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ORIGINAL ARTICLE

Diffusion-weighted magnetic resonance imaging of rectal cancer: tumour volume and perfusion fraction predict chemoradiotherapy response and survival

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ABSTRACT

Background: In locally advanced rectal cancer (LARC), responses to preoperative treatment are highly heterogeneous and more accurate diagnostics are likely to enable more individualised treatment approaches with improved responses. We investigated the potential of diffusion-weighted magnetic resonance imaging (DW MRI), with quantification of the apparent diffusion coefficient (ADC) and perfusion fraction (F), as well as volumetry from T2-weighted (T2W) MRI, for prediction of therapeutic outcome.

Material and methods: In 27 LARC patients receiving neoadjuvant chemotherapy (NACT) before chemoradiotherapy (CRT), T2W- and DW MRI were obtained before and after NACT. Tumour volumes were delineated in T2W MRI and ADCs and Fs were estimated from DW MRI using a simplified approach to the intravoxel incoherent motion (IVIM) model. Mean tumour values and histogram analysis of whole-tumour heterogeneity were correlated with histopathologic tumour regression grade (TRG) and 5-year progression-free survival (PFS).

Results: At baseline, high tumour F predicted good tumour response (TRG1-2) (AUC = 0.79, $p = 0.01$), with a sensitivity of 69% and a specificity of 100%. The combination of F and tumour volume (F_{pre}/V_{pre}) gave the highest prediction of poor tumour response (AUC = 0.93, $p < 0.001$) with a sensitivity of 88% and a specificity of 91%, and also predicted PFS ($p < 0.01$). Baseline tumour ADC was not significantly related to therapeutic outcome, whereas a positive change in ADC from baseline to after NACT, ΔADC, significantly predicted good tumour response (AUC = 0.83, $p < 0.01$, 83% sensitivity, 73% specificity), but not PFS.

Conclusions: The MRI parameter F/V at baseline was a remarkably strong predictor of both histopathologic tumour response and 5-year PFS in patients with LARC.

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Introduction

Standard of care for locally advanced rectal cancer (LARC) is chemoradiotherapy (CRT) followed by surgical removal of residual tumour component [1]. Multimodal treatment gives excellent local control, but distant metastasis is a remaining challenge and disseminated disease is the major cause of death in LARC [2].

Tumour responses to CRT are highly heterogeneous and current LARC research is therefore focused on individualised treatment approaches. Watch-and-wait (deferred surgery) programs are running for patients who achieve complete or near-complete response to CRT [3]. Other individualised treatment options include induction (neoadjuvant) chemotherapy aimed at targeting distant metastasis in high-risk patients [4]. Further, radiotherapy may be omitted for selected patients who achieve good response to neoadjuvant chemotherapy [4].

Biomarkers predicting and monitoring treatment responses are indispensable for individualising LARC treatment. Predictive markers are essential when choosing between organ-preserving or intensified systemic treatment, and monitoring biomarkers are necessary to assure or adjust the planned treatment course. Magnetic resonance imaging (MRI) is integral in the diagnostic work-up and treatment response monitoring in LARC [2], where T2-weighted (T2W) and diffusion weighted (DW) MRI sequences are used in most examinations. Further use of these techniques, through extraction of quantitative measures, represents an easy and cost-efficient approach to facilitate individualised treatment.

There have been several attempts to use DW MRI with calculation of the quantitative marker apparent diffusion

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coefficient (ADC) for assessing tumour aggressiveness and predicting tumour response to CRT in LARC, but results have been inconsistent [5]. Results from baseline measurements have shown both positive [6] and negative [7] correlation to pathologic tumour response following CRT, as well as no statistically significant association [8].

DW MRI is sensitive to the motion of water molecules, where the signal decreases as the motion increases, and the residual signal reflects various tissue microstructures [9]. There are essentially two sources of motion of water molecules in tissue: diffusion and flow. Diffusion is the random motion in bulk water, in both extracellular as well as intracellular components. The mechanism of diffusion in tissue is not fully understood but is hindered by tissue microstructures, in particular the cell membranes. Therefore, in cancer diagnostics, DW MRI and ADC are often interpreted as an expression of the tumour cellularity. However, the motion of water molecules in blood (flow) is much faster than diffusion and do not reflect the cellularity. The standard mono-exponential method for calculating ADC does not differentiate the DW signal from tissue and blood [10]. The more complex intravoxel incoherent motion (IVIM) model seeks to estimate the perfusion fraction (F) and the tissue diffusion separately [11]. Implementing the full model, however, requires time-consuming measurements with a high number of diffusion weightings, or b-values, which is difficult in clinical routine. In this study, we implemented a simplified approach to the IVIM-model in order to estimate both the F and the ADC from a routine DW MRI acquisition in patients with LARC.

Our study aim was to evaluate the potential of tumour ADC and F, from DWMRI acquired both at baseline and during preoperative chemoradiotherapy, as predictors of therapeutic outcome in patients diagnosed with LARC. Because we previously found that tumour volume calculated from T2W MRI was a strong predictor of histopathological tumour response [12], the results from T2W- and DW MRI were compared to investigate the potential of combining volumetry and DW MRI.

Material and methods

Patients

The prospective phase II trial LARC-Radiation Response Prediction (LARC-RPP) (ClinicalTrials.gov NCT00278694) was approved by the Institutional Review Board and the Regional Committee for Medical and Health Research Ethics South East. The study was performed in accordance with the Helsinki Declaration, and written informed consent was required for participation. Inclusion of patients took place between July 26, 2007 and June 17, 2009 and the last follow-up was censored on August 8, 2013. The primary inclusion criterion was histologically confirmed rectal adenocarcinoma, either T4, T3 with mesorectal fascia margin of 3 mm or less or a tumour of any T stage with lymph node involvement. Diagnostic T and N stages (TNM version 5) were assessed by MRI. The current MRI analysis was performed on 27 of the 113 patients enrolled in the clinical study (Supplementary Figure S1).

Treatment

The experimental preoperative treatment consisted of neoadjuvant chemotherapy (NACT) followed by CRT. NACT was given as two cycles of Nordic FLOX (oxaliplatin 85 mg/m^2 day 1 and bolus 5-fluorouracil 500 mg/m^2 and folinic acid 100 mg days 1 and 2) in week 1 and week 3. In week 5 the patients commenced CRT. Radiotherapy was given in 2 Gy fractions 5 days per week; the initial 23 fractions to the macroscopic tumour volume and areas at risk followed by two final boost fractions adapted to the macroscopic tumour as planned by computed tomography. Concomitant chemotherapy was 50 mg oxaliplatin every week, plus 825 mg capecitabine twice a day on days with radiotherapy. Patients were referred to curatively intended surgery 6–8 weeks after completed CRT. We previously reported that 90% of the patients enrolled in the LARC-RRP study obtained an R0 resection [13]. None of the patients received postoperative adjuvant chemotherapy.

MRI

MRI was obtained before and after NACT (including three 2 Gy fractions of RT). The study included 113 patients, with 79 patients eligible for analysis, (Supplementary Figure S1). The first patients were imaged using an older MRI scanner with insufficient image quality for quantitative DW MRI analysis. Hence, only DW MRI data from the last 27 patients, imaged using a 1.5T Siemens Espree scanner (Siemens, Erlangen, Germany) were of sufficient quality for quantitative calculations. Four of these lacked the follow-up MRI during treatment. All MR examinations were performed according to the standards of the MERCURY study [14]. The imaging parameters for the T2W- and DW sequences are summarised in Supplementary Table S1. For DW MRI, a spin-echo echo-planar-imaging sequence with b-values of 0, 300 and 900 s/mm^2 in three perpendicular directions was used. All images were stored in the institutional picture archiving and communication system.

Tumour delineation

All T2W images were transferred to the Oncentra Masterplan treatment planning system (3.0 SP1; Nucletron, Veenendaal, Netherlands). Tumours (both solid and mucinous) were manually contoured in transversal T2W images by a radiologist with 12 years' experience in pelvic MRI, who was unaware of therapeutic outcomes.

Data analysis

Tumour volumes were calculated by multiplying the contoured area with the slice thickness, adding the slice gap. The contours were transferred to calculated parameter maps for extraction of all pixel values into frequency histograms using MATLAB (R2015b). All parameters were calculated both at baseline (V_{pre}, ADC_{pre}, F_{pre}), and after NACT (V_{NACT}, ADC_{NACT}, F_{NACT}). In addition, the difference between the two

time-points (ΔV, ΔADC, ΔF), were calculated as percentage change from baseline.

To ensure that the quality of the DW MR images was sufficient to perform quantitative calculations, the signal-to-noise-ratio (SNR) was calculated in the images with the highest b-value (b_{900}):

$$\mathrm{SNR} = \frac{\mathrm{mean(signal)}}{\mathrm{std(noise)}}$$

where the mean signal was measured in the central slice of the tumour, and std denotes the standard deviation.

Tumour apparent diffusion coefficient

ADC values were calculated using MATLAB and a mono-exponential equation with the b-values 300 and 900 s/mm^2,

$$\mathrm{ADC} = \frac{1}{b_{900} - b_{300}} \ln \frac{SI_{300}}{SI_{900}}$$

where SI denotes the pixel signal intensity. This was done individually for each of the three DW MRI acquisition directions before averaging.

Tumour perfusion fraction

After calculating the ADC from the b_{300} and b_{900} images, a line back to the *y*-axis (b = 0) was extrapolated asymptotically, as a simplified IVIM-approach, previously described by Wirestam et al. [15]. The discrepancy between this extrapolated signal intensity and the original signal intensity at b_0 was calculated and makes an approximation to the signal decay in the fast decaying phase of the signal. We denoted this as the tumour perfusion fraction, F (Supplementary Figure S2), calculated as

$$F = \frac{SI_0}{SI_{300}} e^{-ADC * b_{300}}$$

Study endpoints

Resected tumour specimens were prepared according to validated protocols [14], and tumour regression grade (TRG) was quantified using the five-point scale proposed by Bouzourene et al. [16]. Patients were defined as either good (TRG1–2) or poor (TRG3–5) responders. Long-term patient outcome was assessed by five-year progression free survival (PFS). PFS was calculated from study enrolment until date of diagnosis of local recurrence, distant metastasis, and death of any cause or end of follow-up.

Statistical analysis

The Mann–Whitney U test was used to compare MR parameters for the good and poor responders. Differences in PFS were assessed using the Kaplan–Meier method and log-rank test, after evaluating the optimal cutoff by receiver operating characteristic (ROC) curve analysis. In ROC analysis, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) was calculated. The optimal cutoff was identified by giving equal weights to sensitivity and specificity (overall accuracy).

To investigate the predictive potential of tumour heterogeneity measures, promising parameters (significant at the 0.05 level), were further analysed with histogram analysis extracting all percentile values from 1 to 100, see Supplementary File 1. Data and statistical analysis were performed in MATLAB and SPSS (IBM SPSS Statistics 22). *p* Values <0.05 were considered statistically significant.

Table 1. Mean tumour values for the different MRI parameters quantified for good responders (TRG1–2) and poor responders (TRG3–5) to neoadjuvant chemotherapy (NACT) followed by chemoradiotherapy (CRT), with associated *p* values obtained from the Mann–Whitney *U* test.

Parameter	Good responder (TRG1–2)	Poor responder (TRG3–5)	*p* Value[a]
ADC_{pre} ($\times 10^{-4}$ mm^2/s)	74.1 ± 22.7	61.0 ± 12.6	>0.1
ADC_{NACT} ($\times 10^{-4}$ mm^2/s)	65.1 ± 35.6	69.3 ± 15.4	>0.1
ΔADC (%)	−15.7 ± 25.3	14.9 ± 23.4	<0.01*
F_{pre} (a.u.)	25.4 ± 16.9	12.6 ± 4.1	0.01*
F_{NACT} (a.u.)	23.0 ± 14.3	15.6 ± 3.9	>0.1
ΔF (%)	41.7 ± 168.8	39.6 ± 67.1	>0.1
V_{pre} (cm^3)	17.1 ± 21.6	43.5 ± 31.1	<0.01*
V_{NACT} (cm^3)	7.1 ± 11.3	24.9 ± 19.8	0.02*
ΔV (%)	−70.3 ± 13.5	−42.6 ± 35.3	0.06
F_{pre}/V_{pre}	3.5 ± 4.3	0.51 ± 0.6	<0.001*
F_{NACT}/V_{NACT}	11.4 ± 11.8	3.7 ± 9.4	<0.01*
Δ(F/V)	26.4 ± 14.9	51.7 ± 36.5	>0.1

[a]Parameters with significant difference between good and poor responders are marked with *.

Results

Of the27 patients, 16 were defined as good responders (TRG1–2) and 11 as poor responders (TRG3–5). Long-term patient outcome data showed that 9 of the patients had PFS events (all metastatic disease) and 18 patients had no PFS event. In the subgroup of 23 patients with MRI after NACT, 12 were defined as good responders and 11 as poor responders. The 9 patients with PFS events were also in this cohort, accordingly 14 patients were without PFS event.

Tumour apparent diffusion coefficient

The mean SNR of the b_{900} images for all tumours at baseline was 21.4 ± 4.0. The absolute tumour ADC_{pre} and ADC_{NACT} were not significantly associated with TRG (Table 1), but the change, ΔADC, was. ROC-curve analysis showed that ΔADC differentiated good and poor responders with 83% sensitivity and 73% specificity (AUC = 0.83, $p < 0.01$, confidence interval (CI) = 0.67–1.00), PPV of 85% and NPV of 80%, at the optimal cutoff of 4%. Hence, an increase in ADC after NACT was associated with poor tumour response to CRT, complementary; a decrease in ADC was associated with good tumour response. Percentile analysis showed that this association was stronger for the lower percentiles of ΔADC (Supplementary Figure S3). Tumour ADC did not predict PFS at any time-point.

Tumour perfusion fraction

Baseline perfusion fraction, F_{pre}, was significantly associated with tumour response to CRT, with a high F associated with

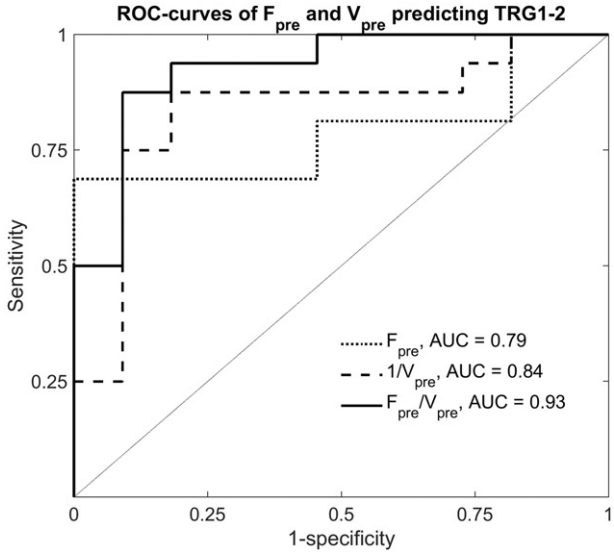

Figure 1. Receiver operating characteristic (ROC) curves for baseline tumour perfusion fraction (F_{pre}), tumour volume (V_{pre}), as well as the combined parameter F_{pre}/V_{pre} for prediction of TRG1–2, i.e., good responders to neoadjuvant chemotherapy (NACT) followed by chemoradiotherapy (CRT). Area under curve (AUC) for the different parameters is indicated.

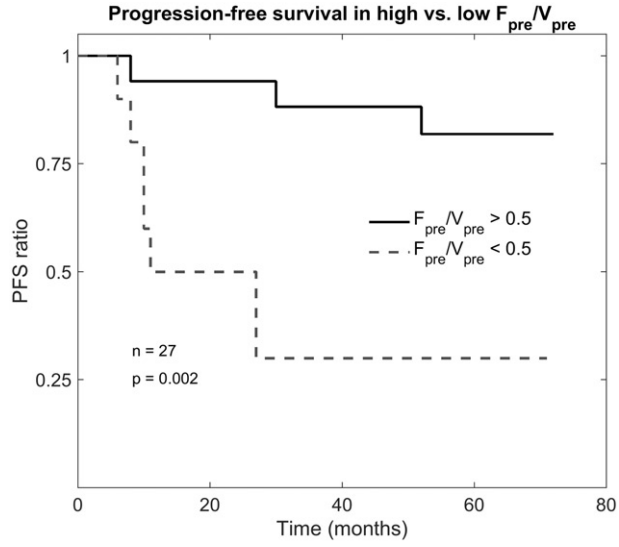

Figure 2. Differences in 5-year progression-free survival (PFS) for patients with baseline tumour perfusion fraction (F_{pre}) divided by baseline tumour volume (V_{pre}), i.e., F_{pre}/V_{pre}, above and below 0.5, respectively. The number of patients and *p* values are indicated.

good response (Table 1). Figure 1 shows the ROC-curve for mean tumour F_{pre} predicting TRG1–2 (AUC = 0.79, $p = 0.01$, CI = 0.61–0.97), with a sensitivity of 69%, specificity of 100%, PPV = 100% and NPV = 69%. Percentile analysis did not further contribute to these results. Tumour F_{pre} did not predict PFS at any time-point.

Tumour volume

There was also an association between tumour volume and response to CRT (Table 1). Figure 1 shows the ROC-curve for tumour volume predicting TRG1–2 (AUC = 0.84, $p < 0.01$, CI = 0.67–1.00), with a sensitivity of 75%, specificity of 91%, PPV = 88%, NPV = 82%. V_{pre} was also associated to PFS ($p = 0.03$) with a cutoff at 13.7 cm^3. This resulted in estimated 5-year survival of 83% versus 47% for patients with tumour volumes below and above 13.7 cm^3, respectively.

Perfusion fraction combined with volume

The combination of F_{pre} with V_{pre} into F_{pre}/V_{pre} gave the most significant prediction of TRG1–2 (AUC = 0.93, $p < 0.001$, CI = 0.82–1.00) with a sensitivity of 88%, specificity of 91%, PPV = 93% and NPV = 83% (Figure 1). This combination also gave a significant prediction of PFS. When separating patients above and below the optimal cutoff of 0.5, the respective estimated 5-year PFS were 82% and 30% ($p < 0.01$) (Figure 2).

Discussion

In this study, we found that the tumour perfusion fraction, F_{pre}, estimated from DW MRI, significantly predicted histopathological tumour response to NACT and CRT in LARC. Combined with tumour volume the association was highly significant and also predicted 5-year PFS.

High F_{pre} was favourable for obtaining good tumour response. Although F is a parameter derived from DW MRI, it reflects water molecule movement due to flow, not diffusion [11]. Hence, a high F indicates tissue with good vascularisation, and a low F indicates poorly vascularised tissue. In rectal cancer, F has been shown to correlate with the vascular area fraction measured by CD31 staining [17]. A low F may also reflect tumour hypoxia, a known cause of therapy resistance [18]. Previously, high F from IVIM has been linked to pathologic complete response (pCR) in locally advanced breast cancer [19]. A very recent study in rectal cancer found no differences in F between pCR and non-pCR [20]. However, this study categorised near-complete responders (near-pCR) along with poor responders. Because current imaging techniques cannot differentiate between pCR and near-pCR [21], the difference between the groups may have been lost. Furthermore, Zhu et al. used a more complex model for calculation of F, and in their discussion they also concluded that the model was unsuitable for tumour assessment due to noise.

To assess perfusion-related parameters with MRI, it is generally more common to use dynamic contrast-enhanced (DCE) MRI. Tong et al. have recently shown that the perfusion-related parameter K^{trans} from DCE MRI, was associated with favourable treatment [22], supporting that well-vascularised tumours respond well to treatment.

We found that a decrease in ADC was associated with a favourable response. This differs from previous studies that have found increased tumour ADC during first [23], second [6, 8] and third [24] week of concomitant CRT in patients with favourable response. Low tumour ADC generally reflects high cellularity; therefore, ADC is expected to increase during cytotoxic treatment. We measured ΔADC after a systemic induction treatment of two 2-week cycles of NACT, which caused extensive tumour shrinkage [25]. At the time of ADC

measurement, most of the tumour cells were probably already replaced by ingrowth of fibrosis. Thus, the measured ADC no longer reflects tumour cell density, but the tissue composition following treatment-induced changes. Fibrotic tissue generally has low ADC. Hence, the early tumour shrinkage after NACT may explain why we found decreased ΔADC in good responders.

The main limitations of our study are the low number of patients and the use of experimental NACT before CRT, and also three b-values for estimation of the tumour perfusion fraction may be an oversimplification. Since the study was initiated in 2005, the quality of the DW MR images may be lower than current standards, and a low SNR at $b = 900\,s/mm^2$ might have led to underestimation of ADC and overestimation of F. However, our SNR of 21.4 should be sufficient for quantitative calculations. And further, even if F would be overestimated, our findings support that there exists a cutoff value that discriminate good and poor responders. However, further investigations in other, independent cohorts are required. The main strengths of our study are experienced investigators in all disciplines, balanced response groups, and long-term follow-up with PFS as a highly relevant clinical endpoint.

In conclusion, the MRI parameter F/V at baseline was a remarkably strong predictor of both histopathologic tumour response and 5-year PFS for LARC patients. However, the study population was small and the study treatment was experimental. If our results can be confirmed in larger studies with standard treatment, F/V may prove to be a useful clinical tool for individualised treatment planning.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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