Diagn Interv Radiol 2024; DOI: 10.4274/dir.2024.243004

ABDOMINAL IMAGING

ORIGINAL ARTICLE

The role of multiparametric magnetic resonance imaging in the differentiation of low- and high-grade non-muscle invasive bladder cancer

Merve Nur Taşdemir[1]
Uluhan Eryürük[1]
Ural Oğuz[2]
Birgül Tok[3]
Serdar Aslan[1]

[1]Giresun University Faculty of Medicine, Department of Radiology, Giresun, Türkiye

[2]Giresun University Faculty of Medicine, Department of Urology, Giresun, Türkiye

[3]Giresun University Faculty of Medicine, Department of Pathology, Giresun, Türkiye

PURPOSE

To evaluate the diagnostic efficacy of apparent diffusion coefficient (ADC) measurements and semi-quantitative dynamic contrast enhancement (DCE) parameters in predicting the differentiation between low- and high-grade tumors in non-muscle invasive bladder cancers (NMIBC).

METHODS

Patients with NMIBC, who were histopathologically confirmed between August 2020 and July 2023, were analyzed by 2 radiologists with different levels of experience. DCE semi-quantitative parameters such as wash-in rate (WiR), wash-out ratio (WoR), time to peak (TTP), and peak enhancement (PE) were calculated. ADC measurements were performed using the three-region-of-interest (ADCt) and whole volume (ADCw) methods; ADCt ratio (ADCtR) and ADCw ratio (ADCwR) were also calculated. Receiver operating characteristic curve analysis was performed to demonstrate the cut-off values of ADCt, ADCw, ADCtR, and ADCwR to differentiate low- and high-grade tumors. The intraclass correlation coefficient was used to evaluate inter-reader agreement.

RESULTS

A total of 89 patients were included in this study. Of these patients, 48 had low-grade NMIBC, and 41 had high-grade NMIBC. There was no significant difference in mean WoR, WiR, TTP, and PE values between low- and high-grade NMIBC ($P > 0.05$). The ADCt, ADCw, ADCtR, and ADCwR values of high-grade NMIBC were significantly lower than those of low-grade NMIBC ($P < 0.001$). With cut-off values of 0.449 and 0.435, ADCtR had the best diagnostic value for both readers, showing better accuracy, sensitivity, specificity, and area under the curve (85.4%–83.1%, 87.5%–85.4%, 82.9%–80.4%, and 0.879–0.857, respectively, with confidence intervals). Additionally, ADCtR and ADCt showed acceptable diagnostic performance for both readers, with cut-off values of 0.439 and 0.431, respectively, for differentiating Ta- and T1-stages. The inter-reader agreement was almost perfect for ADC measurements.

CONCLUSION

While DCE semiquantative parameters did not yield significant outcomes in distinguishing between low and high grades, ADCtR holds promise for enhancing patient management in NMIBC cases and stands as a potential preoperative radiological asset.

CLINICAL SIGNIFICANCE

Individuals diagnosed with NMIBC may require different treatment approaches; therefore, it is very important to distinguish between low- and high-grade cases preoperatively. The differentiation between the Ta- and T1-stages is recognized as crucial in patient treatment strategies. Furthermore, ADCtR shows promise for improving patient management in NMIBC cases.

KEYWORDS

Apparent diffusion coefficient reference, apparent diffusion coefficient ratio, non-muscle invasive bladder cancer, magnetic resonance imaging, diffusion-weighted imaging, apparent diffusion coefficient

Corresponding author: Merve Nur Taşdemir

E-mail: mervetsdmr@gmail.com

Received 29 August 2024; revision requested 02 October 2024; last revision received 10 October 2024; accepted 20 October 2024.

Epub: 25.11.2024

Publication date: xx.xx.2024

DOI: 10.4274/dir.2024.243004

You may cite this article as: Taşdemir MN, Eryürük U, Oğuz U, Tok B, Aslan S. The role of multiparametric magnetic resonance imaging in the differentiation of low- and high-grade non-muscle invasive bladder cancer. *Diagn Interv Radiol*. 25 November 2024 DOI: 10.4274/dir.2024.243004 [Epub Ahead of Print].

Bladder cancer ranks as the second most prevalent genitourinary malignancy, following prostate cancer, and accounts for over 500,000 new cases and 200,000 fatalities each year.[1] The majority of bladder cancers are urothelial cell carcinomas and are tissue-based, categorized into low- or high-grade tumors.[2] While ultrasound and computed tomography are commonly employed in the diagnosis of bladder cancer,[3] magnetic resonance imaging (MRI) is regularly utilized in the local staging of bladder cancer due to its capability to evaluate muscle invasion.[4]

The most critical factor that affects the prognosis of bladder cancer is muscle invasion.[5] Muscle-invasive bladder cancer (T2–T4) has a poor outcome and typically requires aggressive interventions such as cystectomy, systemic treatment, or a mix of both.[2] Non-muscle invasive bladder cancer (NMIBC) (Ta–T1) typically exhibits low-grade characteristics and demonstrates a non-aggressive demeanor.[2] Roughly 70% of tumors constitute NMIBC, with over 50% being Ta-stage tumors. Despite the majority of cases being identified at a non-muscle invasive stage, there is a substantial risk of disease progression and recurrence.[6,7] Treatment approaches primarily concentrate on reducing local recurrence and impeding stage advancement, with the overarching objective of preserving and improving the patient's quality of life.[2]

According to the treatment guidelines of the American Cancer Society, intravesical chemotherapy is recommended for Ta-stage tumors in the presence of low-grade tumors, whereas intravesical bacillus calmette-guerin is recommended in the presence of high-grade tumors. For T1-stage tumors, cystectomy may be recommended in the presence of high-grade tumors if there are multiple tumors or if the tumor is large when first detected.[8] Stöckle et al.[9] highlighted the significance of differentiating between Ta- and T1-stages in the distinction of treatment. According to this study, the prognosis of patients with T1-stage tumors who underwent late cystectomy is worse than that of patients with T2 tumors.[9] Transurethral resection (TUR) is ineffective in managing lymphogenic micrometastases that initiate during the pT1-stage. According to Jakse et al.[10], 50% of all patients with T1 carcinomas developed a muscle-infiltrating recurrence within 40 months after TUR. The crucial point for therapeutic outcomes appears to be the onset of invasive growth (i.e., lamina propria invasion). This means that even tumor stage TI is too advanced to consider TUR as a reliable curative treatment.[9] Individuals diagnosed with NMIBC may require different treatment approaches; therefore, it is crucial to preoperatively differentiate between low- and high-grade cases.[4]

Main points

- It is crucial to preoperatively differentiate between low- and high-grade cases in non-muscle invasive bladder cancer (NMIBC).
- Apparent diffusion coefficient (ADC) measurements of high-grade NMIBC were significantly lower than those of low-grade NMIBC.
- The ADC three region-of-interest ratio is a promising avenue for optimizing NMIBC treatment and a potential preoperative radiological aid.

Dynamic contrast-enhanced (DCE) MRI, also known as functional MRI, has been shown to offer insights into the characterization of tissue microvasculature and distinguish the tumor from adjacent tissues.[11] The efficacy of diffusion-weighted imaging (DWI) in predicting the histologic grade of bladder cancer has also been discussed in the literature. In these studies, apparent diffusion coefficient (ADC) values acquired from DWI have been proposed as being potentially valuable in facilitating differentiation.[12] However, the related studies were not focused exclusively on NMIBC and relied on very small sample sizes.

This study aims to examine the effectiveness of ADC values from DWI and the semiquantitative parameters obtained from DCE-MRI in distinguishing between low- and high-grade tumors in patients with NMIBC, as well as to assess the consistency among readers with varying levels of experience.

Methods

This retrospective investigation was approved by the institutional ethics board, and informed consent was relinquished (Giresun Training and Research Hospital/KAEK-217/23.10.2023/25). The study protocol aligned with the ethical standards of the 1975 Declaration of Helsinki.

Study group

Patients with NMIBC who were histopathologically confirmed between August 2020 and July 2023 were analyzed retrospectively.

Patients were incorporated into the study based on the following criteria:

1. MRI evaluation contained the required sequences.

2. MRI assessment was conducted within 2 weeks before TUR bladder or cystectomy.

3. Low- or high-grade urothelial carcinoma of the bladder was pathologically confirmed.

Patients were removed from the study based on the following criteria:

1. Patients with ADC images of low or invisible quality.

2. Patients with tumors measuring less than 1 cm.

3. Patients with other histopathologically confirmed types of bladder cancer.

4. Patients with hyperintense urine in the bladder lumen on the T1 sequence.[13]

Figure 1 shows the patient selection.

Image acquisition

A 1.5-T MRI system (Magnetom Aera, Siemens Medical Solutions, Erlangen, Germany) was used for MRI examinations. Ultrasonography was performed before the procedure to ensure that the patients had adequate bladder distension. Images were acquired in a supine position with a pelvic phased-array coil. T1-weighted images (T1-WI), axial, coronal, and sagittal fast spin-echo T2-WI, DCE images with three-dimensional high temporal resolution, and DWI with *b*-values of 0, 800, and 1200 s/mm^2 were acquired. An ADC map was generated using a *b*-value of 1200 s/mm^2. Gadopentetate dimeglumine (Gadovist, 0.2 mL per kilogram of body weight; Bayer Healthcare, Berlin, Germany) was delivered via a power injector at a rate of 2 mL per second, followed by a further infusion of 20 mL of normal saline. Following the injection of the intravenous contrast agent, axial DCE images were captured in post-contrast phases with no gap between them.

Image analysis

Each MRI scan was uploaded to the picture archiving communication system. Two radiologists with varying levels of expertise (reader 1: a board-certified radiologist with 11 years of urogenital radiology experience; reader 2: a radiology resident with 3 years of training) assessed the images separately from histopathology. The readers maintained a blinded approach and had no access to the patients' demographic or surgical data.

Measurements were performed on the slice showing the largest diameter of the lesions and the most contrast enhancement, with minimal artifacts. In patients with multiple tumors, measurements were made for the tumor with the maximum diameter. To ensure the accuracy of the ADC values, lesions with a diameter of less than 1 cm and areas containing artifacts were excluded. The 3 regions of interest (ROIs), each 20 mm^2, were drawn in distinct regions of the tumor. Next, the average ADC was calculated for the three-ROIs method (ADCt). Freehand ROIs along the low signal of the tumor's border on ADC maps were applied in the whole-volume ROIs technique (ADCw).[14] The ROIs were placed while avoiding blood vessels, necrosis, and tumor stalk. ADC measurements with different ROI methods are shown in Figure 2. The most appropriate ADC reference value for calculating the ADC ratio was obtained from the bladder lumen. The ROI was placed in the center of the bladder lumen urine while avoiding artifacts.[13] Patients with hyperintense bladder contents on the T1 sequence were excluded. Three 20 mm^2 ROIs were placed in the center of the bladder, and the average ADC was calculated for reference ADC. Additionally, ADCt ratio (ADCtR) was calculated as the ADC (three-ROIs method)/ ADC reference, and ADCw ratio (ADCwR) was calculated as the ADC (whole-volume ROIs method)/ADC reference.

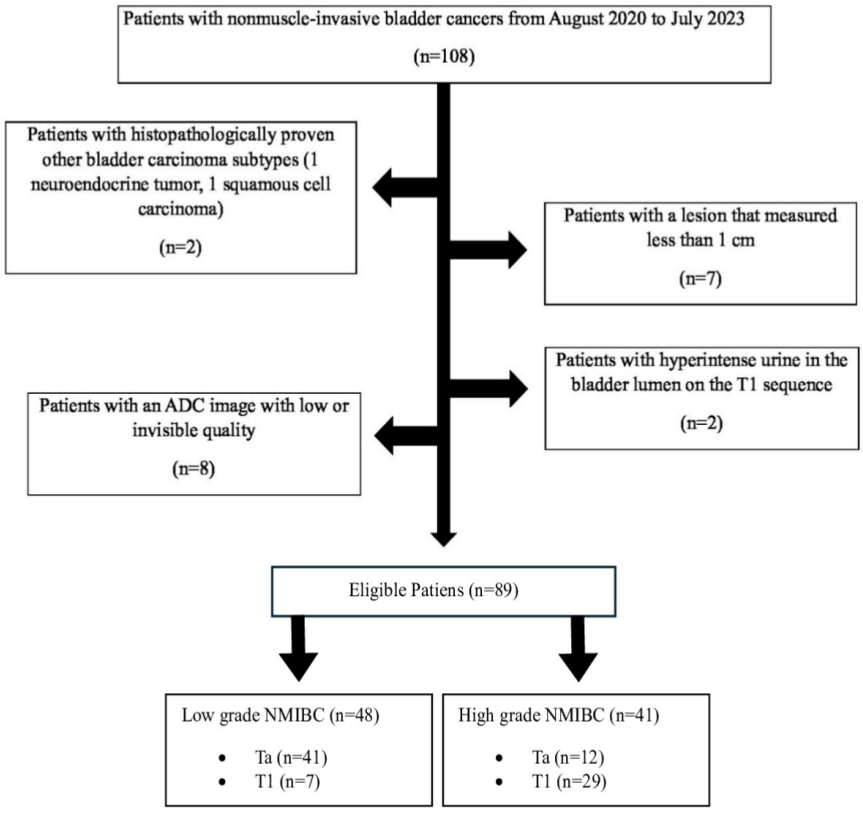

Figure 1. Flowchart of patient selection. ADC, apparent diffusion coefficient; NMIBC, non-muscle invasive bladder cancer.

The ROIs were positioned in regions of tumors displaying maximum enhancement within a homogeneous area. The time signal intensity (SI) curves of all tumors were documented. Furthermore, SI measurements from tumors were normalized using the formula $(SI-S_0) / S_0$ with reference to the pre-contrast SI (S_0). Subsequently, the following parameters, which were initially outlined by Tsili et al.[15], were computed based on the normalized values. Peak enhancement (PE) was described as the maximum S_i of the tumor. Time to peak (TTP) was described as the duration required to reach the maximum S_i of the tumor. The wash-in rate (WiR) was defined as the greatest slope of tumor enhancement and computed using the following formula: $WiR = \max S_i(PE) - S_{i-1}/\max t_i - t_{i-1}$. Conversely, the wash-out rate (WoR) was described as $\max S_i(PE) - S7$, indicating the difference between the peak signal and the signal at the last time point.

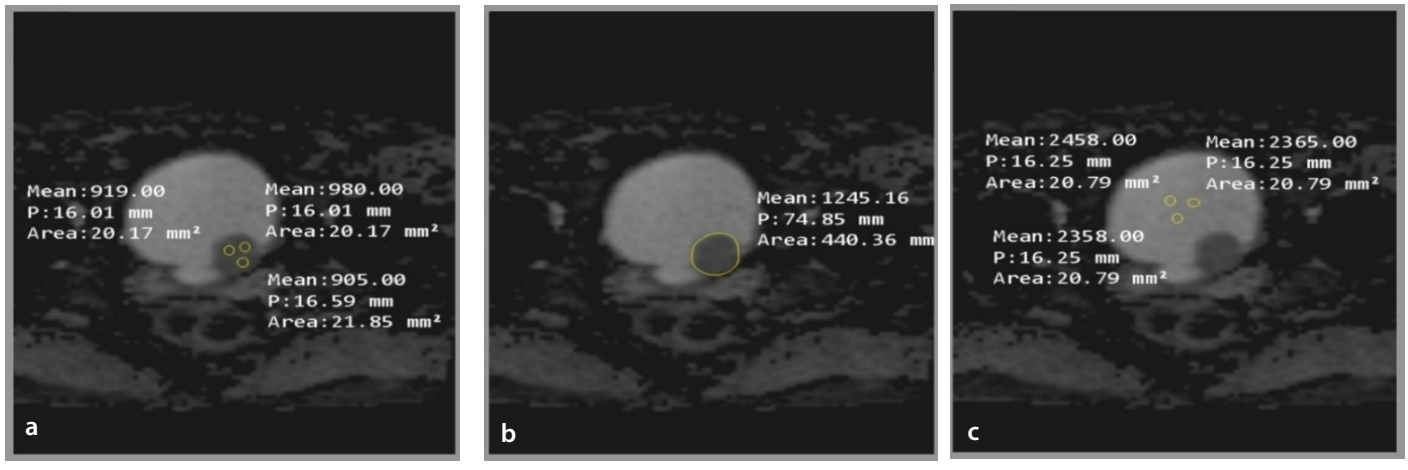

Figure 2. A 54-year-old patient with non-muscle-invasive bladder cancer performed different apparent diffusion coefficient (ADC) values and ADC ratios. **(a)** Three regions of interest (ROI) were drawn, and the average ADC three ROI (ADCt) was calculated as 0.934. **(b)** Freehand ROI along the low signal of the tumor's border on ADC maps. The whole ADC (ADCw) was calculated as 1.245. **(c)** Three ROI were drawn in the center of the bladder, and the average ADC was calculated. The reference ADC was 2.393. Based on these findings, ADCw and ADCwR are consistent with low-grade tumors, whereas ADCtR and ADCt are compatible with high-grade tumors. Histopathological examination revealed high-grade, non-muscle-invasive papillary urothelial carcinoma after transurethral resection of the bladder. ADCtR, three-ROIs method ADC ratio; ADCwR, whole-ROIs method ADC ratio.

Statistical analysis

The data analysis was conducted using IBM SPSS Statistics software version 25.0 (IBM SPSS Corp.; Armonk, NY, USA). The normality of the data was assessed using the Kolmogorov–Smirnov test. For normally distributed data, mean values were presented with standard deviations (SD). The independent t-test was utilized to compare the mean values of ADC, PE, TTP, WiR, and WoR between low- and high-grade NMIBC. A receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off values for ADCt, ADCw, ADCtR, and ADCwR in distinguishing between low- and high-grade cases. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated. The intraclass correlation coefficient (ICC) was used to assess inter-reader reliability for ADC measurements. Data were reported as mean ± SD and n (%), with *P* values below 0.05 considered statistically significant.

Results

We identified 108 patients with pathologically confirmed NMIBC. Two patients had other histopathologically confirmed bladder carcinoma subtypes (one neuroendocrine tumor and one squamous cell carcinoma). Seven patients had a lesion that measured less than 1 cm. Eight patients had an ADC image with low or invisible quality, and two patients had hyperintense urine in the bladder lumen on the T1 sequence. These individuals were removed from the study. Consequently, 89 patients (85 men with a median age of 68 years) were enrolled in this study. Within our study population, 48 had low-grade tumors, and 41 had high-grade tumors. The average maximum diameter of low-grade NMIBCs was 21.7 mm (range: 12–89 mm), whereas that of high-grade NMIBCs was 27.6 mm (range: 11–63 mm). A total of 31 tumors were classified as T1-stages, and 58 tumors were classified as Ta-stages based on histopathology.

Table 1. Mean values of semiquantitative dynamic contrast-enhanced parameters and apparent diffusion coefficient measurements for low- and high-grade non-muscle invasive bladder cancers

	Low-grade NMIBC	High-grade NMIBC	*P* value
ADCtR			
Reader 1	0.54 ± 0.1	0.39 ± 0.1	***P* < 0.001**
Reader 2	0.50 ± 0.16	0.42 ± 0.13	***P* < 0.001**
ADCwR			
Reader 1	0.58 ± 0.10	0.44 ± 0.08	***P* < 0.001**
Reader 2	0.56 ± 0.11	0.43 ± 0.09	***P* < 0.001**
ADCt			
Reader 1	1.19 ± 0.24	0.93 ± 0.17	***P* < 0.001**
Reader 2	1.17 ± 0.23	0.94 ± 0.16	***P* < 0.001**
ADCw			
Reader 1	1.27 ± 0.24	1.05 ± 0.18	***P* < 0.001**
Reader 2	1.22 ± 0.23	1.12 ± 0.22	***P* < 0.001**
TTP			
Reader 1	110 ± 7	119 ± 10	*P* = 0.55
Reader 2	113 ± 31	125 ± 34	*P* = 0.61
PE			
Reader 1	3.1 ± 0.14	3.6 ± 0.22	*P* = 0.06
Reader 2	3.4 ± 0.21	3.7 ± 0.26	*P* = 0.07
WoR			
Reader 1	0.04 ± 0.01	0.07 ± 0.1	*P* = 0.07
Reader 2	0.03 ± 0.1	0.07 ± 0.2	*P* = 0.09
WiR			
Reader 1	1.44 ± 0.35	2.03 ± 0.53	*P* = 0.34
Reader 2	1.28 ± 0.31	1.95 ± 0.67	*P* = 0.36

NMIBC, non-muscle invasive bladder cancer; ADCtR, three-ROIs method ADC ratio; ADCwR, whole-ROIs method ADC ratio; ADCt, three-ROIs method ADC; ADCw, whole-ROIs method ADC; TTP, time to peak; PE, peak enhancement; WoR, wash-out rate; WiR, wash-in rate; ADC, apparent diffusion coefficient.

There was no significant difference in the mean WoR, WiR, TTP, and PE values between low- and high-grade NMIBC for both readers ($P > 0.05$). The ADCt, ADCw, ADCtR, and ADCwR values of high-grade NMIBC were significantly lower than those of low-grade NMIBC for both readers ($P < 0.001$). The mean values of the ADC measurements and semi-quantative DCE parameters for both readers are shown in Table 1.

Moreover, there was no significant difference in the mean values of WoR, WiR, TTP, and PE between Ta- and T1-stages NMIBC for both readers ($P > 0.05$). The ADCt, ADCw, ADCtR, and ADCwR values of T1-stage NMIBC were significantly lower than those of Ta-stage NMIBC for both readers ($P < 0.001$). Table 2 shows the mean values of ADC measurements and semi-quantitative DCE parameters for both readers.

Receiver operating characteristic analysis of apparent diffusion coefficient measurements for the differentiation of low- and high-grade non-muscle invasive bladder cancer

ROC curve analysis showed that ADCtR had the highest area under the curve (AUC) values for both readers (0.879–0.857) (Figure 3). With cut-off values of 0.449 and 0.435, ADCtR had the best diagnostic performance for both readers, with 85.4%–83.1% accuracy, 87.5%–85.4% sensitivity, and 82.9%–80.4% specificity. Table 3 shows the diagnostic performance of ADC values and ADC ratios for each reader.

Additionally, ADCtR had valuable AUC values for both readers (0.827–0.806) for differentiating the Ta- and T1-stages (Figure 4). With cut-off values of 0.439 and 0.431, ADCtR had acceptable diagnostic performance for both readers, with 76.4%–74.1% accuracy, 82%–80% sensitivity, and 69.2%–66.7% specificity. Table 4 shows the diagnostic performance of ADC values and ADC ratios for each reader for differentiating the Ta- and T1-stages.

Inter-reader agreement was almost perfect for ADC measurements ($P < 0.001$). Inter-reader ICCs between reader 1 and reader 2 were as follows: ADCt = 0.939 [95% confidence interval (CI): 0.908–0.959]; ADCw = 0.968 (95% CI: 0.952–0.979); ADCtR = 0.958 (95% CI: 0.936–0.972); ADCwR = 0.969 (95% CI: 0.953–0.979).

Table 2. Mean values of semiquantitative dynamic contrast-enhanced parameters and apparent diffusion coefficient measurements for Ta- and T1-stage non-muscle invasive bladder cancers

	Ta NMIBC	T1 NMIBC	*P* value
ADCtR			
Reader 1	0.52 ± 0.1	0.39 ± 0.09	***P* < 0.001**
Reader 2	0.51 ± 0.1	0.40 ± 0.08	***P* < 0.001**
ADCwR			
Reader 1	0.56 ± 0.11	0.45 ± 0.08	***P* < 0.001**
Reader 2	0.55 ± 0.12	0.45 ± 0.08	P < 0.001
ADCt			
Reader 1	1.17 ± 0.24	0.93 ± 0.17	***P* < 0.001**
Reader 2	1.17 ± 0.23	0.92 ± 0.18	***P* < 0.001**
ADCw			
Reader 1	1.25 ± 0.25	1.05 ± 0.17	***P* < 0.001**
Reader 2	1.25 ± 0.24	1.06 ± 0.17	***P* < 0.001**
TTP			
Reader 1	115 ± 7	113 ± 11	*P* = 0.92
Reader 2	91 ± 5	80 ± 6	*P* = 0.15
PE			
Reader 1	3.1 ± 0.13	3.7 ± 0.23	*P* = 0.16
Reader 2	3.1 ± 0.12	3.7 ± 0.21	*P* = 0.17
WoR			
Reader 1	0.04 ± 0.01	0.07 ± 0.1	*P* = 0.35
Reader 2	0.07 ± 0.1	0.08 ± 0.2	*P* = 0.26
WiR			
Reader 1	1.43 ± 0.32	2.09 ± 0.58	*P* = 0.29
Reader 2	2.26 ± 0.42	2.93 ± 0.64	*P* = 0.38

NMIBC, non-muscle invasive bladder cancer; ADCtR, three-ROIs method ADC ratio; ADCwR, whole-ROIs method ADC ratio; ADCt, three-ROIs method ADC; ADCw, whole-ROIs method ADC; TTP, time to peak; PE, peak enhancement; WoR, wash-out rate; WiR, wash-in rate; ADC, apparent diffusion coefficient.

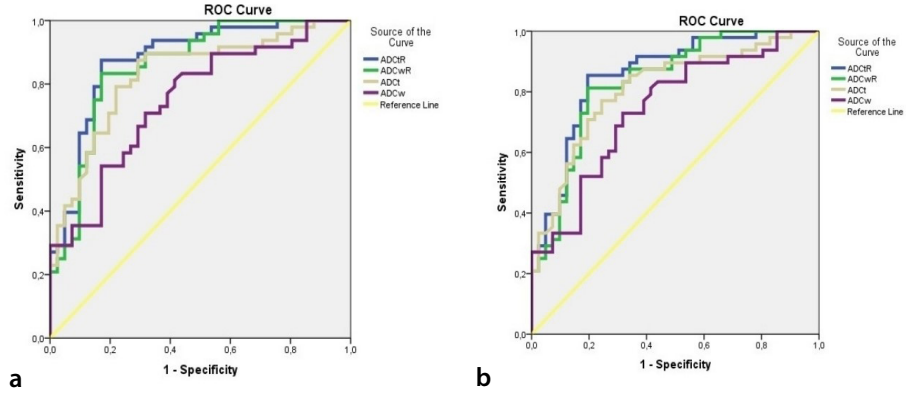

Figure 3. Receiver operating characteristic curve analysis for the differentiation of high- and low-grade non-muscle invasive bladder cancer for reader 1 **(a)** and reader 2 **(b)**. ADC, apparent diffusion coefficient; ADCtR, three-ROIs method ADC ratio; ADCwR, whole-ROIs method ADC ratio.

Discussion

Of the 89 patients with NMIBC in our study, 48 had low-grade bladder cancer. There was no significant difference in DCE semi-quantitative parameters-WoR, WiR, TTP, and PE-in the differentiation of low- and high-grade NMIBCs. Four methods-ADCt, ADCw, ADCtR, and ADCwR-were compared to distinguish between low- and high-grade NMIBC. The AUC of the ROC for the ADCtR (0.879 ± 0.074) was significantly larger ($P < 0.001$) than that of the other methods for separating low- and high-grade NMIBC. With a cut-off ADCtR value of 0.449, the sensitivity and specificity were 87.5% and 82.9% for reader 1. With a cut-off ADCtR value of 0.435, the sensitivity and specificity were 85.4% and 80.4% for reader 2. Additionally, ADCtR demonstrated the best diagnostic performance in distinguishing between Ta- and T1-stages for both readers, with respective cut-off values of 0.439 and 0.431. In our study, the majority of low-grade tumors were in the Ta-stage, whereas the majority of high-grade tumors were in the T1-stage. This might explain the similar cut-off values and statistical performance in distinguishing between Ta- and T1-stages, as seen in the discrimination between high- and low-grade cases. Thus, it is required to conduct extensive studies that have a more homogeneous distribution.

DWI, in combination with ADC measurement, provides valuable information for quantifying structural tissue changes at a cellular level and aiding in tissue characterization.[16,17] Low ADC values signify high cellularity, whereas high ADC values signify low cellularity.[16] The intralesional voxels with the lowest ADC values are likely to represent the most aggressive tumors, as they include the highest levels of cellularity.[18,19] ADC values can be used in multiple myeloma, lymphoma, breast, lung, and testis malignancies and the treatment response of malignancies.[20] In previous studies, reference ADC has been useful in brain, liver, pancreas, prostate, and bone lesions, as well as lymph node evaluation.[21,22] In bladder cancers, ADC values for high- and low-grade tumors were highly variable among the four studies using 1.5T scanners.[23-25] Due to variable ADC values, Wang et al.[13] studied three reference ADC values and obtained the highest accuracy within the bladder lumen. To reduce variability, we also used the bladder lumen as the reference ADC in this study.

Table 3. Diagnostic performance of apparent diffusion coefficient values and ratios for each reader in differentiating patients with low- and high-grade non-muscle invasive bladder cancer

	Reader 1	Reader 2
ADCtR		
Cut-off	0.449	0.435
AUC	0.879 (0.805–0.952)	0.857 (0.778–0.936)
P	<0.001	<0.001
Sensitivity (95% CI)	87.5 (74.7–95.2)	85.4 (72.2–93.9)
Specificity (95% CI)	82.9 (67.9–92.8)	80.4 (65.1–91.1)
PPV (95% CI)	85.7 (75.1–92.2)	83.6 (73.1–90.6)
NPV (95% CI)	85 (72.5–92.3)	82.5 (70.1–90.4)
Accuracy (95% CI)	85.4 (76.3–92)	83.1 (73.7–90.2)
ADCwR		
Cut-off	0.494	0.490
AUC	0.857 (0.776–0.937)	0.833 (0.747–0.918)
P	<0.001	<0.001
Sensitivity (95% CI)	83.3 (69.7–92.5)	81.2 (67.3–91)
Specificity (95% CI)	82.9 (67.9–92.8)	80.4 (65.13–91.1)
PPV (95% CI)	85.1 (74.2–91.9)	82.9 (72–90.2)
NPV (95% CI)	80.9 (68.9–89)	78.5 (66.6–87)
Accuracy (95% CI)	83.1 (73.7–90.2)	80.9 (71.1–88.4)
ADCt		
Cut-off	1.030	0.998
AUC	0.829 (0.743–0.915)	0.811 (0.721–0.901)
P	<0.001	<0.001
Sensitivity (95% CI)	79.1 (65–89.5)	77 (62.6–87.9)
Specificity (95% CI)	78 (62.3–89.4)	75.6 (59.7–87.64)
PPV (95% CI)	80.8 (69.9–88.4)	78.7 (67.8–86.6)
NPV (95% CI)	76.1 (64.3–85)	73.8 (61.9–82.9)
Accuracy (95% CI)	78.6 (68.6–86.6)	76.4 (66.2–84.7)
ADCw		
Cut-off	1.101	1.093
AUC	0.748 (0.648–0.849)	0.745 (0.643–0.847)
P	<0.001	<0.001
Sensitivity (95% CI)	70.8 (55.9–83)	72.9 (58.1–84.7)
Specificity (95% CI)	68.2 (51.9–81.9)	68.2 (51.9–81.9)
PPV (95% CI)	72.3 (61.7–80.9)	72.9 (62.4–81.3)
NPV (95% CI)	66.6 (55.1–76.5)	68.2 (56.4–78.1)
Accuracy (95% CI)	69.6 (59–78.9)	70.7 (60.1–79.9)

ADCtR, three-ROIs method ADC ratio; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; ADCt, three-ROIs method ADC; ADCw, whole-ROIs method ADC; ADCwR, whole-ROIs method ADC ratio; ADC, apparent diffusion coefficient.

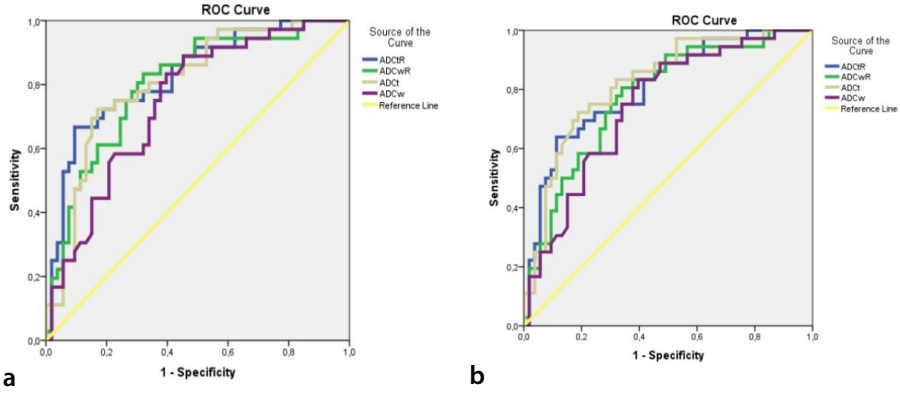

Figure 4. Receiver operating characteristic curve analysis for the differentiation of pTa- and pT1-stage non-muscle invasive bladder cancer for reader 1 **(a)** and reader 2 **(b)**. ADC, apparent diffusion coefficient; ADCtR, three-ROIs method ADC ratio; ADCwR, whole-ROIs method ADC ratio.

In our study, as each method was evaluated separately to differentiate between low- and high-grade NMIBC, the ADCtR with 87.5% sensitivity and 82.9% specificity was the best method. In comparing the diagnostic performance of ADC values for the differentiation of low- and high-grade bladder cancer in the literature, Wang et al.[12] reported higher sensitivity and specificity values (100% and 95%), with a cut-off of 0.899 mm^2/s. The lower specificity and sensitivity in our study can be related to the differences in the research population. The study conducted by Wang et al.[12] included both T1 and T2 bladder cancers. However, we specifically focused on bladder tumors that were non-muscle invasive and utilized a larger sample of patients.

Li et al.[14] reported interobserver agreement for three different methods of measuring ADC values in bladder cancer: single section ROI, three ROI, and whole volume ROI. The average ADC value did not vary significantly in terms of inter-observer consistency across any of the ROI positioning methods in the assessment of tumor grade.[14] Our results were similar to those of Li et al.[14] in that there was excellent consistency between readers with varying levels of experience across all four methods. The agreement between different readers may be attributed to the decreased fibrosis and necrosis in bladder cancer, which suggests that the degree of diffusion is almost homogeneous in bladder cancer.[14] This nature of bladder tumors also aids in the high diagnostic performance of the ADC value in low- and high-grade differentiation for all readers, regardless of experience.

In our study, we found that DCE semi-quantitative parameters-WiR, TTP, and PE-were not efficient in differentiating low- and high-grade NMIBCs. Zhou et al.[11] classified bladder tumors into three groups based on their pathological phenotype: low aggressiveness, intermediate aggressiveness, and high aggressiveness, and they examined the effectiveness of semiquantitative parameters derived from DCE imaging in distinguishing between each of these groups. In contrast to our study, Zhou et al.[11] obtained a high diagnostic performance in determining the aggressiveness of bladder cancer with a WoR. The difference in our results could be due to our exclusive focus on patients with non-muscle-invasive bladder cancer patients.

Our study has some limitations. First, we did not include lesions smaller than 1 cm.

Table 4. Diagnostic performance of apparent diffusion coefficient values and ratios for each reader in differentiating Ta- and T1-stages in patients with low- and high-grade non-muscle invasive bladder cancer

	Reader 1	Reader 2
ADCtR		
Cut-off	0.439	0.431
AUC	0.827 (0.739–0.914)	0.806 (0.714–0.897)
P	<0.001	<0.001
Sensitivity (95% CI)	82 (68.5–91.4)	80 (66.3–90)
Specificity (95% CI)	69.2 (52.4–83)	66.7 (49.8–81)
PPV (95% CI)	77.3 (67.7–84.8)	75.4 (65.9–83.1)
NPV (95% CI)	75 (61.6–84.9)	72.2 (58.9–82.5)
Accuracy (95% CI)	76.4 (66.2–84.8)	74.16 (63.8–82.9)
ADCwR		
Cut-off	0.486	0.494
AUC	0.800 (0.707–0.894)	0.776 (0.678–0.873)
P	<0.001	<0.001
Sensitivity (95% CI)	81.3 (67.4–91.1)	79.2 (46.9–77.9)
Specificity (95% CI)	65.9 (49.4–79.9)	63.4 (46.9–77.9)
PPV (95% CI)	73.6 (64.1–81.3)	71.7 (62.3–79.5)
NPV (95% CI)	75 (61.5–84.9)	72.2 (58.8–82.5)
Accuracy (95% CI)	74.2 (63.8–82.9)	71.9 (61.4–80.9)
ADCt		
Cut-off	1.030	0.993
AUC	0.806 (0.715–0.898)	0.822 (0.734–0.910)
P	<0.001	<0.001
Sensitivity (95% CI)	77.3 (63.8–87.7)	81.1 (68–90.5)
Specificity (95% CI)	75 (57.8–87.9)	72.2 (54.8–85.8)
PPV (95% CI)	82 (71.8–89.1)	81.1 (71.4–88)
NPV (95% CI)	69.2 (56.9–79)	72.2 (58.9–82.4)
Accuracy (95% CI)	76.4 (66.2–84.7)	77.5 (67.4–85.7)
ADCw		
Cut-off	1.136	1.115
AUC	0.745 (0.644–0.847)	0.755 (0.653–0.856)
P	<0.001	<0.001
Sensitivity (95% CI)	77.2 (62.2–88.5)	76.6 (62–87.7)
Specificity (95% CI)	57.8 (42.2–72.3)	59.5 (43.2–74.4)
PPV (95% CI)	64.2 (55.1–72.3)	67.9 (58.7–75.9)
NPV (95% CI)	72.2 (58.8–82.6)	69.4 (56.1–80.1)
Accuracy (95% CI)	67.4 (56.7–77)	68.5 (57.8–78)

ADCtR, three-ROIs method ADC ratio; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; ADCt, three-ROIs method ADC; ADCw, whole-ROIs method ADC; ADCwR, whole-ROIs method ADC ratio; ADC, apparent diffusion coefficient.

However, this was effective in preventing the partial volume effect. Second, ADC measurements are prone to errors. However, we aimed to minimize this potential by utilizing four different methods and two different readers. Third, this study was a single-institution retrospective study, but it had the largest sample reported in the literature. Larger multicenter studies are required to validate our findings. Finally, the ADC maps were obtained using a monoexponential algorithm; using a multiple exponential fit with additional *b*-values could potentially enhance accuracy and be a more favorable approach.

In conclusion, while DCE semiquantative parameters did not yield significant outcomes in distinguishing between low- and high-grade tumors, ADCtR holds promise for enhancing patient management in NMIBC cases and stands as a potential preoperative radiological asset for NMIBC. The results of our study demonstrated consistency even between readers with different experience levels.

Footnotes

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Eryuruk U, Tasdemir MN, Aslan S. Comparison of the diagnostic performance of biparametric and multiparametric MRI in detecting muscle invasion of bladder cancer located at the ureteral orifice. *Abdom Radiol (NY)*. 2023;48(10):3174-3182. [CrossRef]
2. Josephson D, Pasin E, Stein JP. Superficial bladder cancer: part 2. management. *Expert Rev Anticancer Ther*. 2007;7(4):567-581. [CrossRef]
3. Fujimura M, Sakamoto S, Sekita N, et al. Apparent diffusion coefficient value for estimating clinicohistological factors in bladder cancer including infiltration style and lymphatic invasion. *Springerplus*. 2016;5(1):848. [CrossRef]
4. Soukup V, Čapoun O, Cohen D, et al. Prognostic performance and reproducibility of the 1973 and 2004/2016 World Health Organization Grading Classification Systems in non-muscle-invasive bladder cancer: A European Association of Urology Non-muscle Invasive Bladder Cancer Guidelines Panel Systematic Review. *Eur Urol*. 2017;72(5):801-813. [CrossRef]
5. Akcay A, Yagci AB, Celen S, Ozlulerden Y, Turk NS, Ufuk F. VI-RADS score and tumor contact length in MRI: a potential method for the detection of muscle invasion in bladder cancer. *Clin Imaging*. 2021;77:25-36. [CrossRef]
6. Delli Pizzi A, Mastrodicasa D, Marchioni M, et al. Bladder cancer: do we need contrast injection for MRI assessment of muscle invasion? A prospective multi-reader VI-RADS approach. *Eur Radiol*. 2021;31(6):3874-3883. [CrossRef]
7. Panebianco V, Pecoraro M, Del Giudice F, et al. VI-RADS for bladder cancer: current applications and future developments. *J Magn Reson Imaging*. 2022;55(1):23-36. [CrossRef]
8. American Cancer Society. Cancer treating bladder cancer. Accessed 19 December 2022. [CrossRef]

9. Stöckle M, Alken P, Engelmann U, Jacobi GH, Riedmiller H, Hohenfellner R. Radical cystectomy--often too late? *Eur Urol*. 1987;13(6):361-367. [CrossRef]
10. Jakse G, Loidl W, Seeber G, Hofstädter F. Stage T1, grade 3 transitional cell carcinoma of the bladder: an unfavorable tumor? *J Urol*. 1987;137(1):39-43. [CrossRef]
11. Zhou G, Chen X, Zhang J, Zhu J, Zong G, Wang Z. Contrast-enhanced dynamic and diffusion-weighted MR imaging at 3.0T to assess aggressiveness of bladder cancer. *Eur J Radiol*. 2014;83(11):2013-2018. [CrossRef]
12. Wang HJ, Pui MH, Guo Y, et al. Multiparametric 3-T MRI for differentiating low-versus high-grade and category T1 versus T2 bladder urothelial carcinoma. *AJR Am J Roentgenol*. 2015;204(2):330-334. [CrossRef]
13. Wang HJ, Pui MH, Guo Y, et al. Value of normalized apparent diffusion coefficient for estimating histological grade of vesical urothelial carcinoma. *Clin Radiol*. 2014;69(7):727-731. [CrossRef]
14. Li H, Liu L, Ding L, Zhang Z, Zhang M. Quantitative assessment of bladder cancer reflects grade and recurrence: comparing of three methods of positioning region of interest for adc measurements at diffusion-weighted MR imaging. *Acad Radiol*. 2019;26(9):1148-1153. [CrossRef]
15. Tsili AC, Sylakos A, Ntorkou A, et al. Apparent diffusion coefficient values and dynamic contrast enhancement patterns in differentiating seminomas from nonseminomatous testicular neoplasms. *Eur J Radiol*. 2015;84(7):1219-1226. [CrossRef]
16. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. *AJR Am J Roentgenol*. 2007;188(6):1622-1635. [CrossRef]
17. Tsili AC, Argyropoulou MI, Giannakis D, Tsampalas S, Sofikitis N, Tsampoulas K. Diffusion-weighted MR imaging of normal and abnormal scrotum: preliminary results. *Asian J Androl*. 2012;14(4):649-654. [CrossRef]
18. Le Bihan D. Apparent diffusion coefficient and beyond: what diffusion MR imaging can tell us about tissue structure. *Radiology*. 2013;268(2):318-322. [CrossRef]
19. Schnapauff D, Zeile M, Niederhagen MB, et al. Diffusion-weighted echo-planar magnetic resonance imaging for the assessment of tumor cellularity in patients with soft-tissue sarcomas. *J Magn Reson Imaging*. 2009;29(6):1355-1359. [CrossRef]
20. Donners R, Blackledge M, Tunariu N, Messiou C, Merkle EM, Koh DM. Quantitative whole-body diffusion-weighted MR imaging. *Magn Reson Imaging Clin N Am*. 2018;26(4):479-494. [CrossRef]
21. Oh J, Henry RG, Pirzkall A, et al. Survival analysis in patients with glioblastoma multiforme: predictive value of choline-to-N-acetylaspartate index, apparent diffusion coefficient, and relative cerebral blood volume. *J Magn Reson Imaging*. 2004;19(5):546-554. [CrossRef]
22. Park SO, Kim JK, Kim KA, et al Relative apparent diffusion coefficient: determination of reference site and validation of benefit for detecting metastatic lymph nodes in uterine cervical cancer. *J Magn Reson Imaging*. 2009;29(2):383-390. [CrossRef]
23. Kobayashi S, Koga F, Yoshida S, et al. Diagnostic performance of diffusion-weighted magnetic resonance imaging in bladder cancer: potential utility of apparent diffusion coefficient values as a biomarker to predict clinical aggressiveness. *Eur Radiol*. 2011;21(10):2178-2186. [CrossRef]
24. Kobayashi S, Koga F, Kajino K, et al. Apparent diffusion coefficient value reflects invasive and proliferative potential of bladder cancer. *J Magn Reason Imaging*. 2014;39(1):172-178. [CrossRef]
25. Avcu S, Koseoglu MN, Ceylan K, Bulut MD, Unal O. The value of diffusion-weighted MRI in the diagnosis of malignant and benign urinary bladder lesions. *Br J Radiol*. 2011;84(1006):875-882. Erratum in: *Br J Radiol*. 2011;84(1007):1059. [CrossRef]