BMC Medical Imaging

RESEARCH

Open Access

Diffusion-weighted MRI-Derived ADC and tumor volume as predictive imaging markers for neoadjuvant chemotherapy response in muscle-invasive bladder cancer

Abolfazl Razzaghdoust[1†], Anya Jafari[2†], Arash Mahdavi[3], Bahram Mofid[2*] and Abbas Basiri[4*]

Abstract

Background This prospective study tested the hypothesis that the apparent diffusion coefficient (ADC) value and tumor volume (TV) measured in diffusion-weighted magnetic resonance imaging (DW-MRI) before, during, and after the treatment are quantitative imaging markers to assess tumor response in muscle-invasive bladder cancer (MIBC) patients undergoing neoadjuvant chemotherapy (NAC).

Methods Multi-parametric MRI was prospectively done for MIBC patients at 3 time points. Pre-treatment ADC value, pre-treatment TV, as well as, percent of changes (ΔADC%, and ΔTV%) in these parameters at mid- and post-treatment relative to baseline were calculated and compared between the patients with and without clinical complete response (CR). Also, further analysis was carried out based on the groups of patients with and without overall response (OR). Two different methods of ADC estimation including single-slice ADC measurement ($ADC_{single\text{-}slice}$) and whole-lesion ADC measurement ($ADC_{whole\text{-}lesion}$) were used.

Results A total of 50 eligible patients were included in the analysis. Of these, 20 patients (40%) showed clinical CR to treatment, while 30 (60%) did not. Our results showed that although there was no significant difference between the two groups of patients with and without CR in terms of mid-treatment ΔADC% and mid-treatment ΔTV%, significant differences were observed in terms of the pre-treatment ADC ($p < 0.01$), pre-treatment TV ($p < 0.001$), post-treatment ΔADC% ($p < 0.05$), and post-treatment ΔTV% ($p < 0.05$). The results of the OR-based analysis were in line with the CR-based results. There was also a strong and significant correlation between $ADC_{single\text{-}slice}$ and $ADC_{whole\text{-}lesion}$ measurements ($r > 0.9$, $P < 0.001$).

Conclusion Pre-treatment ADC, pre-treatment TV, post-treatment ΔADC%, and post-treatment ΔTV% could be considered as promising quantitative imaging markers of tumor response in MIBC patients undergoing NAC.

†Abolfazl Razzaghdoust and Anya Jafari contributed equally to this work.

*Correspondence:
Bahram Mofid
mofid429@sbmu.ac.ir
Abbas Basiri
basiri@unrc.ir

Full list of author information is available at the end of the article

Moreover, mid-treatment ΔADC% and mid-treatment ΔTV% should not be used as predictors of tumor response in these patients. Further larger studies are required to confirm these results.

Keywords Diffusion-weighted magnetic resonance imaging, Apparent diffusion coefficient, Muscle-invasive bladder cancer, Neoadjuvant chemotherapy, Tumor response

Introduction

Muscle-invasive bladder cancer (MIBC) is one of the leading causes of mortality in patients with genitourinary cancer [1]. Neoadjuvant chemotherapy (NAC) is nowadays widely used for the treatment of MIBC, but only less than half of patients experience a substantial response to the NAC [2]. Thus, early assessment of the response to the NAC may allow to prevent the potential toxicity from ineffective therapy. Integrating non-invasive biomarkers into clinical practice could significantly enhance patient management in MIBC. Key advantages of these markers include avoiding unnecessary chemotherapy, making early treatment decisions, and using personalized therapy [3, 4]. This emphasizes the need for non-invasive markers for predicting and assessing tumor response.

Diffusion-weighted magnetic resonance imaging (DW-MRI) can provide functional information related to tumor characteristics and response to chemotherapy [5, 6]. There is an increasing body of evidence exploring the role of apparent diffusion coefficient (ADC) value measured in DW-MRI, as a promising imaging marker for predicting and monitoring response to chemotherapy in different tumor types [6–12], but research in bladder cancer patients treated with NAC is scarce. In a recent study by Hafeez et al. [11], the predictive role of post-treatment ADC has been shown in MIBC patients but, no mid-treatment MRI was done to evaluate the association of mid-treatment values with tumor response. In another study by Zhang et al. [12], MIBC patients who underwent MRI before and after the NAC were considered but, the mid-treatment MRI was overlooked. However, early identification of clinical response based on a mid-treatment imaging marker may help us in detecting the responders, and provide a chance to obtain alternative effective therapy for non-responders. To the best of our knowledge, there is no study on the simultaneous investigation of the pre- mid-, and post-treatment imaging markers, as potential indicators of tumor response in these patients.

Therefore, this prospective study was performed to investigate whether the ADC value measured in DW-MRI, as well as tumor volume (TV) before, during, and after the treatment are potential imaging markers to determine tumor response in MIBC patients treated with NAC.

Methods

Study design

This prospective cohort study was conducted at two tertiary hospitals in Tehran, Iran, from July 2019 to July 2021. Consecutive male and female patients with histologically confirmed MIBC (clinical stage T2-T4a) who had undergone initial transurethral resection of bladder tumor (TURBT) were assessed for eligibility. All patients were candidates for platinum-based neoadjuvant chemotherapy and had a performance status of 0–2. The study included patients with adequate baseline bone marrow and hepatic function. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.UNRC.REC1398.14). The patients provided signed informed consent before inclusion in the study.

Treatment

The patients with creatinine clearance greater than 60 ml/min were given cisplatin on days 1 and 8 every 21 days at a dose of 35 mg/m2 for 60 min. They were also given gemcitabine intravenously at a dose of 1250 mg/m2 for 30 min on days 1 and 8, every 21 days for up to four cycles. Patients with creatinine clearance less than 60 ml/min were given carboplatin (AUC=4, intravenously over 30 min) on day 1 every 21 days. In addition, they were given gemcitabine at a dose of 1000 mg/m2 for 30 min on days 1 and 8, every 21 days for up to four cycles. The carboplatin doses were adjusted for renal function using the Cockcroft-Gault formula as per label.

MRI examination

All MRI examinations were performed using a 1.5 Tesla MRI machine (Magnetum Avanto, Siemens, Erlangen, Germany) with a pelvic phased array coil. Pelvic MRI including DW imaging was performed before (pre-treatment), after two cycles (mid-treatment), and after completion of chemotherapy (post-treatment), based on the protocol proposed for multiparametric MRI (MP-MRI) for bladder cancer by Panebianco et al. [13]. Dynamic contrast-enhanced (DCE) study was only performed in the pre-treatment setting. The specifications of MP-MRI performed for the patients were as follows: axial, coronal and sagittal T2 weighted images (T2WI) (slice thickness: 4 mm; slice gap: 0.3 mm; number of excitation (NEX): 1; field of view (FOV): 23 cm; Matrix: 256*189–256; time of repetition (TR): 5000; time of echo (TE): 80), axial DWI

(slice thickness: 4 mm; slice gap: 0.3 mm; NEX: 10–15; b values: 0-800-1000; FOV: 27 cm; Matrix: 128*109; TR: 4500; TE: 88), axial pre-contrast non-fat saturated T1WI (slice thickness: 5 mm; slice gap: 1 mm; NEX: 1; FOV: 30 cm; Matrix: 256*189–256; TR: 540; TE: 20), and axial DCE fat saturated T1WI (slice thickness: 2 mm; slice gap: 0.3 mm; NEX: 1; FOV: 30 cm; Matrix: 256*214; time of TR: 3.2; TE: 1.2).

Image analysis

All the performed images were evaluated by a radiologist with 10 years of experience in body MRI who was blinded to the pathology result of the patient. For TV evaluation, ROI was drawn in each axial T2WI image from the first image with tumor appearance until the last one in each pre-, mid-, and post-treatment MRI study. For ADC extraction, the ROIs were drawn in DWI images with the highest b-value and then transferred to ADC maps in each pre-, mid-, and post-treatment MRI (Fig. 1). To ensure the measurements' accuracy and prevent the inclusion of the uninvolved bladder wall, the DWI/ADC maps and DCE (only in pre-treatment MRI) studies were reviewed in conjunction with the T2WI sequence. It is important to note that using a consistent slice thickness and slice gap for both the T2WI and DWI sequences facilitated the localization of the lesion in a similar position across all slices. Two different methods of ADC estimation including single-slice ADC measurement ($ADC_{single-slice}$) and whole-lesion ADC measurement ($ADC_{whole-lesion}$) were used. The rationale for employing two distinct methods of ADC estimation was the intratumoral heterogeneity characteristic of bladder cancer and its potential impact on treatment outcomes [14]. We utilized a single-slice ADC map for the largest segment of the lesion to identify the most aggressive part of the tumor potentially. This approach also aimed to minimize the influence of artificially high ADC values from urine in the bladder periphery, thereby ensuring a more accurate assessment of the tumor itself. For extraction of $ADC_{whole-lesion}$, the ROI was drawn from the first image with tumor appearance until the last one, and for extraction of $ADC_{single-slice}$, the ROI was drawn at the largest cross-sectional area of the tumor. Drawing the ROI for ADC evaluation in bladder cancer is challenging due to the potential interference of high ADC values from adjacent urine, particularly in small lesions where the peripheral region is proportionally larger. Despite these challenges, considering the relatively small size of our cohort, we decided to include these smaller lesions to maintain a comprehensive analysis. To mitigate the impact of urine on the ADC measurements, we employed the single-slice ADC method, aiming to reduce distortion and enhance accuracy. OsiriX DICOM viewer 13.0.1 (Pixmeo SARL, Bernex, Switzerland) was used to draw the ROIs.

Percentage changes of ADC (ΔADC%), and TV (ΔTV%) in mid-treatment and post-treatment values were calculated as the percent change of ADC and TV relative to the baseline value for each parameter. In cases with no lesion visualization in mid-/post-treatment DW-MRI, the higher ADC value measured in our study was considered the ADC of the disappeared lesions.

Outcomes and assessment

The primary outcome of the study was to evaluate the clinical complete response (CR) to chemotherapy [15, 16]. If there was no evidence of a primary tumor (T0) on cystoscopy with tumor site biopsy, urine cytology, and cross-sectional imaging, the patient was considered to have a clinical CR. Also, clinical overall response (OR) was considered as the secondary endpoint, and defined as downstaging to non-MIBC (<T2) [11, 17]. This assessment was conducted four weeks after the completion of treatment using a cystoscopy procedure and imaging. A timeline flowchart indicating the sequence of events is shown in Fig. 2. The cystoscopy was performed by an independent urologist who was blinded to the treatment. Only eligible patients who had pre-treatment MRI, and post-treatment cystoscopy were selected to be included in an available-case analysis.

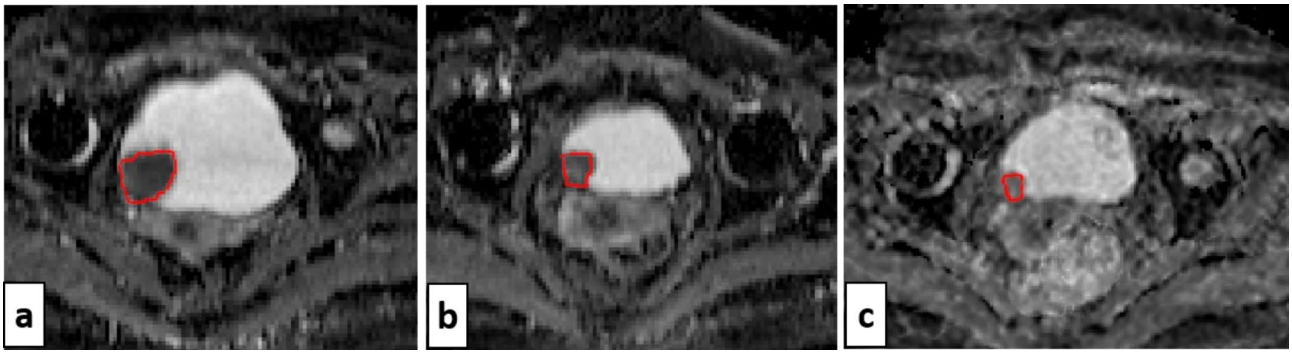

Fig. 1 Representative images indicating ROIs in ADC maps of (**a**) pre-treatment, (**b**) mid-treatment, and (**c**) post-treatment MRIs. For ADC extraction, the ROIs were drawn in DWI images with the highest b-value and then transferred to ADC maps in each pre-, mid-, and post-treatment MRI

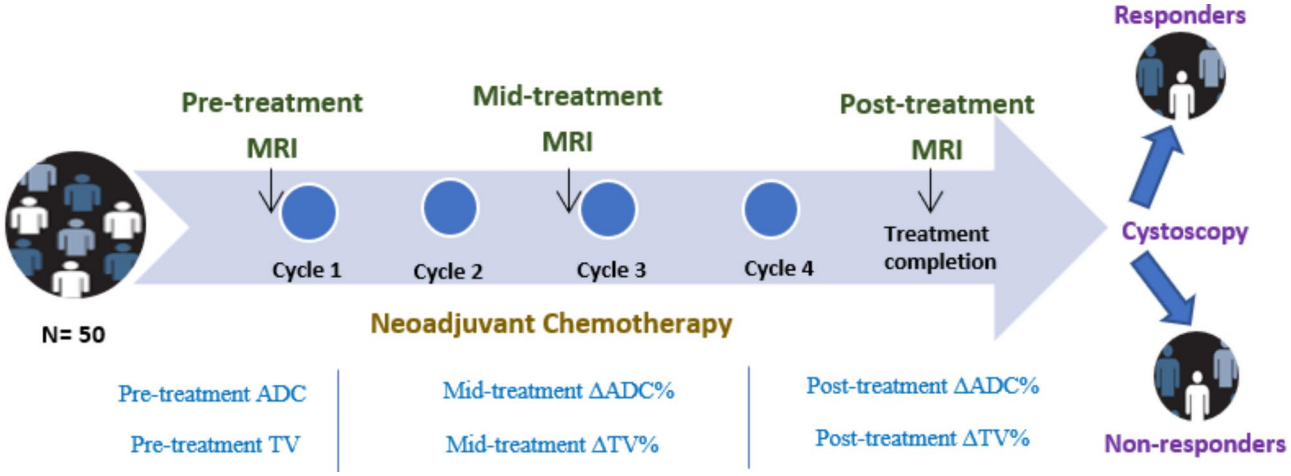

Fig. 2 Timeline flowchart indicating the sequence of events

Table 1 The association between patients' characteristics and clinical complete response

Characteristics	CR, *n* (%)	No CR, *n* (%)	*P*
Age,			0.999
≤65	8 (40)	12 (60)	
>65	12 (40)	18 (60)	
Sex,			0.999
Male	17 (39.5)	26 (60.5)	
Female	3 (42.9)	4 (57.1)	
T stage,			0.248
T2	12 (48)	13 (52)	
T3-4a	8 (32)	17 (68)	
Tumor grade,			0.377
Low	3 (60)	2 (40)	
High	17 (37.8)	28 (62.2)	
Nodal status,			**0.038**
Negative	14 (53.8)	12 (46.2)	
Positive	6 (25)	18 (75)	
Chemotherapy regimen,			0.736
Gem/Cis	5 (45.5)	6 (54.5)	
Gem/Carbo	15 (38.5)	24 (61.5)	

CR, complete response; SD, Standard Deviation; Gem, Gemcitabine; Cis, Cisplatin; Carbo, Carboplatin

Statistical analyses

The association between categorical variables was assessed by Pearson's chi-square and Fisher's exact tests. Imaging parameters were compared between responders and non-responders using the Mann-Whitney U test. Within-group changes in pre-treatment values after treatment were assessed using paired t-test. Pearson's correlation coefficient was used to evaluate the strength of the relationship between two ADC estimation methods, and also their relationship with TV and tumor characteristics. All statistical tests used in the study were two-sided, and any *p*-values that were less than or equal to 0.05 were considered to be statistically significant. The statistical analyses were conducted using IBM SPSS version 23 (IBM Corp., Armonk, NY, USA).

Results

Characteristics of patients

Between July 2019 and July 2021, 62 MIBC patients were prospectively assessed using multi-parametric MRI at 3 time points pre-, mid-, and post-NAC. From these, a total of 50 eligible patients who had pre-treatment ADC value and post-treatment cystoscopy were included in our available-case analysis. Of these, 20 patients (40%) showed clinical CR to the NAC, while 30 (60%) did not. There were also 29 (58%) patients with clinical OR and 21 (42%) without clinical OR. Patients' characteristics are indicated in Supplementary Table 1. Also, the association between patients' characteristics and clinical CR is shown in Table 1. As shown in this Table, age, sex, tumor stage, grade, and chemotherapy regimen were not associated with CR; however, the nodal status was significantly associated with CR. Among baseline variables, a significant association was found between age>65 and Gem/Carbo regimen ($P<0.001$).

Pre-treatment imaging parameters

A significant and strong correlation was found between pre-treatment $ADC_{single\text{-}slice}$ and $ADC_{whole\text{-}lesion}$ ($r=0.926$, $P<0.001$). Also, weak and negative correlations were found between pre-treatment ADC measurements with pre-treatment TV values ($r_{whole\text{-}lesion}$= -0.360, $P=0.015$; $r_{single\text{-}slice}$= -0.312, $P=0.037$). Significant but weak correlations of T stage with pre-treatment TV, $ADC_{single\text{-}slice}$, and $ADC_{whole\text{-}lesion}$ were found ($r=0.353$, $P=0.016$; $r=$ -0.321, $P=0.026$; $r=$ -0.308, $P=0.032$, respectively). Also, significant weak correlations of nodal status with pre-treatment TV, and $ADC_{single\text{-}slice}$ were observed ($r=0.390$, $P=0.007$; $r=$ -0.357, $P=0.013$, respectively).

The pre-treatment imaging parameters were compared regarding the response status (Table 2). As shown in Table 2, significant differences were observed in terms of pre-treatment $ADC_{single\text{-}slice}$, $ADC_{whole\text{-}lesion}$, and TV

Table 2 Comparison of pre-treatment imaging parameters between patients with and without clinical complete response to chemotherapy

Pre-treatment variables	Patient group		Between-group difference	*P*
	CR	**No CR**		
$ADC_{single-slice}$	1.220 (0.059)	1.024 (0.032)	0.196 (0.062)	**0.005**
$ADC_{whole-lesion}$	1.265 (0.049)	1.095 (0.031)	0.170 (0.055)	**0.007**
TV	6.18 (1.93)	25.32 (5.96)	-19.14 (6.27)	**0.001**
	OR	**No OR**		
$ADC_{single-slice}$	1.160 (0.046)	1.026 (0.041)	0.134 (0.064)	0.055
$ADC_{whole-lesion}$	1.226 (0.040)	1.075 (0.035)	0.151 (0.055)	**0.014**
TV	14.22 (5.32)	21.31 (4.69)	-7.09 (7.64)	**0.027**

CR, complete response; OR, overall response; ADC, apparent diffusion coefficient; TV, tumor volume; ADC and TV were reported as mean (SEM); ADC unit, 10^{-3} mm^2/s; TV unit, cm^3

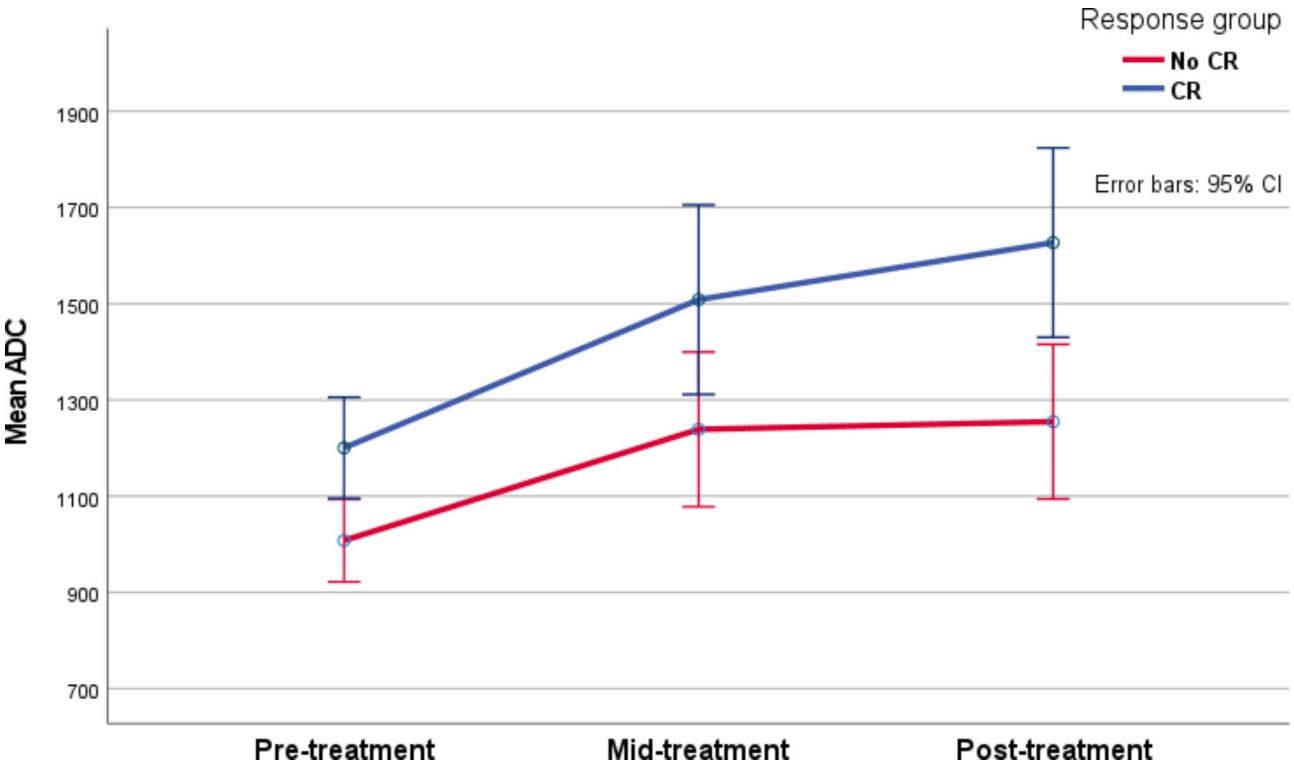

Fig. 3 Comparison of mean $ADC_{single-slice}$ between patients with and without CR at each time point. The pre-treatment ADC values significantly increased in both groups of patients with and without CR at the mid- and post-treatment MRIs (within-group changes, $P < 0.01$)

between patients with and without clinical CR to the NAC. Compared with non-responders, the mean ADC of responders was higher, and their mean TV was lower at the pre-treatment time point. Almost similar results were observed when patients were divided into clinical OR and non-OR groups. Thus, significant differences were observed regarding pre-treatment $ADC_{whole-lesion}$, and TV between patients with and without clinical OR (Table 2), although for $ADC_{single-slice}$, a trend towards significance was reported ($P=0.055$).

Mid-treatment imaging parameters

As noted for pre-treatment ADC values, a significant strong correlation was also found between mid-treatment $ADC_{single-slice}$ and $ADC_{whole-lesion}$ ($r=0.962$, $P<0.001$).

As shown in Fig. 3, the pre-treatment ADC values significantly increased in both groups of patients with and without CR at the mid- and post-treatment MRIs (within-group changes, $P<0.01$). Also, a significant decrease relative to the pre-treatment TV was observed at the mid- and post-treatment images in the two groups of patients (within-group changes, $P<0.05$).

As indicated in Table 3, there was no significant difference between patients with and without CR in terms of mid-treatment ΔADC% and ΔTV%. Similar results were

Table 3 Comparison of percent changes in mid-treatment parameters between patients with and without clinical complete response to chemotherapy

Mid-treatment Variables	Patient group		Between-group difference	*P*
	CR	**No CR**		
$\Delta ADC\%_{single-slice}$	37.33 (11.58)	22.90 (6.64)	14.43 (13.35)	0.672
$\Delta ADC\%_{whole-lesion}$	33.92 (10.86)	21.26 (5.79)	12.66 (12.31)	0.766
ΔTV%	-54.73 (15.34)	-45.60 (9.26)	-9.13 (17.00)	0.191
	OR	**No OR**		
$\Delta ADC\%_{single-slice}$	37.18 (9.26)	18.84 (7.51)	18.34 (11.92)	0.281
$\Delta ADC\%_{whole-lesion}$	34.54 (8.92)	16.99 (5.96)	17.54 (10.72)	0.299
ΔTV%	-56.67 (12.36)	-40.70 (10.71)	-15.96 (16.76)	0.100

CR, complete response; OR, overall response; ADC, apparent diffusion coefficient; TV, tumor volume; ΔADC% and ΔTV% were reported as mean % (SEM)

Table 4 Comparison of percent changes in post-treatment parameters between patients with and without clinical complete response to chemotherapy

Post-treatment Variables	Patient group		Between-group difference	*P*
	CR	**No CR**		
$\Delta ADC\%_{single-slice}$	54.84 (9.71)	23.54 (6.78)	31.30 (11.60)	**0.018**
$\Delta ADC\%_{whole-lesion}$	44.94 (10.64)	18.16 (5.90)	26.78 (12.17)	**0.042**
ΔTV%	-77.49 (9.23)	-62.69 (7.81)	-14.80 (12.27)	**0.042**
	OR	**No OR**		
$\Delta ADC\%_{single-slice}$	53.88 (7.60)	14.16 (7.05)	39.72 (10.42)	**< 0.001**
$\Delta ADC\%_{whole-lesion}$	43.41 (8.13)	9.76 (5.81)	33.64 (10.35)	**0.003**
ΔTV%	-81.27 (6.46)	-51.48 (9.92)	-29.79 (11.38)	**0.004**

CR, complete response; OR, overall response; ADC, apparent diffusion coefficient; TV, tumor volume; ΔADC% and ΔTV% were reported as mean % (SEM)

observed when patients were divided into clinical OR and non-OR groups.

Post-treatment imaging parameters

The post-treatment $ADC_{single-slice}$ and $ADC_{whole-lesion}$ were found to be strongly correlated ($r=0.977$, $P<0.001$).

Significant differences were observed in terms of the post-treatment $\Delta ADC\%_{single-slice}$, $\Delta ADC\%_{whole-lesion}$, and ΔTV% between patients with and without CR to the NAC (Table 4). In the clinical CR group, our results showed an average increase of 54.84%, and 44.94% for $\Delta ADC\%_{single-slice}$, and $\Delta ADC\%_{whole-lesion}$, respectively, but in the non-CR group, data only showed an average increase of 23.54%, and 18.16% for $\Delta ADC\%_{single-slice}$, and $\Delta ADC\%_{whole-lesion}$, respectively. Also, an average decrease of 77.49% and 62.69% was observed for ΔTV% in responders, and non-responders, respectively. Similar results were observed when patients were divided into clinical OR and non-OR groups (Table 4).

Discussion

In recent years, ADC measured in DW-MRI has gained interest as a potential imaging marker for chemotherapy response. During cancer therapy, a decrease in cellular density due to treatment-induced cell death and apoptosis can lead to an increase in ADC values [6]. This increase in ADC is associated with favorable treatment response, and changes in tumor size. Some previous studies have shown that changes in TV and ADC after the start of NAC can be indicative of the final response to treatment [5, 7, 18–20].

Our study supports findings from a recent study in MIBC patients treated with NAC, indicating a greater increase of post-treatment ADC in responders versus non-responders. In a study of 48 MIBC patients, Hafeez et al. [11] showed that NAC response (<T2) was associated with a significant increase in post-treatment ΔADC% compared to poor response (21.70% versus 8.23%, respectively; $p=0.013$). Also, similar results were indicated by the authors in 34 MIBC patients treated with chemoradiation [17]. However, no mid-treatment MRI was done in these studies to assess the association of mid-treatment values with the outcome. As an important result in our study, we observed that mid-treatment ΔADC% was not related to tumor response, probably in order to slow changes of ADC during the treatment course of these patients. Thus, the mid-treatment ΔADC could not be considered a reliable tool to assess early treatment response in MIBC patients.

It should be noted that the timing of ADC increase is substantially variable depending on the type of tumor and treatment. Some studies in breast, head and neck, cervical, and rectal cancers have indicated an increase in ADC within the initial two weeks of chemotherapy or radiotherapy [5, 19, 20]. Nevertheless, several other studies in other patients including breast, and prostate cancer patients reported an ADC increase at later time points (e.g. at 3 months or beyond) [8, 21]. In patients

with locally advanced breast cancer undergoing neoadjuvant chemotherapy, Sharma et al. [19] reported that the highest sensitivity in distinguishing between responders and non-responders was observed after the third cycle of treatment, although an increase in ADC could be observed after the first cycle. In a prospective multicenter study of 272 breast cancer patients enrolled at 10 institutions, Partridge et al. [8] indicated that ΔADC was not predictive of CR at early treatment (3 weeks), but after 12 weeks, the mean ΔADC was higher in CR patients than in non-CR patients (50% and 36%, respectively). These results are highly consistent with our study, in which a significant difference in ADC value was observed after 12 weeks of treatment initiation.

In our study, the mean pre-treatment ADC of the CR group was significantly higher than that of the non-CR group. The relationship between pre-treatment ADC values and tumor response has been studied in various contexts, but conflicting results have been reported. Although some previous studies, consistent with ours, have indicated that a higher pre-treatment ADC value may be related to better tumor response [22], several other studies showed paradoxical results [23, 24]. Moreover, in some studies conducted in breast cancer patients undergoing NAC, no statistical differences were reported in pre-treatment ADC between responders and non-responders [7, 8, 25].

In our study, no association was found between NAC response and the main characteristics of patients, including age, sex, tumor stage, grade, and chemotherapy regimen, except for nodal status. Our results are consistent with previous studies, where no association was found between age, sex, tumor stage, and chemotherapy regimen with NAC response [26–28].

Previous studies indicated the overall agreement between DWI findings and histopathological results was significantly better than that of conventional imaging methods, with a Kappa value indicating strong agreement (Kappa = 0.756). This suggests that DWI can be a reliable method for accurately staging bladder cancer [29]. High diagnostic performance of mp-MRI, including the DWI sequence, was found for detecting muscle invasion in different subtypes of urothelial carcinoma [30]. Also, previous studies stated that the shape of the tumor signal on DWI could potentially serve as an imaging biomarker to predict the clinical aggressiveness of bladder cancer [31].

Some previous studies consistent with our results indicate that lower ADC values correlate with higher tumor stages across different types of cancers [29, 32–34]. This relationship suggests that ADC derived from DWI can be an effective imaging biomarker for evaluating tumor characteristics and staging. Gupta et al. [34] in a study on patients with bladder cancer concluded that MRI is an effective tool for determining T stage. Another research showed that ADC values are negatively correlated with pathological T stages in bladder cancer [29]. As the T stage increases, ADC values tend to decrease, highlighting the potential of ADC as a biomarker for assessing tumor invasiveness. Further research with a larger number of patients is warranted to solidify these findings and explore their clinical applications in oncology.

This study has some limitations. As the main limitation, the patient population is relatively small, and further larger studies are required to confirm the findings. Also, some *P*-values in our study are close to the threshold of significance, and thus, these results should be interpreted with caution. As a technical limitation, it was difficult to delineate a region of interest on an ADC map in cases of small bladder cancer. This challenge arises particularly due to the very high ADC values in the adjacent urine within the bladder and very low ADC values in the normal bladder muscularis layer, potentially reducing the reliability of ADC values in these small bladder lesions. Moreover, due to technical factors, findings from a single study are not widely generalizable. The lack of standardization for ADC measurement technique should be considered as an inherent limitation of such studies, and thus a certain cut-off for ADC value could not be universally applied. However, previous studies showed that ADC measurements appear to be highly reproducible in different settings [5]. As a positive point, the coefficient of variance of ADC measurements in different studies was found to be about 7% [35, 36]. Moreover, the strong correlation between single-slice and whole-lesion ADC measurements in our study suggests that both methods can provide complementary information regarding tumor characteristics, and may also refer to the reliability and reproducibility of the two measurement methods. Further testing for technical validation of our results is warranted.

Finally, our primary results showed that pre-, and post-treatment DW-MRI offer insights into tumor response in MIBC patients treated with NAC. After validation in larger studies, our significant findings could improve patient management. The clinical benefits of pre-treatment markers may include preventing unnecessary chemotherapy and facilitating prompt treatment decisions. Also, post-treatment markers may predict long-term outcomes and enable personalized therapy approaches.

Conclusion

We reported a prospective study in MIBC patients undergoing NAC, indicating the promising role of pre-, mid-, and post-treatment DW-MRI in the assessment of tumor response. We concluded that pre-treatment ADC, pre-treatment TV, post-treatment ΔADC%, and post-treatment ΔTV% could be considered noninvasive imaging markers of tumor response in MIBC patients undergoing

NAC. Moreover, considering slow changes of ADC and TV over the treatment course, mid-treatment changes should not be considered predictors of tumor response in these patients. The potential utility of pre-treatment markers may include preventing unnecessary chemotherapy and facilitating prompt treatment decisions. Also, post-treatment markers may predict long-term outcomes and enable personalized therapy approaches. Further larger studies are required to confirm these results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12880-024-01547-3.

Supplementary Material 1

Acknowledgements
The authors would like to acknowledge Dr. Zahra Mahboubi for their helpful comments.

Author contributions
Conception and design: AR, BM, and AB. Acquisition of data: AR, AJ, and AM. Analysis and interpretation of data: AR, AJ, AM, AB, and BM. Writing, review, and/or revision of the manuscript: AR, AJ, AM, AB, and BM.

Funding
Not applicable.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Human ethics and consent to participate
This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.UNRC.REC1398.14). Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

Author details
[1]Urology and Nephrology Research Center, Research Institute for Urology and Nephrology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Radiation Oncology, Shohada-e Tajrish Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Radiology, University of Washington School of Medicine, Seattle, WA, USA
[4]Urology and Nephrology Research Center, Research Institute for Urology and Nephrology, Shahid Labbafinejad Hospital, Shahid Beheshti University of Medical Sciences, No.103, Shahid Jafari St., Pasdaran Ave., Tehran 1666677951, Iran

Received: 21 October 2024 / Accepted: 24 December 2024
Published online: 02 January 2025

References

1. Siegel RL, Giaquinto AN, Jemal A, Cancer statistics. 2024. 2024;74(1):12–49.
2. Schardt J, Roth B, Seiler R. Forty years of cisplatin-based chemotherapy in muscle-invasive bladder cancer: are we understanding how, who and when? World J Urol. 2019;37(9):1759–65.
3. Li H, Hu J, Zu X, Chen M, Chen J, Zou Y, et al. A novel signature to predict the neoadjuvant chemotherapy response of bladder carcinoma: results from a territory multicenter real-world study. Front Genet. 2022;13:1047481.
4. Razzaghdoust A, Ghajari M, Basiri A, Torbati PM, Jafari A, Fattahi MR, et al. Association of immunohistochemical markers of tumor subtype with response to neoadjuvant chemotherapy and survival in patients with muscle-invasive bladder cancer. Investig Clin Urol. 2021;62(3):274–81.
5. Afaq A, Andreou A, Koh DM. Diffusion-weighted magnetic resonance imaging for tumour response assessment: why, when and how? Cancer imaging: the official publication of. Int Cancer Imaging Soc. 2010;10(1a):S179–88. Spec no A(.
6. Fliedner FP, Engel TB, El-Ali HH, Hansen AE, Kjaer A. Diffusion weighted magnetic resonance imaging (DW-MRI) as a non-invasive, tissue cellularity marker to monitor cancer treatment response. BMC Cancer. 2020;20(1):134.
7. Pereira NP, Curi C, Osório CABT, Marques EF, Makdissi FB, Pinker K, et al. Diffusion-weighted magnetic resonance imaging of patients with breast Cancer following neoadjuvant chemotherapy provides early prediction of pathological response – a prospective study. Sci Rep. 2019;9(1):16372.
8. Partridge SC, Zhang Z, Newitt DC, Gibbs JE, Chenevert TL, Rosen MA, et al. Diffusion-weighted MRI findings predict pathologic response in Neoadjuvant treatment of breast Cancer: the ACRIN 6698 Multicenter Trial. Radiology. 2018;289(3):618–27.
9. Qureshi P, Aleem J, Mushtaq N, Noor MA, Khalid Niazi I, Altaf MO. Role of diffusion-weighted imaging in the evaluation of Post-treatment Tumor response in rectal carcinoma. Cureus. 2021;13(8):e17471.
10. Raafat TA, Kaddah RO, Bokhary LM, Sayed HA, Awad AS. The role of diffusion-weighted MRI in assessment of response to chemotherapy in osteosarcoma. Egypt J Radiol Nuclear Med. 2021;52(1):29.
11. Hafeez S, Koh M, Jones K, Ghzal AE, D'Arcy J, Kumar P, et al. Diffusion-weighted MRI to determine response and long-term clinical outcomes in muscle-invasive bladder cancer following neoadjuvant chemotherapy. Front Oncol. 2022;12:961393.
12. Zhang X, Wang Y, Zhang J, Xu X, Zhang L, Zhang M, et al. Muscle-invasive bladder cancer: pretreatment prediction of response to neoadjuvant chemotherapy with diffusion-weighted MR imaging. Abdom Radiol (NY). 2022;47(6):2148–57.
13. Panebianco V, Narumi Y, Altun E, Bochner BH, Efstathiou JA, Hafeez S, et al. Multiparametric magnetic resonance imaging for bladder Cancer: development of VI-RADS (Vesical Imaging-Reporting and Data System). Eur Urol. 2018;74(3):294–306.
14. Lavallee E, Sfakianos JP, Mulholland DJ. Tumor heterogeneity and consequences for bladder Cancer Treatment. Cancers. 2021;13(21).
15. Wu J, Xie RY, Cao CZ, Shang BQ, Shi HZ, Shou JZ. Disease Management of Clinical Complete responders to Neoadjuvant Chemotherapy of muscle-invasive bladder Cancer: a review of literature. Front Oncol. 2022;12:816444.
16. Lee HW, Kwon WA, Nguyen NT, Phan DTT, Seo HK. Approaches to clinical complete response after Neoadjuvant Chemotherapy in muscle-invasive bladder Cancer: possibilities and limitations. Cancers. 2023;15(4).
17. Hafeez S, Koh M, Jones K, El Ghzal A, D'Arcy J, Kumar P, et al. Assessing bladder Radiotherapy Response with quantitative diffusion-weighted magnetic resonance imaging analysis. Clin Oncol (R Coll Radiol (G B)). 2022;34(10):630–41.
18. Hottat NA, Badr DA, Lecomte S, Besse-Hammer T, Jani JC, Cannie MM. Value of diffusion-weighted MRI in predicting early response to neoadjuvant chemotherapy of breast cancer: comparison between ROI-ADC and whole-lesion-ADC measurements. Eur Radiol. 2022;32(6):4067–78.
19. Sharma U, Danishad KK, Seenu V, Jagannathan NR. Longitudinal study of the assessment by MRI and diffusion-weighted imaging of tumor response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. NMR Biomed. 2009;22(1):104–13.
20. Li XR, Cheng LQ, Liu M, Zhang YJ, Wang JD, Zhang AL et al. DW-MRI ADC values can predict treatment response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. Medical oncology (Northwood, London, England). 2012;29(2):425 – 31.
21. Takayama Y, Kishimoto R, Hanaoka S, Nonaka H, Kandatsu S, Tsuji H, et al. ADC value and diffusion tensor imaging of prostate cancer: changes in carbon-ion radiotherapy. J Magn Reson Imaging. 2008;27(6):1331–5.

22. Zhao L, Zhao M, Liu J, Yang H, Zhou X, Wen C, et al. Mean apparent diffusion coefficient in a single slice may predict tumor response to whole-brain radiation therapy in non-small-cell lung cancer patients with brain metastases. Eur Radiol. 2021;31(8):5565–75.
23. Surov A, Pech M, Meyer HJ, Bitencourt AGV, Fujimoto H, Baxter GC, et al. Evaluation of pretreatment ADC values as predictors of treatment response to neoadjuvant chemotherapy in patients with breast cancer - a multicenter study. Cancer Imaging: Official Publication Int Cancer Imaging Soc. 2022;22(1):68.
24. Zhao M, Zhao L, Yang H, Duan Y, Li G. Apparent diffusion coefficient for the prediction of tumor response to neoadjuvant chemo-radiotherapy in locally advanced rectal cancer. Radiat Oncol. 2021;16(1):17.
25. Hu XY, Li Y, Jin GQ, Lai SL, Huang XY, Su DK. Diffusion-weighted MR imaging in prediction of response to neoadjuvant chemotherapy in patients with breast cancer. Oncotarget. 2017;8(45):79642–9.
26. Pokuri VK, Syed JR, Yang Z, Field EP, Cyriac S, Pili R, et al. Predictors of complete pathologic response (pT0) to Neoadjuvant Chemotherapy in muscle-invasive bladder carcinoma. Clin Genitourin Cancer. 2016;14(1):e59–65.
27. Einerhand SMH, Black AJ, Zargar H, Fairey AS, Dinney CP, Mir MC, et al. Multicenter evaluation of neoadjuvant and induction gemcitabine-carboplatin versus gemcitabine-cisplatin followed by radical cystectomy for muscle-invasive bladder cancer. World J Urol. 2022;40(11):2707–15.
28. Sainont G, Santingamkun A, Ratchanon S, Opanurak J, Panumatrassamee K, Sowanthip DJIU. Predictors of pathologic response to neoadjuvant chemotherapy in muscle-invasive bladder cancer. 2022;43(1):64–74.
29. Abd elsalam SM, Abdelbary AM. Accuracy of diffusion-weighted magnetic resonance imaging in evaluation of muscle invasion and histologic grading of the urinary bladder carcinoma. Egypt J Radiol Nuclear Med. 2020;51(1):48.
30. Arita Y, Yoshida S, Shigeta K, Kwee TC, Edo H, Okawara N, et al. Diagnostic value of the Vesical Imaging-Reporting and Data System in bladder urothelial carcinoma with variant histology. Eur Urol Oncol. 2023;6(1):99–102.
31. Yajima S, Yoshida S, Takahara T, Arita Y, Tanaka H, Waseda Y, et al. Usefulness of the inchworm sign on DWI for predicting pT1 bladder cancer progression. Eur Radiol. 2019;29(7):3881–8.
32. Peng Y, Tang H, Hu X, Shen Y, Kamel I, Li Z, et al. Rectal Cancer invasiveness: whole-lesion diffusion-weighted imaging (DWI) Histogram Analysis by comparison of reduced field-of-view and conventional DWI techniques. Sci Rep. 2019;9(1):18760.
33. Chang CC, Lin CY, Huang LT, Chuang MT, Lu YH, Huang WL, et al. Diagnostic value of apparent diffusion coefficient in predicting pathological T stage in patients with thymic epithelial tumor. Cancer Imaging: Official Publication Int Cancer Imaging Soc. 2022;22(1):56.
34. Gupta N, Sureka B, Kumar MM, Malik A, Bhushan TB, Mohanty NK. Comparison of dynamic contrast-enhanced and diffusion weighted magnetic resonance image in staging and grading of carcinoma bladder with histopathological correlation. Urol Ann. 2015;7(2):199–204.
35. Koh DM, Blackledge M, Collins DJ, Padhani AR, Wallace T, Wilton B, et al. Reproducibility and changes in the apparent diffusion coefficients of solid tumours treated with combretastatin A4 phosphate and bevacizumab in a two-centre phase I clinical trial. Eur Radiol. 2009;19(11):2728–38.
36. Sasaki M, Yamada K, Watanabe Y, Matsui M, Ida M, Fujiwara S, et al. Variability in absolute apparent diffusion coefficient values across different platforms may be substantial: a multivendor, multi-institutional comparison study. Radiology. 2008;249(2):624–30.

Publisher's note