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MAGNETIC RESONANCE

Predictive role of diffusion-weighted MRI in the assessment of response to total neoadjuvant therapy in locally advanced rectal cancer

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Abstract

Objective To investigate the predictive role of diffusion-weighted magnetic resonance imaging (DW-MRI) in the assessment of response to total neoadjuvant therapy (TNT) in patients with locally advanced rectal cancer (LARC).

Methods In this single-center retrospective study, patients with LARC who underwent staging MRI and TNT were enrolled. MRI-based staging, tumor volume, and DWI-ADC values were analyzed. Patients were classified as complete responders (pCR) and non-complete responders (non-pCR), according to post-surgical outcome. Pre-treatment ADC values were compared to pathological outcome, post-treatment downstaging, and reduction of tumor volume. The diagnostic accuracy of DWI-ADC in differentiating between pCR and non-pCR groups was calculated with receiver operating characteristic (ROC) analysis.

Results A total of 36 patients were evaluated (pCR, $n = 20$; non-pCR, $n = 16$). Pre-treatment ADC values were significantly different between the two groups ($p = 0.034$), while no association was found between pre-TNT tumor volume and pathological response. ADC values showed significant correlations with loco-regional downstaging after therapy ($r = -0.537$, $p = 0.022$), and with the reduction of tumor volume ($r = -0.480$, $p = 0.044$). ADC values were able to differentiate pCR from non-pCR patients with a sensitivity of 75% and specificity of 70%.

Conclusions ADC values on pre-treatment MRI were strongly associated with the outcome in patients with LARC, both in terms of pathological response and in loco-regional downstaging after TNT, suggesting the use of DW-MRI as a potential predictive tool of response to therapy.

Key Points

- *ADC values of pre-TNT MRI examinations of patients with LARC were significantly associated with a pathological complete response (pCR) and with post-treatment regression of TNM staging.*
- *An ADC value of 1.042 × 10^{-3} mm^2/s was found to be the optimal cutoff value for discriminating between pCR and non-pCR patients, with a sensitivity of 75% and specificity of 70%.*
- *DW-MRI proved to have a potential predictive role in the assessment of response to therapy in patients with LARC, throughout the analysis of ADC map values.*

Keywords Rectal neoplasms · Diffusion magnetic resonance imaging · Neoadjuvant therapy

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Abbreviations

ADC	Apparent diffusion coefficient
AUC	Area under curve
ChT	Chemotherapy
CRT	Chemoradiotherapy
DWI	Diffusion-weighted imaging
ICC	Intraclass correlation coefficient
LARC	Locally advanced rectal cancer
MRI	Magnetic resonance imaging
pCR	Pathological complete response
ROC	Receiver operating characteristic
RT	Radiotherapy
TME	Total mesorectal excision
TNT	Total neoadjuvant therapy

Introduction

Rectal cancer remains one of the most frequent malignancies, with over 700,000 new diagnoses and 300,000 deaths in 2020, worldwide [1].

Standard treatment of local advanced rectal cancer (LARC) consists of a trimodal approach combining radiotherapy (RT), chemotherapy (ChT), and subsequent surgery with total mesorectal excision (TME).

Recent studies have reported promising outcomes using a total neoadjuvant treatment (TNT) which has shown to improve pathological complete response (pCR) and clinical complete response (cCR) from 14 to 36% [2]. TNT is defined as induction ChT with mFOLFOX6 (folinic acid, fluorouracil, and oxaliplatin) for 8 cycles, CAPOX (capecitabine and oxaliplatin) for 5 cycles, or FLOX (weekly fluorouracil/folinic acid and biweekly oxaliplatin) prior to chemoradiotherapy (CRT) [3]. More specifically, earlier introduction of systemic ChT within TNT has been associated with increased downstaging, lower risk of disease progression (including possible micrometastases), and identification of patients for whom surgical resection can be safely omitted [3, 4].

Magnetic resonance imaging (MRI) represents the best imaging modality for local staging and assessment of response to therapy in LARC at different times during CRT course. Particularly, diffusion-weighted imaging (DWI) explores the random Brownian motion of water molecules in intracellular and extracellular space, identifying areas with high cellularity reflecting the presence of tumor tissue [5].

The aim of our study was to perform DWI analysis in patients with LARC before TNT and to explore the potential predictive role of DWI values in differentiating pCR from non-pCR patients.

Materials and methods

This single-center analysis was approved by the local ethic committee and written informed consent was waived due to the retrospective nature of the study.

Study population

Patients affected by LARC who received TNT between March 2016 and November 2019 were retrospectively enrolled. MRI examinations were performed at three-time points (staging MRI before TNT; 2 weeks from the end of last induction ChT cycle; and 6 weeks after the end of TNT) according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [6]. During a time frame of 6 to 8 weeks after the completion of TNT, all patients underwent TME [7].

Staging MRI and post-TNT examinations were evaluated. The inclusion criteria were as follows: (i) histologically proven rectal adenocarcinoma on endoscopic biopsy; (ii) clinical MRI staged as T3–4 and/or with positive regional lymph nodes; (iii) no evidence of distant metastases. The exclusion criteria were as follows: (i) evidence of synchronous tumors; (ii) incomplete administration of TNT; (iii) history of pelvic RT; (iv) examinations performed with different MRI scanners or different MRI protocols; (v) presence of imaging artifacts.

Final population was then divided into two groups, pCR and non-pCR, based on post-surgical histological outcome (pCR was defines as ypT0N0); for group non-pCR, residual tumor volume was calculated on last MRI before surgery. A flowchart of our study population is represented in Fig. 1.

Treatment plan

All patients were treated with an intensified total neoadjuvant therapy (TNT) (ethical committee 88569-140/5638). Details of TNT protocol were previously described [8]. Induction ChT included target-based (bevacizumab in mutated Ras-BRAF or panitumumab/cetuximab in wild-type Ras-BRAF) FOLFOXIRI (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan) prior to concomitant CRT and surgical approach [6]. CRT consisted of 5-fluorouracil and oxaliplatin plus RT using intensity modulated technique (IMRT) to a total dose of 45 Gy (1.8 Gy per fraction) to the whole pelvis, plus 5.4 to 9 Gy (1.8 Gy per fraction) to the tumor volume, with 6–15 MV energy photons.

Magnetic resonance imaging protocol

All examinations were performed with a 3.0-T MR system (Discovery 750, GE Healthcare). Imaging protocol consisted of panoramic T2-weighted single-shot fast-spin echo (SSFSE) sequences followed by high-resolution T2-weighted fast

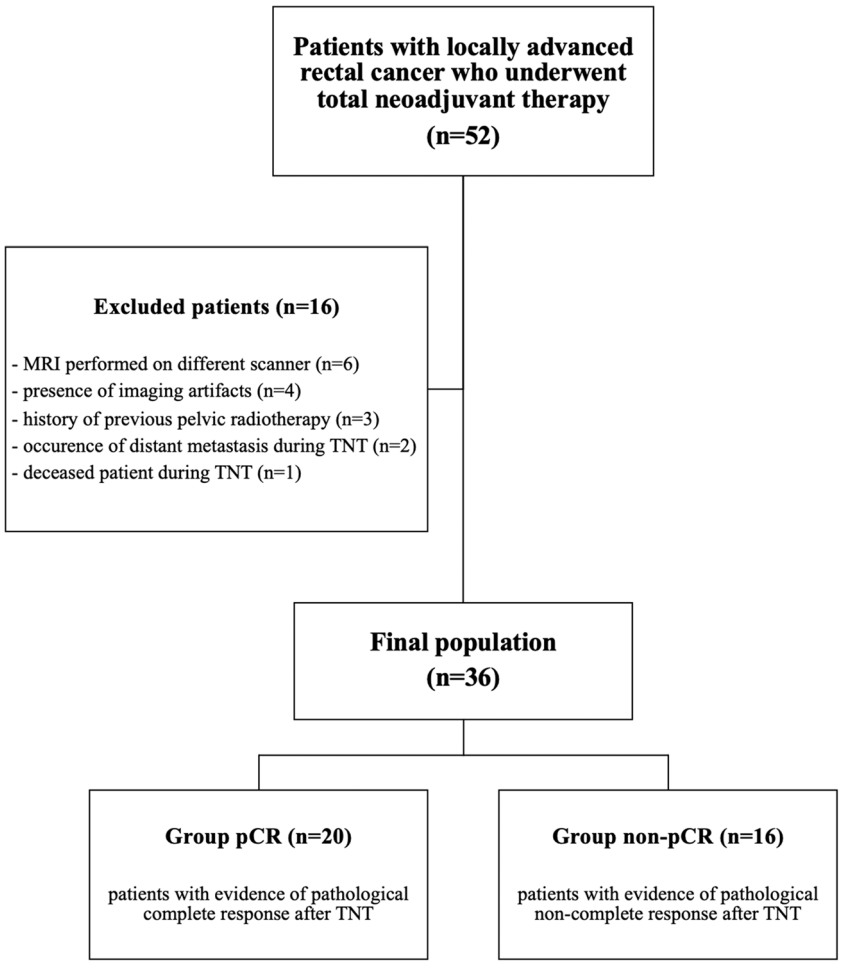

Fig. 1 Flowchart of study population

recovery fast-spin echo (FRFSE) sequences on axial oblique, coronal oblique, and sagittal planes, orthogonal and parallel to the long axis of the rectum, with the following parameters: TR: 4373–6575 ms; TE: 97–133 ms; slice thickness: 3 mm; matrix: 320 × 224. Axial DWI images were obtained using a single-shot echo-planar imaging sequence with spectral adiabatic inversion recovery fat saturation technique (TR: 4400 ms; TE: 81.4 ms; slice thickness: 4 mm; matrix: 256 × 256; *b* values: 0, 500, 1000 s/mm^2). Lastly, axial T1-weighted gradient echo sequences (TR: 5 ms; TE: 2 ms; slice thickness: 2 mm; matrix: 288 × 288) were obtained before and after intravenous administration of gadolinium-based contrast media (gadoteric acid, Claricyclic, GE Healthcare, 0.1 mmol/kg) at 2 mL/s followed by 15 mL of saline flush at the same flow rate. ADC map was automatically generated during image reconstruction (DWI: *b* values of 0 and 1000 s/mm^2).

Image analysis

All MRI examinations were evaluated by one senior radiology resident (F.C., 4th year of training) and one abdominal radiologist (F.I., 15 years of experience), both blinded to the pathological outcomes of patients. According to the AJCC (American Joint Committee on Cancer) guidelines, the depth of tumor infiltration and the involvement of regional lymph nodes were evaluated, and an MRI-based staging was provided for all patients [9].

LIFEx software (Inserm-U1288) was used both for tumor volume measurement and for ADC value extraction [10].

Volume was obtained on axial oblique T2-weighted images, manually drawing a region of interest (ROI) along the margins of the rectal primitive lesion on each contiguous slice for the whole extent of the tumor (Fig. 2a, b); lumen artifacts were carefully excluded from the ROI.

Similarly, a ROI was drawn on ADC map on each slice of the tumor, and mean ADC values were extracted for each case (Fig. 2c, d).

Statistical analysis

Data were analyzed using a statistical software (SPSS version 25.0, IBM Corp). The frequencies of demographic and clinical characteristics were expressed as the number (percentage) of occurrences and were compared using the 2-tailed χ^2 test or Fisher's exact test. Continuous variables were expressed as median value (interquartile range (IQR)). The Mann-Whitney and Levene's tests were used for comparing tumor

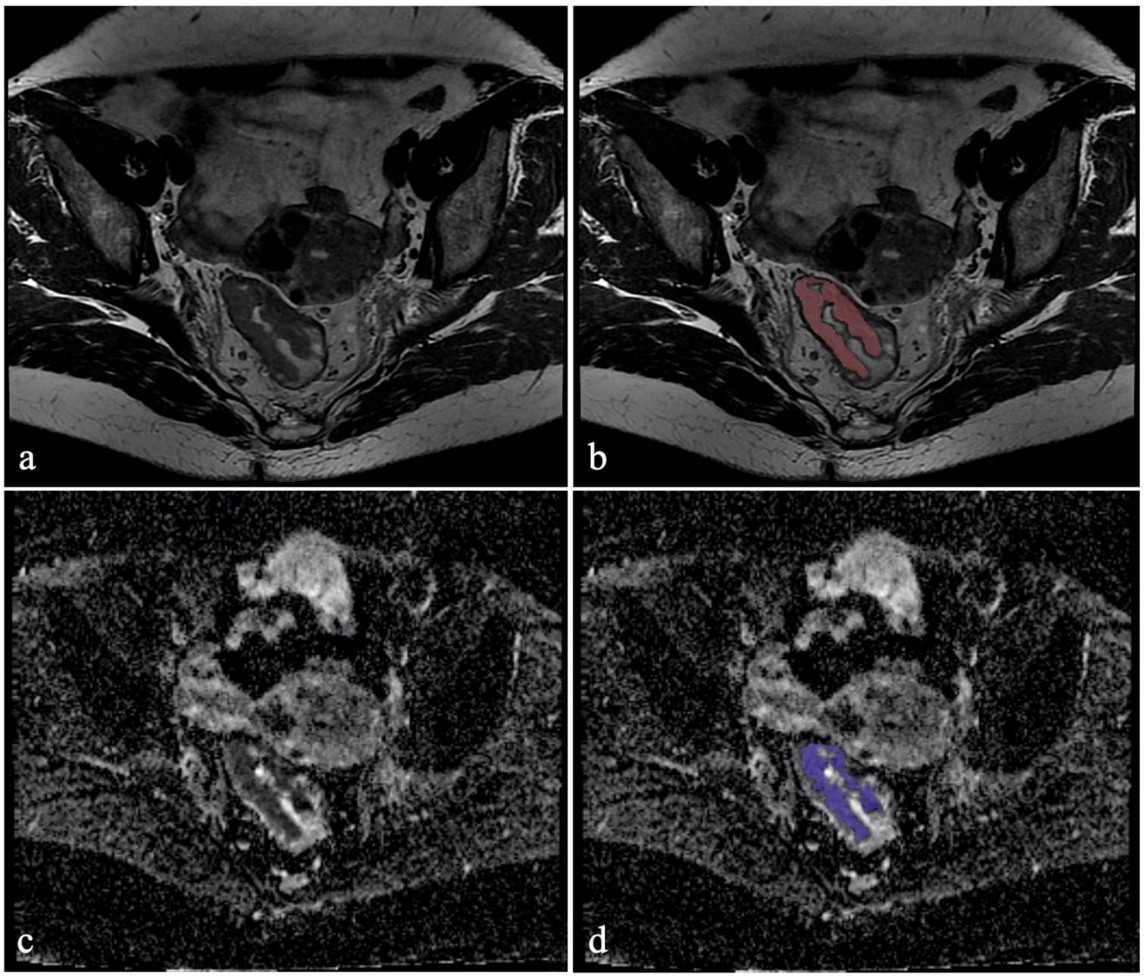

Fig. 2 Example of a T3 locally advanced rectal cancer before and after segmentation of tumor lesion on axial T2-weighted image (**a**, **b**) and ADC map (**c**, **d**)

volumes and ADC values between the two groups. Pearson correlation test was used for correlation between ADC values and percentage of reduction in tumor volume and for correlation between ADC values and stage modification.

Receiver operating characteristic (ROC) analysis was also applied to ADC values related to the pathological outcome of patients and a cutoff value was established according to Youden's *J* test. Differences for which $p < 0.05$ were considered statistically significant.

Intraclass correlation coefficients (ICCs) were used to investigate interobserver variability: ICC values < 0.40 signified poor agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; > 0.80, excellent agreement.

Results

Study population's characteristics

Out of 52 patients, 16 were excluded from the study due to staging MRI performed on different MRI systems or at other institutions ($n = 6$), previous pelvic RT for prostatic carcinoma ($n = 2$) and ovarian carcinoma ($n = 1$), occurrence of distant metastasis during TNT ($n = 2$), presence of major imaging artifacts ($n = 4$), and deceased patient during TNT ($n = 1$).

Final population consisted of 36 patients (group pCR, $n = 20$; group non-pCR, $n = 16$).

Before treatment with TNT, at MRI staging, T3 was found in 8/20 (40%) patients in group pCR, T4a in 6/20 (30%) patients, and T4b in 6/20 (30%) patients; in the non-pCR group, T3 was observed in 8/16 (50%) patients, T4a in 2/16 (12.5%) patients, and T4b in 6/16 (37.5%) patients. Concerning nodal involvement, in group pCR, 2/20 (10%) patients were classified as N1a, 2/20 (10%) as N2a, and 16/20 (80%) as N2b; in group non-pCR, 2/16 (12.5%) patients were staged as N1a, 2/16 (12.5%) as N1b, 2/16 (12.5%) as N2a, and 10/16 (62.5%) as N2b. According to AJCC, pre-treatment MRI-based TNM stage was IIIC for all patients in group pCR ($n = 20$, 100%) and for the majority of patients in group non-pCR ($n = 14$, 87.5%); the remaining 2 patients were staged as IIIB. Demographic characteristics and staging of our study population are provided in Table 1.

Table 1 Characteristics of the study population

Characteristic	Group pCR (n = 20)	Group non-pCR (n = 16)	p value
Gender			0.741
Male	11 (55%)	10 (62.5%)	
Female	9 (45%)	6 (37.5%)	
Age*	66 [44, 71]	63 [58, 66]	> 0.999
T stage			0.737
T3	8 (40%)	8 (50%)	
T4	12 (60%)	8 (50%)	
N stage			0.374
N1	2 (10%)	4 (25%)	
N2	18 (90%)	12 (75%)	
TNM stage			0.191
IIIB	0 (0%)	2 (12.5%)	
IIIC	20 (100%)	14 (87.5%)	

Except where indicated, data are expressed as number of patients (percentage). *Data are expressed as median value (interquartile range (IQR)). *pCR*, pathological complete response

While in pCR patients there was no evidence of residual tumor or involvement of regional lymph nodes after treatment, in the non-pCR group ypT1 stage was observed in 2/16 (12.5%) patients, ypT2 in 10/16 (62.5%) patients, and ypT3 in 4/16 (25%) patients; among the same group, ypN0 stage was found in 14/16 (87.5%) patients and ypN1c in 2/16 (12.5%) patients. Overall stage in the non-pCR group after treatment was I in 12/16 (75%) patients, IIA in 2/16 (12.5%) patients, and IIIB in 2/16 (12.5%) patients.

Tumor volume and DWI/ADC image analysis

Tumor volume calculated on pre-TNT T2-weighted images showed no significant difference between group pCR and non-pCR, with a median value of 21.3 cm^3 [15.6, 23.6] and 24 cm^3 [19.8, 42.2] (p = 0.315), respectively.

While in group pCR there was a complete reduction of tumor volume after treatment with TNT, in group non-pCR a median reduction of 83.8% [76.5, 91.2] was observed.

In DWI analysis, ADC values were significantly lower in group pCR compared to those in group non-pCR, with a median value of 0.94 [0.86, 1.07] $\times 10^{-3}$ mm^2/s and 1.12 [1.03, 1.21] $\times 10^{-3}$ mm^2/s, respectively (p = 0.034) (Figs. 3 and 4).

Pre-treatment ADC values negatively correlated with the reduction of tumor volume (r = −0.480, p = 0.044), downstaging of T factor (r = −0.481, p = 0.043), and post-TNT overall staging (r = −0.537, p = 0.022), while no significant correlation was observed between ADC values and post-treatment N stage modification (r = −0.024, p = 0.925).

In ROC curve analysis, when an ADC value of 1.042 $\times 10^{-3}$ mm^2/s was used as the cutoff value for discriminating between the pCR and non-pCR groups, an area under curve (AUC) of 0.797 was obtained with a sensitivity of 75%, specificity of 70%, PPV of 66.7%, and NPV of 77.8% (95% CI: 0.653, 0.940) (p = 0.002) (Fig. 5; Table 2).

The interobserver variability analysis between the two readers showed an excellent agreement both for ADC values and for tumor volume calculation (Table 3).

Discussion

Several research studies have recently highlighted how the multimodal approach with TNT has been associated with higher pCR rates, disease-free survival (DFS), overall survival (OS), and no significant increase in adverse events compared to standard neoadjuvant therapy in patients with LARC [11–13].

MRI is widely considered the best imaging modality for in vivo loco-regional assessment in patients with rectal cancer both for clinical staging and for the evaluation of treatment response during follow-up. The addition of diffusion-weighted sequences to conventional MRI has shown to

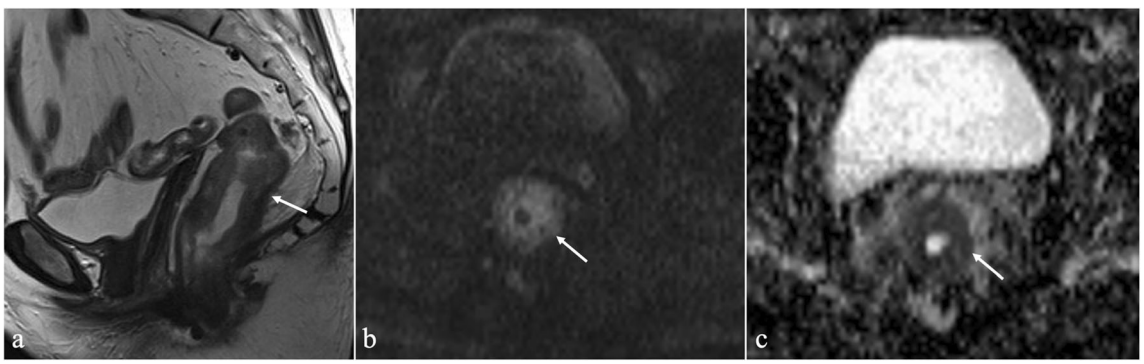

Fig. 3 Case of a cT3 cN2b rectal cancer on T2-weighted image on sagittal plane (**a**), DWI at b = 1000 s/mm^2 (**b**), and ADC map (**c**). In this case, pre-TNT ADC median value was 1087 mm^2/s. Pathological outcome was pT0 pN0 (pCR)

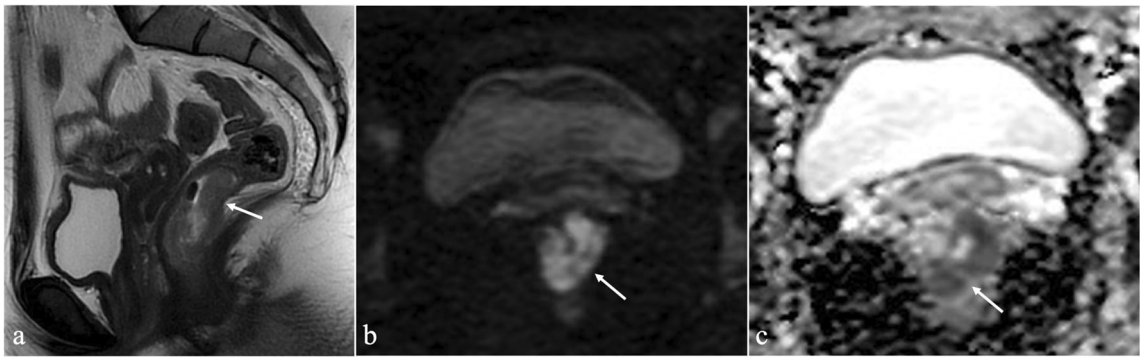

Fig. 4 Case of a cT3 cN2b rectal cancer on T2-weighted image on sagittal plane (**a**), DWI at b = 1000 s/mm^2 (**b**), and ADC map (**c**). In this case, pre-TNT ADC median value was 1224 mm^2/s. Pathological outcome was pT3 pN1c (non-pCR)

improve diagnostic accuracy in the evaluation of response to CRT in these patients [14–16].

In this study, we performed DWI analysis using ADC map values of the primitive lesion in a cohort of 36 patients affected by LARC (20 patients with pCR and 16 without pCR) to investigate a possible association between ADC values and post-treatment outcomes.

As a main result, lower ADC values of pre-TNT examinations were significantly associated with a complete pathological response (p = 0.034), suggesting a potential role of DW-MRI in the prediction of tumor response to TNT. These results are consistent with those reported in similar clinical studies, which analyzed pre-treatment ADC values of rectal tumor, and found a significant association between lower ADC values and good responders [15, 17–19]. Considering that signal intensity in diffusion-weighted sequences is directly related to tissue cellularity, we can presume that low values in the corresponding ADC map are characteristic of tissues with high proliferation indices, as also observed in recent studies, in which both intravoxel incoherent motion DWI and apparent diffusion coefficient (ADC) were analyzed [20, 21]. Moreover, phenotypes with accelerated cell cycle are more likely to respond to anti-cancer agents [22] and we can therefore assume that low ADC values of the primitive lesion may represent a more susceptible target of chemoradiation, resulting in a better response after TNT compared to tumors with higher ADC values.

The role of DWI and ADC maps in the assessment of loco-regional response of LARC to chemoradiation therapy has been widely validated in previous research studies. Lambregts et al reported increased diagnostic accuracy in detecting local recurrence using both T2-weighted images and DWI, also with a reduction of equivocal findings, while Sassen et al demonstrated the added value of DWI compared to T2-weighted images for identifying complete responders and the improvement of diagnostic accuracy among readers with different levels of experience [23–25]. Other authors have also investigated the role of DWI on post-CRT restaging

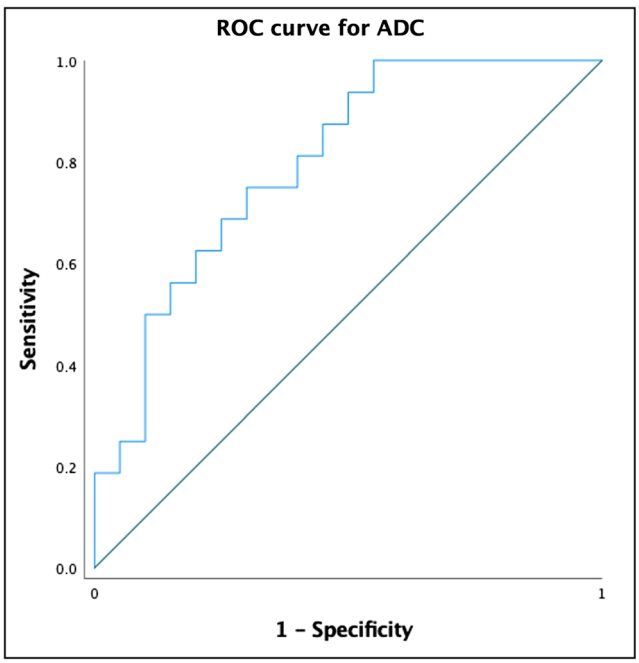

Fig. 5 ROC curve for an optimal cutoff of and ADC values to discriminate the pCR group from the non-pCR group

Table 2 Diagnostic predictive ADC values for assessment of response to total neoadjuvant therapy

Statistic parameter	ADC
AUC	0.797
Sensitivity (%)	75
Specificity (%)	70
PPV (%)	66.7
NPV (%)	77.8
95% CI	0.653, 0.940
p value	0.002

ADC, apparent diffusion coefficient; *AUC*, area under curve; *PPV*, positive predictive value; *NPV*, negative predictive value; *CI*, confidence interval

Table 3 Median values of pre-TNT ADC and tumor volume in patients with local advanced rectal cancer with the respective interobserver variabilities

MRI feature	Group pCR (n = 20)	Group non-pCR (n = 16)	p value	ICC*
ADC (mm^2/s)	0.94 [0.86, 1.07] $\times 10^{-3}$	1.12 [1.03, 1.21] $\times 10^{-3}$	0.034	0.857 [0.583, 0.881]
Volume (cm^3)	21.3 [15.6, 23.6]	24 [19.8, 42.2]	0.315	0.879 [0.562, 0.896]

Except where indicated, data are expressed as median value (interquartile range (IQR)). *Data are expressed as median value (95% confidence interval (CI)). *ADC*, apparent diffusion coefficient; *pCR*, pathological complete response; *ICC*, intraclass correlation coefficient

MRI in patients with LARC, demonstrating an increase in sensitivity from 80 to 100% and in specificity from 50 to 67% [26]. In a recent study, intra-tumor heterogeneity analysis was performed on histograms of ADC values observing that the ADC 75th and 90th percentiles after CRT were higher in the responder group than the non-responder group, suggesting a potential selection of responders for a more conservative approach [27].

In our study, pre-treatment ADC values were significantly associated with post-treatment regression of T stage (r = −0.481, p = 0.043) and overall staging (r = −0.537, p = 0.022), supporting the pivotal role of DWI/ADC in the assessment of potential response to therapy. This result further strengthens the association between rectal tumors with lower ADC values and good response to treatment, whose main reason could also be explained by a lesser amount of necrosis within these tumors, as hypothesized both by Dzik-Jurasz et al and Amodeo et al [15, 19].

On the other hand, no correlation was found between the regression of N stage after TNT and ADC values (r = −0.024, p = 0.925): this can be explained by the fact that some patients with ypT0 still present nodal disease as reported both by Baucom et al and Newton et al, who highlighted several risk factors for the persistence of nodal involvement, such as lymphovascular invasion, poor histology, and elevated carcinoembryonic antigen (CEA) [28, 29].

Pre-TNT ADC values negatively correlated with tumor volume regression (r = −0.480, p = 0.044), whose median value was 83.8% [76.5, 91.2] for group non-pCR and, obviously, 100% for group pCR, meaning that higher restriction values are associated with a greater reduction of tumor volume.

No association was found between tumor volume calculated on pre-treatment T2-weighted images and pathological response, meaning that the efficacy of TNT is not as much influenced by the extent of the primitive lesion as by its cellularity: this result further strengthens the role of DWI values in differentiating between pCR and non-PCR groups.

The diagnostic performance of ADC values for the prediction of pathological response to TNT in patients with LARC was analyzed with ROC analysis and showed good results: ADC values were able to discriminate between pCR and non-pCR patients with a sensitivity of 75% and specificity of 70% (using a cutoff value of 1.042 $\times 10^{-3}$ mm^2/s).

The main limitation of this research is the size of our study population, which is relatively small, due to the purpose of performing all examinations in the same institution with the same MRI system in order to have a homogeneous sample, avoiding possible bias from different machine parameters. Moreover, we extracted only mean DWI and ADC values without considering the spatial distribution of voxels within the volume of interest; hence, the use of radiomics could validate or even implement our data. Finally, the retrospective nature of our study did not allow us to establish a cause-effect relationship between ADC values and post-treatment outcomes; therefore, future prospective studies should be performed to confirm our results.

Conclusions

Our preliminary analysis suggests how signal intensity values on pre-treatment DWI, and corresponding ADC map, are strongly associated with a better outcome of patients with LARC, both in terms of pathological response and downstaging after TNT. These results promote the use of DW-MRI as a potential predictive tool of response to therapy and could furtherly be helpful to detect the most eligible subjects to total neoadjuvant therapy. Future and larger studies are needed to validate the use of diffusion-weighted imaging as a predictor of patients' response to treatment.

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Declarations

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Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived due to the retrospective nature of the study.

Ethical approval This study was approved by the local ethic committee.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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