

The authors declare that there are no conflict of interest statements.

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