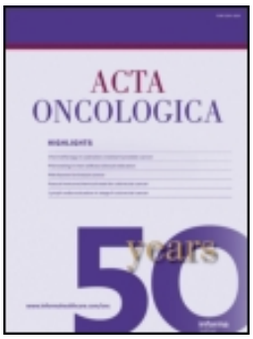

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ORIGINAL ARTICLE

Combined T2w volumetry, DW-MRI and DCE-MRI for response assessment after neo-adjuvant chemoradiation in locally advanced rectal cancer

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ABSTRACT

Background. To assess the value of combined T2-weighted magnetic resonance imaging (MRI) (T2w) volumetry, diffusion-weighted (DW)-MRI and dynamic contrast enhanced (DCE)-MRI for pathological response prediction after neo-adjuvant chemoradiation (CRT) in locally advanced rectal cancer (LARC).

Material and methods. MRI with DW-MRI and DCE-MRI sequences was performed before start of CRT and before surgery. After surgery, the tumor regression grade (TRG) was obtained based on the score by Mandard et al. Pathological complete responders (pCR, TRG 1), and pathological good responders (GR, TRG 1 + 2) were compared to non-pCR and non-GR patients, respectively.

Results. In total 55 patients were analyzed, six had a pCR (10.9%) and 10 a GR (18.2%). Favorable responders had a larger decrease in tumor volume and Ktrans and a larger increase in apparent diffusion coefficient (ADC) values compared to non-responders. ADC change showed the best diagnostic accuracy for pCR. For GR, the model including ADC change and volume change showed the best diagnostic performance. However, this performance was not statistically better compared to the model with ADC change alone. Inclusion of Ktrans change did not increase the diagnostic accuracy for pathological favorable response.

Conclusions. This explorative study showed that ADC change is a promising diagnostic tool for pCR and GR. Volume decrease showed potential limited additional diagnostic value for GR while Ktrans change showed no additional diagnostic value for pCR and GR.

The standard of care treatment for locally advanced rectal cancer (LARC) is neo-adjuvant chemoradiation (CRT) followed by total mesorectal excision surgery [1]. After neo-adjuvant therapy approximately 15% of patients reach a pathological complete response (pCR) which is the state without vital tumor on histological examination [2]. The lack of tumor in these resection specimens questioned the additional value of radical resection in good responders after neo-adjuvant treatment and led to the introduction of organ sparing treatment strategies [3,4]. A major challenge for these strategies is the selection of patients suitable for an organ sparing approach. Ideally, techniques for the selection of patients for this approach need to be accurate for the pathological response after neo-adjuvant therapy to prevent undertreatment of patients.

Magnetic resonance imaging (MRI) is standard of care for staging and re-staging of rectal cancer. In multiple studies it was shown that T2-weighted (T2w) MRI tumor volume reduction was predictive for pathological response after neo-adjuvant therapy [5–8]. Besides, also several studies showed that functional MR imaging is helpful for response prediction after neo-adjuvant therapy. Diffusion-weighted (DW)-MRI and dynamic contrast enhanced

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(DCE)-MRI both showed promising results regarding response prediction after CRT in LARC. Both functional imaging techniques assess different aspects of the tissue. DW-MRI with the apparent diffusion coefficient (ADC) assesses the impedance of water molecules diffusion which is most dependent on the tissue cellularity [9]. DCE-MRI, however, measures a volume transfer constant (Ktrans) which is dependent on the perfusion and the permeability of the tumor vasculature [10]. Both the ADC and Ktrans change after neo-adjuvant therapy were correlated with pathological favorable response in previous studies [11–17].

In this study, we assessed the diagnostic value of combined T2w-MRI volumetry, DW-MRI and DCE-MRI for pathological response after neo-adjuvant CRT in patients with LARC.

Material and methods

We prospectively included patients from December 2008 to March 2012 after obtaining informed consent. The inclusion criteria were a histologically proven locally advanced rectal adenocarcinoma eligible for treatment with neo-adjuvant CRT followed by resection. Locally advanced tumors were tumors with close distance or invasion of the mesorectal fascia and/or > 3 pathological locoregional lymph nodes. Patients with contra-indications for MRI were excluded. The study was approved by the institutional review board of our center.

Treatment

Neo-adjuvant CRT treatment was standard of care treatment. A total radiation dose of 50 Gy, in 25 daily fractions of 2 Gy was delivered over a period of five weeks. The radiotherapy was combined with twice daily oral 5-FU (capecitabine). The CRT was followed by surgery 7–10 weeks after the end of the CRT and was performed by surgeons trained in colorectal oncological surgery.

Magnetic resonance imaging

Before the start of CRT and a week before surgery, an MRI with transverse and sagittal T2w, transverse DW-MRI and transverse DCE-MRI sequences on a 3-Tesla MR (AchievaTX, Philips Medical Systems, Best, The Netherlands) was performed. A phased array 32-element coil was used as receiver coil. All scans were performed in supine position on a flat tabletop without specific bowel preparation. The T2w sequence was a Turbo Spin Echo (TSE) sequence (TR/TE, 5632/120 ms; acquired resolution 0.45×0.45 mm^2, slice thickness 3.0 mm). Diffusion weighting was achieved by using a single-shot Spin-Echo Echo Planar Imaging (ssSE-EPI) sequence (TR/TE: 7600 ms/63 ms; EPI factor: 63), with spectral attenuated inversion-recovery (SPAIR) fat suppression and isotropic diffusion weighting in three directions with b-values: 0, 200, 800 s/mm^2. Images were acquired with a resolution of 2.5×2.5 mm^2, slice thickness was 4.0 mm and the number of averages was three. The DCE-MRI protocol consisted of three-dimensional (3D) spoiled gradient echo sequence (TR/TE, 4/1 ms; acquired resolution $2.5 \times 2.5 \times 4.0$ mm^3; acquisition matrix, $144 \times 132 \times 20$; flip angle 8°). Scans were repeated 120 times at 2.4 s interval. A concentration of 0.1 ml/kg of Gadobutrol (1.0 M) (Gadovist, Schering AG, Berlin, Germany) contrast was injected with 2 ml/s using an automatic power injector, followed by a saline flush. The total examination time including patient preparation was approximately 35 minutes.

Data processing

Using in-house developed software ADC-maps were generated from the diffusion weighted images with b-values of 0, 200, and 800 s/mm^2. A linear regression after a logarithmic transformation of the signal intensity (lnS) was used to calculate the ADC values $\ln(S) = \ln(A)\text{-}b.ADC$, where A is the relative amplitude. For perfusion assessment, contrast-enhanced time series were converted to concentration time series using in-housed developed software. Subsequently, the generalized kinetic model by Tofts et al. was fitted to the concentration time series using a generic, patient averaged, arterial input function (AIF) [10]. The generic AIF was obtained using phase-based measurements from the femoral arteries using the method described by Korporaal et al. [18]. Due to the extent of measurement errors on the patient-specific input functions causing non-significant different AIF between patients a generalized AIF was used as described in earlier publications [19,20]. This resulted in 3D maps of Ktrans.

Data analyses

Tumor delineation was performed by a single expert observer using the in-house developed image analysis package Volumetool [21]. The tumors were delineated as a volume of interest (VOI) on the high b-value DWI-MR image and on the T2w-MRI before and after neo-adjuvant therapy. In cases where no residual tumor was identified after therapy, the VOI was drawn in the apparent tumor bed. The tumor delineated on the T2w-MRI was automatically transferred to the corresponding K-trans map and the VOI on the high b-value image to the ADC map (Figure 1). Corresponding ADC values and Ktrans values of the VOI

were extracted from the ADC and Ktrans maps using Matlab (Matlab, version 7.14.0.739, The Mathworks Inc, USA). Based on the pre- and post-CRT T2w tumor volumes, ADC values and Ktrans values the relative change in these parameters was calculated. These relative changes are shown as ΔVolume, ΔADC and ΔKtrans, respectively.

Pathology

After surgery the resection specimens were evaluated by pathologists specialized in gastrointestinal oncological pathology. Besides standard protocolized macroscopic and microscopic assessments of the resection specimen also tumor regression grade (TRG) analysis was performed [22]. For data analyses, patients were grouped according to the pathological response based on the TRG described by Mandard et al. [23]. Patients classified as pathological complete responders (pCR, TRG 1) were compared with patients without pCR (TRG > 1, non-pCR). Patients with pCR or solitary tumor cells in the resection specimen (TRG 1 + 2) were classified as good responders (GR) and compared with partial and poor responding patients (non-GR).

Statistics

The diagnostic value for pCR and GR of ΔVolume, ΔADC and ΔKtrans and their combinations were assessed with logistic regression analysis using Firth bias-correction [24]. Correlations between the ΔVolume, ΔADC and ΔKtrans were calculated using the Pearson's correlation coefficient. Receiver operating characteristic (ROC) analysis was applied and the area under the ROC curve (AUC) was obtained. ROC curves were compared using the method described by Hanley and McNeil [25]. Calibration of the models was determined by comparing predicted probabilities of response and observed probabilities using a calibration plot. Calibration was also assessed by performing the Hosmer-Lemeshow test. The cut-off values for calculating diagnostic accuracy for the various models was the value with the highest positive likelihood ratio [LR+, sensitivity/(1-specificity)] for favorable response. Accuracy was calculated to assess the discriminative performance of the models, i.e. the ability of the model to distinguish responders and non-responders. The percent of patients accurately classified was compared between models using the McNemar's test. Statistical

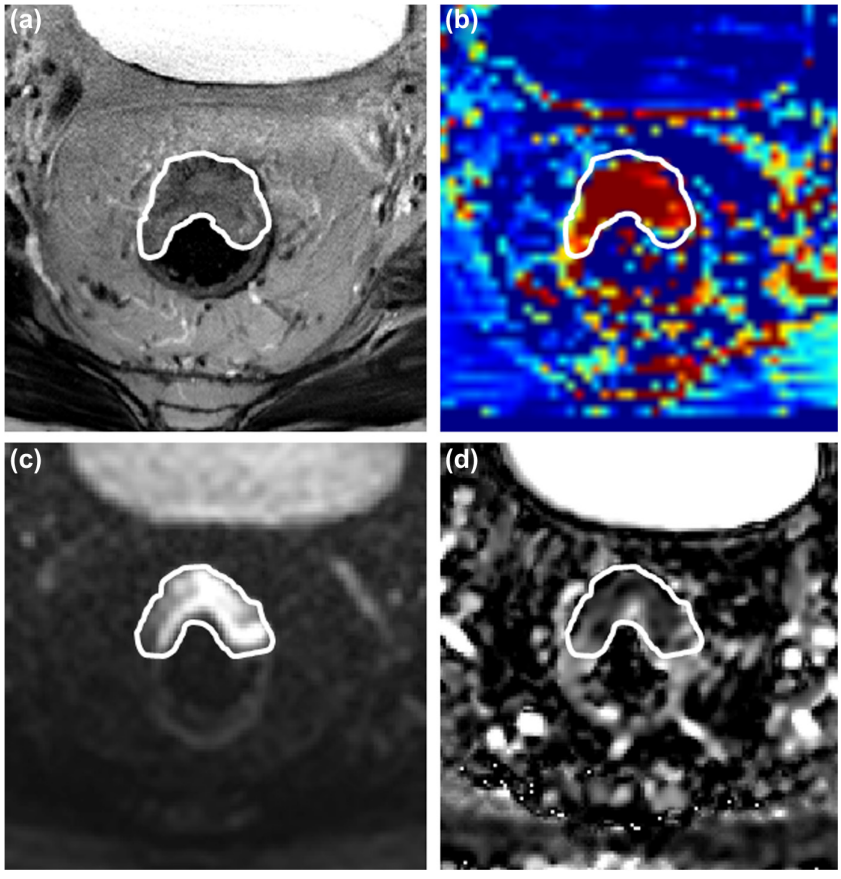

Figure 1. cT3N2 rectal adenocarcinoma in a 60-year-old male patient. T2-weighted imaging (a), Ktrans map (b), b800 image (c) and apparent diffusion coefficient map (d).

analyses were performed using SPSS version 20.0.0, SAS version 9.4, and GraphPad Prism version 6.04.

Results

Patient characteristics

A total of 63 patients were included in the study. Eight patients were excluded from analyses due to refusal of surgery after neo-adjuvant treatment (n = 2), contrast agent intolerance (n = 1), mucinous tumor at pathology (n = 1) or severe imaging artifacts hampering analysis (n = 4). This resulted in 55 patients available for analyses. The pCR group consisted of six patients (10.9%) and the GR group of 10 patients (18.2%).

Univariate analyses

After CRT, pathological favorable responders showed a larger increase in ADC and a larger decrease in tumor volume and Ktrans (Table I). Correlation tests showed a weak negative correlation (Pearson's correlation coefficient −0.41, p = 0.02) between the ΔADC and ΔKtrans. No correlations existed between the other variables. ROC analyses showed the best discriminative value for pathological favorable response with ΔADC in both response analyses. An optimal ΔADC threshold for both pCR and GR was found of 43%. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for prediction of pCR were 83%, 96%, 71% and 98%, respectively (Table II). For GR, these values were 80%, 98%, 89% and 96%, respectively (Table III). The area under the ROC curves for ΔADC was 0.93 for pCR and 0.97 for GR.

Multivariable analyses

The Δvolume, ΔADC and ΔKtrans were combined in a multivariate diagnostic model for pCR and GR. The Hosmer-Lemeshow test showed a non-significant result in all models which shows a good model fit. For pCR, the model with ΔADC alone showed the highest diagnostic accuracy (Table II, Figure 2). For GR, the full model with all three parameters and the model with the ΔADC and the ΔVolume combined performed best, both on discriminating GR form non-GR and on calibration (Table III, Figure 2). As both models performed equivalent the model with the lowest number of parameters, the combined ΔADC and ΔVolume model, was best. This model showed better accuracy compared to the single parameter ΔADC model, however this difference was not statistically significant.

Comparison of ROC curves

ROC curves for the individual parameters and the models are shown in Figure 3. There was no significant difference between the ROC curves for the single parameter and multiparameter prediction models for pCR. For GR the relative volume difference performed inferiorly to the combined ΔADC and ΔVolume model and the model with three parameters. All other ROC curves for GR were not significantly different.

Discussion

This explorative study showed good diagnostic performance of functional MR imaging for favorable pathological response after neo-adjuvant CRT in LARC. ΔADC appeared the parameter with the best diagnostic performance for pCR and GR. For GR addition of volume decrease showed a potential advantage to ΔADC alone, but this was not statistically significant. The addition of ΔKtrans did not increase the diagnostic value in both response groups.

This is one of the first studies to combine functional MR techniques for pathological response assessment after neo-adjuvant CRT in rectal cancer. Single technique studies already showed good response prediction accuracy for functional MRI [11,13,15,26]. For DW-MRI for pCR a sensitivity, specificity and PPV was found of 83%, 96% and 71%, respectively. The optimal cut-off value to

Table I. Comparison of response groups.

	pCR (n = 6)	non-pCR (n = 49)	p-value	GR (n = 10)	non-GR (n = 45)	p-value
Relative Δvolume, % (range)	−76.0 (−83.2 – −63.3)	−53.2 (−88.7 – −14.6)	0.012	−76.0 (−88.7 – −59.3)	−52.4 (−86.8 – −14.6)	0.001
Relative ΔADC, % (range)	48.0 (36.5–63.1)	26.2 (−1–71.8)	< 0.001	48.0 (36.5–71.8)	25.6 (−1–42.7)	< 0.001
Relative ΔKtrans, % (range)	−34.1 (−43.0–1.5)	0.5 (−64.9–64.5)	0.015	−34.1 (−43.7–1.5)	0.8 (−64.9–64.5)	< 0.001

Median therapy induced change in volume, apparent diffusion coefficient (ADC) and Ktrans for the pathological complete response (pCR) versus the non-pCR group and for the pathological good response (GR) versus the non-GR group. Values reported are median values with range. ADC, apparent diffusion coefficient; CRT, chemoradiation.

Table II. Classification tables for the diagnosis of pathological complete response (pCR).

Model	Observed PCR (n = 6)	Observed non-PCR (n = 49)	AUC	Accuracy	PPV	NPV
Predicted						
Δvolume						
PCR	5	11	0.81	78%	31%	97%
non-PCR	1	38				
ΔADC						
PCR	5	2	0.93	95%	71%	98%
non-PCR	1	47				
ΔKtrans						
PCR	4	5	0.80	87%	44%	96%
non-PCR	2	44				
Predicted						
Δvolume ΔADC ΔKtrans						
PCR	4	2	0.95	93%	67%	96%
non-PCR	2	47				
Δvolume ΔADC						
PCR	4	2	0.95	93%	67%	96%
non-PCR	2	47				
Δvolume ΔKtrans						
PCR	3	3	0.90	89%	50%	94%
non-PCR	3	46				
ΔADC ΔKtrans						
PCR	3	1	0.93	93%	75%	94%
non-PCR	3	48				

Classification tables for the diagnosis of pathological complete response (pCR) for the different models. In the individual parameter models the optimal cut-off values for Δvolume, ΔADC and ΔKtrans were −74%, + 43% and -32%, respectively. ADC, apparent diffusion coefficient; AUC, area under the receiver operating curve; NPV, negative predictive value; pCR, pathological complete response; PPV, positive predictive value.

distinct pCR from non-pCR was 43% ADC increase. These values were in accordance with previous DW-MRI response prediction studies. These studies reported sensitivity, specificity and PPV of 83–100%, 70–93% and 37–91% by cut-off values between 30% and 48% ADC increase [11,14,15,27]. The experience with DCE-MR for response prediction in rectal cancer is more limited. In the present study, the sensitivity for pCR with a cut-off value of 32% Ktrans decrease after CRT was 67%. The specificity and PPV were 90% and 44%, respectively. This was comparable with values reported by others groups [16,28].

Besides data from the DW-MRI and DCE-MRI, we also investigated volumetry data in this study. As T2w sequences are part of the standard of care staging and re-staging MRI protocol for rectal cancer, the T2w analyses were also included in the present study. The relative T2w volume difference showed diagnostic value for favorable pathological response. These results were comparable with recent publications [6,7].

To make optimal use of all MRI information, we assessed the diagnostic performance of the combination between T2w volumetry, ADC and Ktrans. For pCR, the best diagnostic parameter for pCR remained ΔADC. For GR, addition of volume data to ΔADC improved the model prediction although this difference was not significant. No additional value was found including DCE-MRI next to T2w imaging and DW-MRI in an MRI protocol used for response assessment in LARC. The lack of added value can be partly explained by the weak correlation which was found between relative ADC difference and relative Ktrans difference. This indicates that there is a correlation between tumor microstructure and vascular permeability. For response prediction, this implies that ΔADC and ΔKtrans partially predicted a good response in the same patients and thus, that combining both methods does not have an additional value. For patients the lack of additional value of DCE-MRI is beneficial because contrast administration in a protocol without DCE-MRI can be omitted. Our results show a better accuracy for detecting GR than pCR. This indicates that the detection of solitary tumor cells with DW-MRI, DCE-MRI or volumetry remains a challenge, even with multiparameter imaging.

A limitation of the study is that the study is underpowered as it was an explorative study

Table III. Classification tables for the diagnosis of pathological good response (GR).

Model	Observed GR (n = 10)	Observed non-GR (n = 45)	AUC	Accuracy	PPV	NPV
Predicted						
Δvolume						
GR	8	8	0.84	82%	50%	95%
non-GR	2	37				
ΔADC						
GR	8	1	0.97	95%	89%	96%
non-GR	2	44				
ΔKtrans						
GR	6	3	0.87	91%	67%	91%
non-GR	4	42				
Predicted						
Δvolume ΔADC ΔKtrans						
GR	9	1	0.99	98%	90%	98%
non-GR	1	44				
Δvolume ΔADC						
GR	9	1	0.99	98%	90%	98%
non-GR	1	44				
Δvolume ΔKtrans						
GR	5	1	0.93	89%	83%	90%
non-GR	5	44				
ΔADC ΔKtrans						
GR	9	2	0.98	95%	82%	98%
non-GR	1	43				

Classification tables for the diagnosis of pathological good response (GR) for the different models. In the individual parameter models the optimal cut-off value for Δvolume, ΔADC and ΔKtrans were −74%, +43% and −32%, respectively. ADC, apparent diffusion coefficient; AUC, area under the receiver operating curve; NPV, negative predictive value; PPV, positive predictive value.

initiated as a prelude to a larger multicenter study. The percentage of pCR in our patient group is with 11% slightly lower compared to the 15% found in a meta-analysis by Sanghera et al. [2]. This is probably due to the mixed composition of the studies included in the meta-analysis compared to this single center study. First, in this study the patient group consisted of a group of patients with locally advanced rectal tumors. This group was a more homogeneous group compared to the patients included in the meta-analyses. The inclusion of only locally advanced instead of also smaller tumors could partially explain the lower amount of good responding patients. Second, we used a standardized pathology protocol with examination of extra tissue blocks in good responding patients to confirm the status of pCR and GR. This thorough search for individual tumor cells could have resulted in a lower number of good responding patients compared with studies with less standardized pathology.

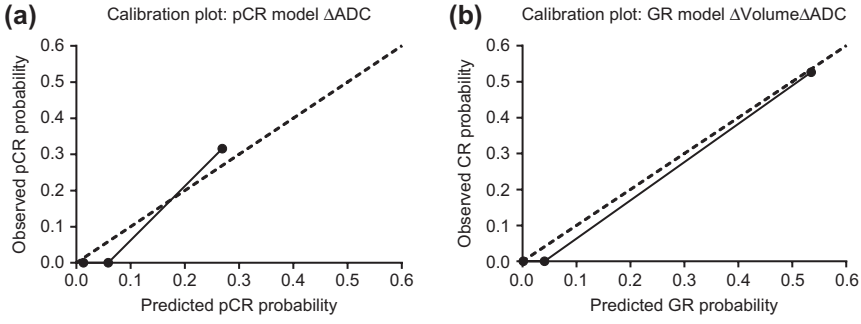

Figure 2. Calibration plots for the best discriminative models for pathological complete response (pCR, a) and pathological good response (GR, b). On the x-axis the true probability of favorable response is shown and on the y-axis the predicted probability. The patient group was divided in three subgroups based on the observed probability. The dashed line shows a perfect calibration. ADC, apparent diffusion coefficient.

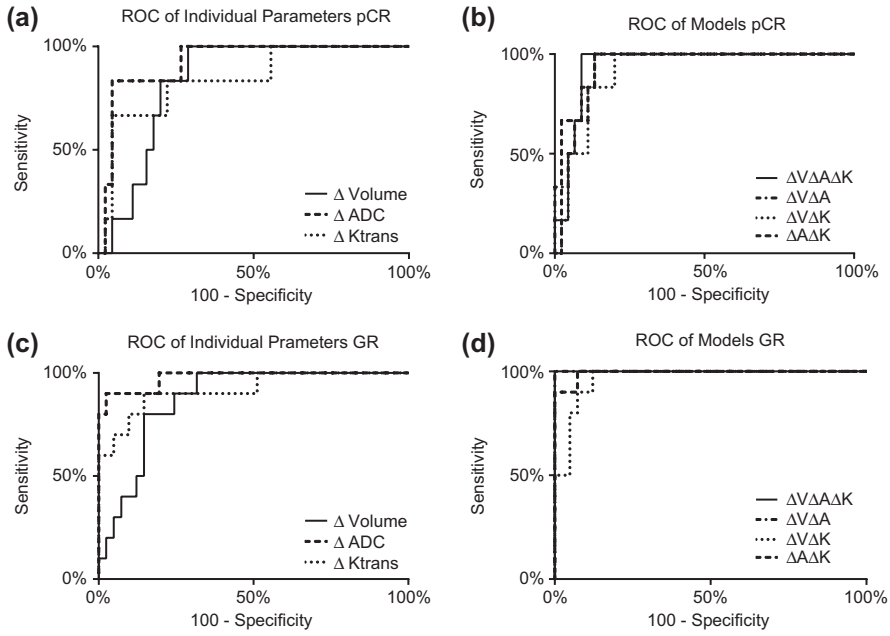

Figure 3. ROC curves for the individual response parameters (a and c) and the multiparameter models (b and d) for pathological complete response (pCR, a and b) and pathological good response (GR, c and d).

The limited patient group restricted the statistical power of the model comparison, which showed no significant differences between the models for pCR. For GR it is shown that volumetry alone performed worse than the combined ΔADC and ΔVolume. When assessed in a larger patient group it is likely that more differences between the predictive models can be seen. This may also reveal whether models containing multiple MR techniques are more predictive than single technique models.

Another limitation of this study is that the models presented in this study are composed from one study set and no external dataset was available to validate the models. Also no pre-selected cut-off value was used to calculate the diagnostic accuracy. Optimally, there is a cut-off value selected before start of study. This has to be done in a larger diagnostic study.

A strength of this study was that relative changes instead of absolute values itself were used in the models. By using the relative parameter changes the results become less dependent on the known inter-machine and protocol variations in ADC or Ktrans values.

In conclusion, this explorative study showed that ADC change is a promising diagnostic tool for both pCR and GR in patients with LARC after neoadjuvant CRT. Volume decrease showed potential limited additional diagnostic value for GR while Ktrans change showed no additional diagnostic value for pCR and GR. Despite the limited patient group, these results justify further research in a larger prospective study with DW-MRI and tumor volumetry.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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