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Locally advanced rectal cancer: qualitative and quantitative evaluation of diffusion-weighted magnetic resonance imaging in restaging after neoadjuvant chemo-radiotherapy

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Abstract

Purpose To determine the added value of qualitative and quantitative evaluation of diffusion-weighted magnetic resonance imaging (DWI) in locally advanced rectal cancer (LARC) restaging after neoadjuvant chemo-radiotherapy (CRT).

Materials and Methods A retrospective study was performed of 21 patients with LARC treated with CRT. All patients were evaluated with 1.5 T conventional magnetic resonance imaging (MRI) and DWI (0–1000 s/mm²) before starting therapy and after neoadjuvant CRT. All included patients underwent surgery after CRT: the histopathological evaluation of surgical specimens represented the reference standard for local staging after neoadjuvant therapy. The qualitative analysis was carried out by two operators in consensus, who reviewed the conventional MR image set [T1-weighted and T2-weighted morphological sequences + dynamic contrast-enhanced sequences (DCE)] and the combined set of conventional and DW images. For the quantitative analysis, the apparent diffusion coefficient (ADC) values were measured at each examination. For each lesion, the mean ADC value (ADCpre and ADCpost) and the ΔADC (ADCpost – ADCpre) were calculated, and values of the three groups of response [complete response (pCR), partial response (pPR), stable disease (pSD)] were compared.

Results In LARC restaging, conventional MRI showed a sensitivity of 80% and a specificity of 50%, with a total diagnostic capacity of 71.40%, while by adding DWI sensitivity increased to 100%, specificity to 67%, and total diagnostic capacity to 90.40%. ΔADC correlates with treatment response and a cutoff of 1.35×10^{-3} mm²/s predicts the pCR with a sensitivity of 93.3% and a specificity of 83.3%.

Conclusions Adding DWI to conventional sequences may improve MRI capability to evaluate tumor response to CRT. The quantitative DWI assessment is promising, but larger studies are required.

Keywords LARC · DWI · Chemo-radiotherapy

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Introduction and objectives

In the last two decades, the introduction of neoadjuvant therapy, the improvement of imaging modalities, and the advanced surgical techniques have greatly modified the treatment of rectal cancer. Since preoperative chemoradiotherapy (CRT) has become the standard treatment of locally advanced rectal cancer (LARC), an increasing attention has been paid to tumor restaging after neoadjuvant therapy. Accurate restaging after CRT could lead to modification of therapeutic strategy: on the one hand, non-responder patients may take advantage of different treatment modalities, for example premature surgery or intensified CRT; on the other hand, patients with clinical complete response may be directed to less invasive surgical options, such as sphincter-saving local excision [1, 2], up to a most desirable "wait-and-see" policy [3], with remarkable reduction of morbidity (postoperative complications, intestinal, bladder, sexual dysfunctions, permanent stoma care) and mortality [4, 5].

According to literature data, 15–27% of CRT-treated tumors get a complete response, while 54–75% get a partial response and a small percentage receive no response [6].

Careful selection of patients with clinical complete response is therefore the key to implementing less invasive or conservative therapeutic strategies and represents a diagnostic challenge. Endoscopic biopsies have low accuracy in identifying tumor residue after CRT [7]. Conventional imaging has a tendency to overstage [8, 9]. As a functional technique, diffusion-weighted magnetic resonance imaging (DWI) is a non-invasive biomarker of tumor aggression [10] as well as a parameter for assessing the tumor response to CRT [11–14].

The aim of this study is to determine the role of DWI in LARC restaging after neoadjuvant CRT, with both qualitative and quantitative evaluation.

Materials and methods

Patients

This study is a retrospective review of magnetic resonance imaging (MRI) examinations of the lower abdomen performed for staging and restaging of LARC between July 2014 and July 2018.

Inclusion criteria were histologically proven rectal cancer, staging MRI, neoadjuvant CRT, restaging MRI, and subsequent surgery with available pathology report.

Exclusion criteria were examinations performed with non-standardized MRI protocol (*e.g.*, absence of DWI), insufficient image quality (*e.g.*, hip prosthetic artifacts, movement artifacts), previous CRT for rectal cancer or tumors in other organs, and surgery performed in other institutions.

21 patients met the above criteria and were enrolled in the study.

Reference standard

All patients underwent surgery after CRT: low anterior resection ($n=17$), abdominoperineal resection ($n=4$); 12/21 patients underwent a temporary ileo- ($n=11$) or colostomy ($n=1$).

The histopathological evaluation of surgical specimens represented the reference standard for local staging after neoadjuvant therapy and was based on the TNM staging system (VIII ed.) [15]. No response to treatment was considered as stable disease (pSD). A partial response (pPR) to treatment was defined as reduction of at least one level in T or N staging compared to the baseline MRI examination. The absence of any tumor cells in the surgical specimen was considered complete response (pCR). Pathological tumor response was also graded according to AJCC-TRG [15].

Neoadjuvant CRT

17/21 patients were preoperatively treated with intensity-modulated radiotherapy with simultaneous integrated boost (IMRT-SIB), at a dose of 50–55 Gy (median 52.5 Gy) delivered in 25 fractions, and concurrent chemotherapy (Xeloda®, capecitabine 1650 mg/m^2/day per os).

4/21 patients underwent short-course radiotherapy, at a dose of 25 Gy in 5 fractions, without associated chemotherapy.

MRI protocol

All included patients underwent MRI examination twice: before neoadjuvant therapy (MRI_{pre}) and after the end of neoadjuvant therapy (MRI_{post}).

All MRI_{pre} and MRI_{post} were performed with a 1.5 T system (Optima 360 Advance, GE Healthcare, Milwaukee, WI, USA), using a 16 channels surface coil (body phased array). Written informed consent to MRI examination was obtained from all patients.

No rectal cleansing was required nor was the distension of rectum performed with air or contrast media. In some cases, antispasmodic drugs (hyoscine butylbromide) were administered to induce intestinal hypotonia.

Table 1 summarizes our MRI protocol.

Table 1 MRI protocol

Sequences	T2-weighted	DWI	DCE
Section thickness (mm)	4	4	4
Interslice gap (mm)	0.4	0.4	/
Repetition time (ms)	6500	3619	6.6
Echo time (ms)	99	67	2.1
FOV (cm)	28	28	37
B values (s/mm^2)	/	0-1000	/
NEX	3	16	1
Flip angle	/	/	12

Synoptic table summarizes the imaging parameters of MRI sequences

Image analysis

The evaluation of MRI examination was performed using a PACS viewer by a radiologist and a resident with experience in body MRI, who were blinded to pathological information.

The qualitative analysis was carried out by the two operators in consensus. They reviewed the two image sets, the conventional MR image set [T1-weighted and T2-weighted morphological sequences + dynamic contrast-enhanced sequences (DCE)] and the combined set of conventional and DW images. To avoid any recall bias, a few weeks passed between the two reading sessions and the order of cases was changed in the second session.

At the first reading session (morphological sequences + DCE), cCR was defined as the absence of masses or wall thickening in the MRI_{post}. cPR was considered as reduction of at least one level in T or N staging between the MRI_{pre} and the MRI_{post}. No response to treatment was classified as cSD.

At the second reading session (morphological sequences + DCE + DWI), cCR was defined as the absence of any signal hyperintensity on DWI, cPR as the presence of a residual hyperintense signal, however reduced in the MRI_{post}, and cSD as stable signal intensity on DWI. In case of discordant findings between the morphological and the functional sequences, priority was given to the latter ones.

According to the quantitative analysis, the two operators in consensus calculated the tumor apparent diffusion coefficient (ADC) values on both MRI_{pre} and MRI_{post} using a workstation with diffusion analysis software (Advantage Workstation 2010, GE Company). For each lesion, three regions of interest (ROIs) were placed on DWI within the rectal wall in the area with higher signal intensity, and then copied onto the corresponding ADC map. If no signal hyperintensity was detected on the MRI_{post}, the ROIs were placed on what was considered as the normal residual rectal wall, as much as possible in the same site of previous tumor. For each lesion, the mean ADC value (ADC_{pre} and ADC_{post}) and the ΔADC (ADC_{post} – ADC_{pre}) were calculated.

Statistical analysis

Statistical analysis and graphs were performed using GraphPad Prism statistical software version 6.01. Normal data distribution was assessed using the D'Agostino-Pearson normality test. Results are presented as median, interquartile range, minimum, and maximum. Comparison between two groups was performed using the Mann–Whitney non-parametric test. Comparison between more than two groups was carried out using the Kruskal–Wallis non-parametric test. A receiver-operating characteristics (ROC) curve was realized by comparing ADC_{post} values in the complete responder patient group (pCR) with ADC_{post} values in the non-complete responder patient group (pPR + pSD).

Results

21 patients were enrolled in the study, with a mean age of 65 years (range 35–83 years) and male prevalence (M/F = 16/5).

The average interval between the MRI_{pre} for tumor staging and the start of treatment was 24 days (range 11–40 days). The average interval between the end of treatment and the MRI_{post} for tumor restaging was 45 days (range 31–69 days). The average interval between the MRI_{post} and surgery was 16 days (range 2–30 days).

Tumor location was as follows: high rectum, more than 10 cm from the anal verge ($n = 4$), middle rectum, within 5–10 cm of the anal verge ($n = 11$), low rectum, and less than 5 cm from the anal verge ($n = 6$).

At pathological evaluation, the following tumor response was obtained: pCR 6/21 patients (28.6%), pPR 8/21 patients (38.1%), and pSD 7/21 patients (33.3%). In particular, yT0 $n = 6$, yT1 $n = 3$, yT2 $n = 5$, and yT3 $n = 7$.

Qualitative analysis

Overall, the diagnostic performance of the second reading session (morphological sequences + DCE + DWI) was better than that of the first one (morphological sequences + DCE), as reported in Tables 2, 3. The additional evaluation of DWI allowed to correct some diagnostic errors ($n = 8$).

Quantitative analysis

Table 4 shows the mean values of ADC_{pre}, ADC_{post}, and ΔADC of all rectal tumors, which are distinct for pCR, pPR, and pSD.

ADC_{post} values were significantly higher than ADC_{pre} values in all tumor response groups.

ADC_{post} values were significantly higher in the pCR group than in the non-complete responder patient group

Table 2 Diagnostic performance of MRI without DWI: concordance 71%, sensitivity 80%, specificity 50%, PPV 80%, NPV 50%, total diagnostic capacity 71.40%

Pathology	Morphologic sequences + DCE			
	cCR	cPR	cSD	Total
pCR				
n	3	1	2	6
%	50.00	16.67	33.33	100
pPR				
n	3	4	1	8
%	37.50	50.00	12.50	100
pSD				
n	0	6	1	7
%	0.00	85.71	14.29	100
Total				
n	6	11	4	21
%	33.33	52.38	14.29	100

Table 3 Diagnostic performance of MRI with DWI: concordance 90%, sensitivity 100%, specificity 67%, PPV 88%, NPV 100%, total diagnostic capacity 90.40%

Pathology	Morphologic sequences + DCE + DWI			
	cCR	cPR	cSD	Total
pCR				
n	4	2	0	6
%	66.66	33.34	0.00	100
pPR				
n	0	7	1	8
%	0.00	87.50	12.50	100
pSD				
n	0	2	5	7
%	0.00	28.57	71.43	100
Total				
n	4	11	6	21
%	19.05	52.38	28.57	100

Table 4 Mean values of ADC_{pre}, ADC_{post}, and ΔADC of all rectal tumors, which are distinct for pCR, pPR, and pSD

	ADC_{pre}	ADC_{post}	ΔADC
All	0.90	1.34	0.44
pCR	0.86	1.65	0.79
pPR	0.86	1.23	0.37
pSD	0.98	1.21	0.22

(pPR + pSD). Evaluation of ΔADC also demonstrated significantly higher values in the pCR group than those in the pPR + pSD group.

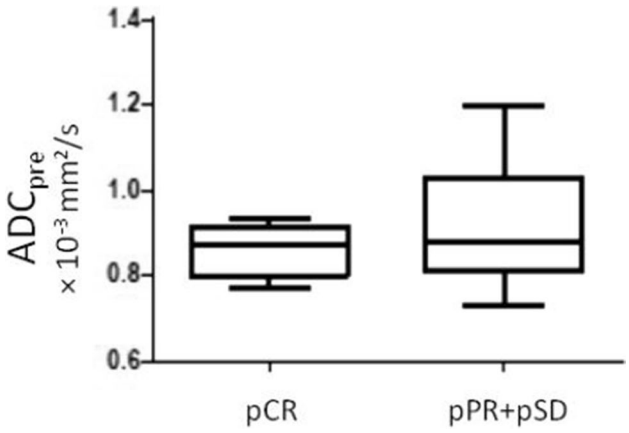

Fig. 1 ADC_{pre} values in the pCR and pPR + pSD groups

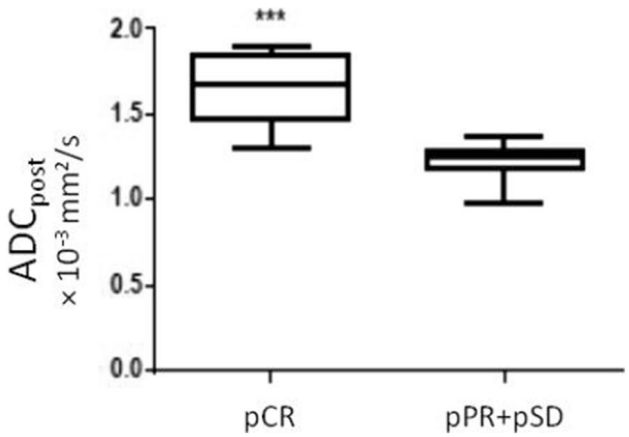

Fig. 2 ADC_{post} values in the pCR and pPR + pSD groups. ***Statistically significant difference, $p < 0.001$

ADC_{pre} values in the pCR group were lower, on average, than those in the pPR + pSD group, but no statistically significant difference was found.

Figures 1, 2, 3, and 4 and Tables 5, 6 summarize the quantitative results of the study.

An ROC curve was created by plotting ADC_{post} values in the pCR group against those in the pPR + pSD group (Fig. 5): the optimal cutoff value was 1.35×10^{-3} mm^2/s (sensitivity 93.3%, specificity 83.3%).

4/21 patients were preoperatively treated with short-course radiotherapy, obtaining a lower overall radiation dose than the other patients and not receiving chemotherapy. Despite the small sample size, a subgroup analysis was performed but no statistically significant differences were observed between the group treated with short-course radiotherapy and the group treated with neoadjuvant CRT when comparing ADC_{pre}, ADC_{post}, and ΔADC values.

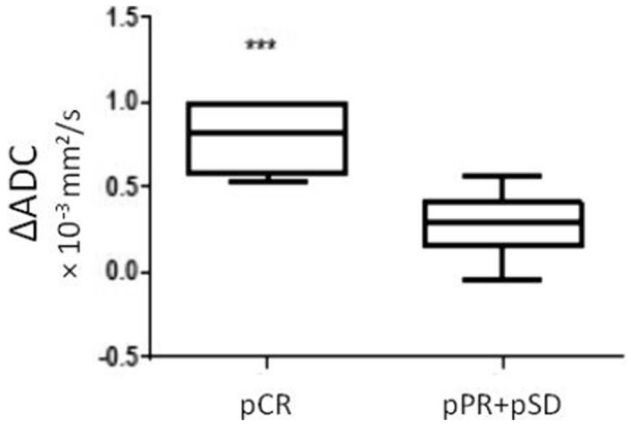

Fig. 3 ΔADC values in the pCR and pPR + pSD groups. ***Statistically significant difference, $p < 0.001$

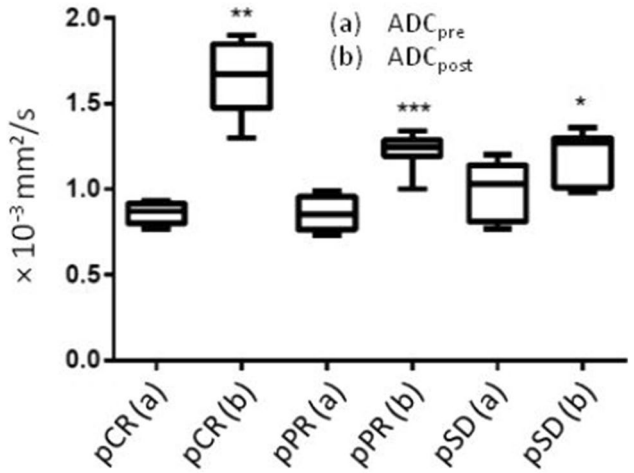

Fig. 4 ADC_{pre} (**a**) and ADC_{post} (**b**) values in the pCR, pPR, and pSD groups. Statistically significant difference, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$

Table 5 Statistical parameters of ADC_{pre} values in the pCR and pPR + pSD groups

	pCR	pPR + pSD
Number	6	15
Minimum	0.7700	0.7300
25% percentile	0.8000	0.8100
Median	0.8700	0.8800
75% percentile	0.9150	1.030
Maximum	0.9300	1.200
Mean	0.8600	0.9153
Std. deviation	0.06325	0.1435
Std. error of mean	0.02582	0.03706

Table 6 Statistical parameters of ADC_{post} values in the pCR and pPR + pSD groups

	pCR	pPR + pSD
Number	6	15
Minimum	1.300	0.9800
25% percentile	1.473	1.180
Median	1.675***	1.250
75% percentile	1.848	1.290
Maximum	1.900	1.360
Mean	1.652	1.216
Std. deviation	0.2299	0.1216
Std. error of mean	0.09386	0.03141

***Statistically significant difference, $p < 0.001$

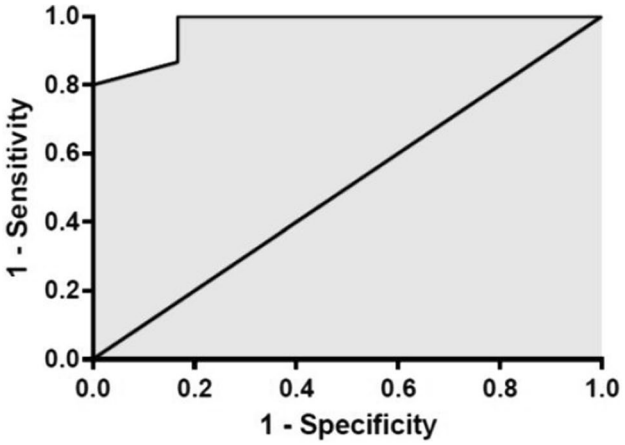

Fig. 5 ROC curve of ADC_{post} pCR vs pPR + pSD. The optimal cut-off is 1.35×10^{-3} mm^2/s (sensitivity 93.3%, specificity 83.3%). Area 0.9722; standard error 0.03327; 95% confidence interval 0.9070, 1.037; p 0.0009442

Discussion and conclusions

DWI is based on the Brownian motion of water molecules, which depends mainly on cellularity, but also reflects intracellular, intravascular, and extravascular factors [16]. The demand for an imaging capable of identifying tumor aggressiveness and the need for accurate evaluation of tumor response after neoadjuvant CRT stimulated research. The growing interest in DWI is undeniably due to its advantages: it does not subject patients to ionizing radiation, does not require contrast agents, does not induce pain or discomfort, and can be achieved relatively quickly if routinely incorporated in the standard MRI [17].

In this study, we evaluated the qualitative and quantitative diagnostic role of DWI in post-CRT restaging of LARC. Regarding the qualitative analysis, our results

demonstrate that additional evaluation of DWI improves the diagnostic performance of MRI in tumor restaging, increasing sensitivity from 80 to 100% and specificity from 50 to 67%. In 8 patients, DWI corrected diagnostic errors based on the interpretation of conventional sequences alone (morphological sequences + DCE). In particular, in 5/7 cases (71.43%) vs 1/7 cases (14.29%) DWI found the persistence of mesorectal infiltration.

In 2 patients with pCR, the qualitative interpretation of DWI was not able to distinguish the tumor residue from the pathological alterations induced by CRT, consisting of fibrosis in one case (Fig. 6) and acellular mucin lakes in the other (Fig. 7). The scientific literature widely reports that radio-induced fibrosis is the major reason for rectal tumor overstaging after neoadjuvant therapy, because of diffusion restriction associated [14, 18]. On the contrary, only few studies analyze the DWI signal intensity of posttreatment colloid response. Colloid response is characterized by low volumetric reduction and significantly increased signal on T2-weighted images [19]. Xie et al. [20] report that, as with necrosis, mucin is associated with increased ADC values, because of decreased cellularity. However, the presence of abundant mucin in the rectal wall may cause false positives, due to high signal intensity on DWI and low signal intensity on the corresponding ADC map. Song et al. [21] reported an ADC value of 1.36×10^{-3} mm^2/s, even lower than ours (1.53×10^{-3} mm^2/s), probably resulting from a different degree of mucin density. In this study, both fibrosis and acellular mucin lakes lead to signal hyperintensity on DWI, even if no residual tumor was found at pathological evaluation.

As regards to the quantitative evaluation, in the pCR group ADC_{post} values were significantly higher than ADC_{pre} values ($p<0.01$) and in the same group both ADC_{post} values and ΔADC were significantly higher than those in the other response groups. ADC values reflect the tumor cellularity. CRT reduces tumor cellularity and promotes parietal necrosis, leading to increased ADC values [12]. Kim et al. [11] showed that neoadjuvant treatment increases ADC values in

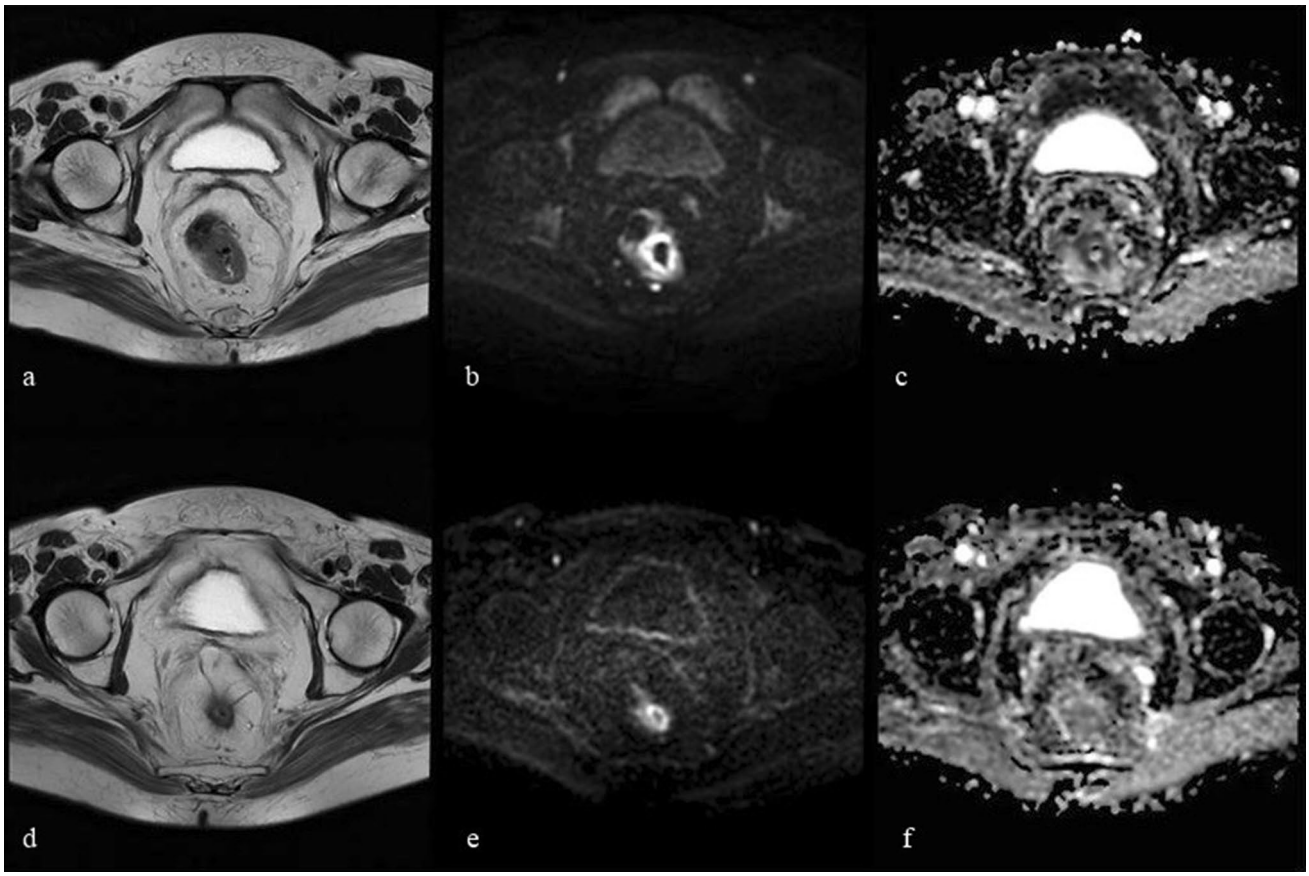

Fig. 6 pCR: a 75-year-old woman classified as cSD in the first reading session (morphological sequences + DCE) and cPR in the second one (morphological sequences + DCE + DWI). In MRI_{pre}, T2-weighted sequences (**a**) show a cancer lesion in the middle rectum, which corresponds to a hyperintense area on DWI at $b=1000$ s/mm^2 (**b**) and a hypointense area on the ADC map (**c**). In MRI_{post}, T2-weighted sequences (**d**) show wall thickening with perirectal fat stranding, which corresponds to a persistent hyperintense area on DWI at b = 1000 s/mm^2 (**e**) and a hypointense area on the ADC map (**f**). $ADC_{pre}=0.77\times10^{-3}$ mm^2/s; $ADC_{post}=1.30\times10^{-3}$ mm^2/s; $\Delta ADC=0.53\times10^{-3}$ mm^2/s. At pathological examination, the lesion was yT0, TRG 0, with the presence of dense fibrosis

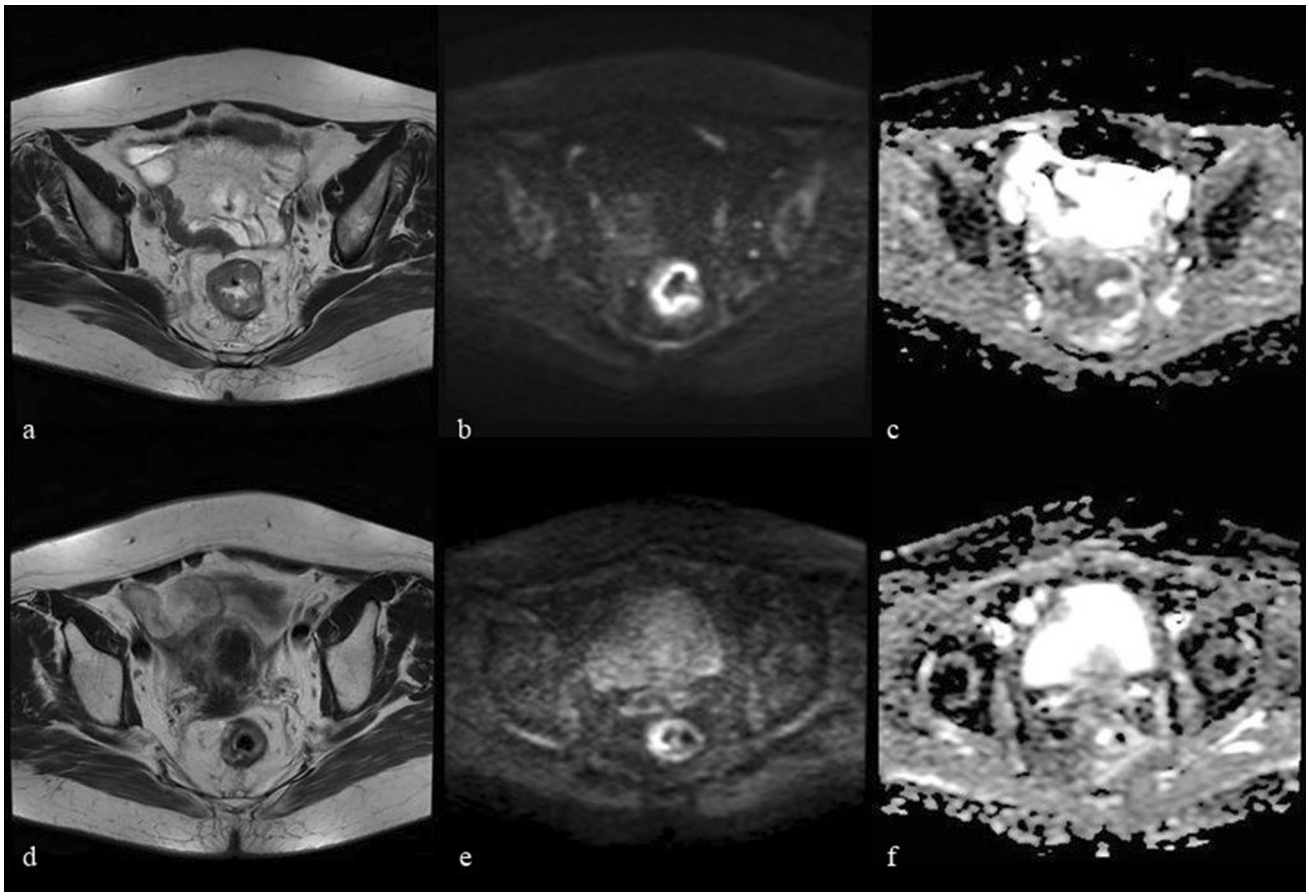

Fig. 7 pCR: a 70-year-old woman classified as cSD in the first reading session (morphological sequences + DCE) and cPR in the second one (morphological sequences + DCE + DWI). In MRI_{pre}, T2-weighted sequences (**a**) show a cancer lesion in the middle rectum, which corresponds to a hyperintense area on DWI at b = 1000 s/mm^2 (**b**) and a hypointense area on the ADC map (**c**). In MRI_{post}, T2-weighted sequences (**d**) show the persistence of wall altered signal intensity, which corresponds to a hyperintense area on DWI at $b = 1000$ s/mm^2 (**e**) and a hypointense area on the ADC map (**f**). $ADC_{pre} = 0.93 \times 10^{-3}$ mm^2/s; $ADC_{post} = 1.53 \times 10^{-3}$ mm^2/s; $\Delta ADC = 0.60 \times 10^{-3}$ mm^2/s. At pathological examination, the lesion was yT0, TRG 0, with the presence of abundant acellular mucin lakes

patients with rectal cancer. Cai et al. [22] demonstrated that ADC values change over the course of treatment and values measured at the second week of therapy are significantly related to tumor response. Just after the start of treatment, a rapid reduction in ADC values can be observed for several hours due to cellular swelling, followed by a progressive increase in the following days because of cellular death [23].

Our results are in line with those of other authors [24, 25], who argue that the rate of change in ADC values is correlated with the pathologic response to CRT. In contrast, Curvo-Semedo et al. [26] proved that ΔADC is not able to predict pCR (sensitivity 54%, specificity 64%). The discrepancy of results is most likely related to the definition of "responders," the technical parameters of image acquisition, and the method of ROI positioning.

ADC_{pre} values in the pCR group were lower, on average, than those in the pPR + pSD group, but no statistically significant difference was reported. Several authors demonstrated that higher pretreatment ADC values in LARC are associated with poor CRT response [13, 27]. In fact, high ADC values result from necrosis and loss of cell membrane integrity, therefore more aggressive tumors [28]. Areas of intratumoral necrosis are generally poorly perfused and less accessible to chemotherapeutic agents. Furthermore, because of necrosis tumor cells are exposed to hypoxic and acidic microenvironment, which reduces the effectiveness of CRT [29]. This theory could explain the relationship between the high ADC_{pre} values and the poor treatment response found in this study. However, necrosis is not always associated with high ADC values. In contrast to liquefactive necrosis, coagulative necrosis does not lead to increased ADC values [30]. This could justify the inadequate response to CRT reported in this study also by tumors with lower ADC_{pre} values.

On the basis of ROC curve analysis, we found a cutoff of 1.35×10^{-3} mm^2/s, which is able to identify the pCR with

a sensitivity of 93.3% and a specificity of 83.3%. When the calculated cutoff was used for distinguishing between the pCR and pPR + pSD groups, a concordance of 95%, a sensitivity of 100%, a specificity of 83%, a positive predictive value (PPV) of 94%, a negative predictive value (NPV) of 100%, and a total diagnostic capacity of 95.2% were achieved. Foti et al. [13] obtained a similar result, establishing a cutoff of 1.3×10^{-3} mm^2/s. Other authors proposed a cutoff of 1.2×10^{-3} mm^2/s [11].

The tumor response to treatment is modulated according to the time interval elapsed since the end of CRT, and therefore also ADC values calculated in restaging MRI may be affected by the temporal distance from the end of treatment. To date, however, there is no agreement on the ideal timing of restaging MRI. A recent Italian meta-analysis of 13 studies showed that a time interval between CRT and surgery over conventional 6–8 weeks is associated with a greater number of cases of pCR [31]. Similar results were obtained by Probst et al. [32]. Delaying surgery over 11 weeks after the end of CRT seems not to add further benefits [33]. While at 8 weeks after CRT cancer cells may be still found in histological samples, after 12 weeks they are completely absent because of mitotic catastrophe and apoptosis [34]. In our case series, the MRI_{post} was executed on average 6 weeks after the end of neoadjuvant treatment, while surgery was performed on average 8 weeks after the end of treatment. In some cases, surgery followed the MRI_{post} of over 4 weeks, influencing the correlation between ΔADC and treatment response.

Scientific debate is still open on what the most suitable method to evaluate treatment response is. The modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria, based on one-dimensional measures, are considered the gold standard method for assessing tumor response in most solid tumors [35]. However, especially for rectal tumors these criteria do not accurately reflect the overall volumetric changes of cancer for several reasons: the measured diameter varies with patient's position and image acquisition planes, the rectum is a hollow organ and the tumor may assume irregular morphology, and the tumor reduction induced by treatment may not be uniform. The tumor volume reduction rate (TVRR), obtained by three-dimensional ROIs placed on T2-weighted images, is more accurate than RECIST criteria in predicting LARC response to CRT [36]. According to a Korean study, the TVRR measured on T2-weighted images at 2 weeks from the beginning of CRT is a more accurate indicator of patient's outcome than ADC values [37]. Other authors showed that the posttreatment tumor volumetry on DWI is useful for recognizing the pCR and is significantly more accurate both of the volumetry on T2-weighted images and of ADC values [26, 38]. Preliminary studies proved the utility of the *D* parameter of the IVIM model (IntraVoxel Incoherent Motion) in LARC restaging, especially with reference to the distinction between responders and non-responders [39].

The role of DCE in restaging of CRT-treated LARC remains unclear. The perfusion curve obtained by a post-processing software (Onco-Vizpack, Gen IQ, GE Healthcare) showed a significant decrease in the mean K_{trans} value between pre- and posttreatment MRI only in patients with favorable response to therapy [40]. However, some authors did not obtain the same results, concluding that the addition of DCE to T2-weighted and DW images in MRI protocol does not improve the performance [41].

The combination of Positron Emission Tomography–Computed Tomography (PET-CT) with ^{18}F-fluorodeoxyglucose, volumetry, and DWI allows to predict the pCR with a sensitivity of 75%, a specificity of 94%, and a PPV of 80%. Functional imaging techniques are able to point out metabolic and microstructural changes before the morphological ones. Biochemical markers of inflammation (interferon-gamma, interleukins, and tumor necrosis factor-alpha) and genetic profiles in addition to imaging parameters were studied by Joye et al. [34] with poor results: no molecular data can be validated to predict tumor response to treatment.

At the beginning of the era of radiomics, the results of a recent Chinese study appear encouraging [42]: a complex analysis of 103 MRI parameters in 48 patients led to the creation of a multiparametric model of tumor restaging with greater accuracy than all parameters taken individually.

With regard to lymph node restaging, it is difficult to differentiate metastatic lymph nodes and lymph node changes induced by CRT on the basis of morphological criteria alone, but also DWI is not resolutive [12]. The main role of DWI is to improve the identification of lymph nodes, because they stand out for their high signal compared to the background due to their high cell density. After treatment, metastatic lymph nodes may become partially necrotic resulting in increased ADC values [43]. Although the absence of any lymph nodes on DWI is infrequent, it represents a reliable predictor of the absence of nodal metastatic disease (yN0) in patients with rectal cancer treated with neoadjuvant therapy [44]. A promising alternative is the use of specific lymphotropic contrast agents, including both those based on superparamagnetic iron oxide nanoparticles and those based on gadolinium, such as gadofosveset trisodium [45, 46].

Our study has some limitations. First of all, the retrospective nature of this study may favor selection bias. Second, the possibility of recall bias should be considered, which we tried to avoid by carrying out the second reading session after a few weeks and in a different order from the first. Third, images were not analyzed by the two operators separately and, therefore, inter- and intraobserver variability was not evaluated. Fourth, for the quantitative analysis we considered two b values (0 and 1000 s/mm^2), without investigating the influence of other b values on the results. Fifth,

the ROI positioning method for ADC values calculation is an extremely subjective process and subject to measurement bias. Blazic et al. [47] demonstrated that the ROI placement method significantly influences the measurement of ADC values, attributing the best accuracy in assessing treatment response to the whole-tumor volume measurement. Sixth, the variability of time intervals between the MRI_{pre} and the start of treatment, between the end of treatment and the MRI_{post}, and between the MRI_{post} and surgery reduces the sample homogeneity. Likewise, the different treatment protocols interfere with the homogeneity of our study population (CRT for 17 patients, only radiotherapy for 4 patients). Finally, the small sample size limits statistical power and larger studies are needed for more precise results.

In conclusion, this preliminary study demonstrates that

- the qualitative DWI assessment in addition to conventional sequences improves the diagnostic performance of MRI in LARC restaging (sensitivity 100%, specificity 67%, total diagnostic capacity 90.4%);
- ΔADC correlates with treatment response; in particular, ΔADC in the pCR group is significantly higher than ΔADC in the pPR + pSD group;
- a cutoff of 1.35×10^{-3} mm^2/s predicts the pCR with a sensitivity of 93.3% and a specificity of 83.3%; and
- in view of the possibility of false positives, the qualitative analysis of DWI is not always able to recognize complete responder tumors, and therefore we believe that it is not yet time to entrust treatment decisions (surgery or "wait-and-see" policy) to MRI and further studies considering quantitative evaluation of ADC values are necessary.

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