Diffusion MRI for prediction of response of rectal cancer to chemoradiation

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Prediction of tumour response before onset of treatment could have considerable clinical benefit. Since the apparent diffusion coefficient (ADC) of a tumour’s water content can show the extent of necrosis, we looked for a possible correlation of ADC with response to treatment. We measured mean tumour water ADC before and after chemotherapy and chemoradiation in 14 patients with locally advanced rectal cancer, with a quantitative magnetic resonance diffusion imaging sequence. We found a strong negative correlation between mean pretreatment tumour water ADC and percentage size change of tumours after chemotherapy ($r=-0.67$, $p=0.01$) and chemoradiation ($r=-0.83$, $p=0.001$). Persistence of low ADC in responders after chemotherapy could represent loss of a non-viable fraction of the treated tumour.

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A tumour’s response to treatment cannot be reliably predicted, and such a capacity might be of considerable clinical benefit. Diffusion-weighted magnetic resonance studies have shown the potential for assessment of early response in animal and human tumours.1 In quantitative diffusion-weighted imaging, the magnetic resonance signal arises from both intracellular and extracellular compartments, and the result is given in terms of the apparent diffusion coefficient (ADC), which is a weighted sum of these contributions. The ADC is a measure of restrictions to diffusion of molecules by structures such as cell membranes, allowing inferences to be made about microstructure of the cellular environment. Our aim was to establish whether there is an association between an in-vivo magnetic resonance-based measure of tumour water ADC and response of clinically advanced rectal adenocarcinoma to neoadjuvant chemoradiation.

We studied 14 patients (ten male, four female) with a mean age of 65 years (SD 11·2) with clinically advanced rectal adenocarcinoma without metastatic disease who were recruited at diagnosis from local surgical clinics. We did magnetic-resonance studies with a 1·5 T Magneton-Vision system (Siemens, Erlangen, Germany) and a four-element body phased-array coil, before and after chemotherapy and chemoradiation. We obtained axial T2-weighted images through the tumours for assessment, staging, and positioning of the single slice for subsequent proton-diffusion imaging. We used the burst diffusion imaging sequence; this sequence and assessment of ADC in vivo have been described.2

We calculated water ADC values on a pixel-by-pixel basis by fitting a linear regression function to pixel intensities of 16 images acquired with increasing diffusion weightings (0–345 s/mm2). T2-related signal loss was corrected for by use of T2 values generated by a standard multiple spin-echo T2 mapping sequence. We outlined the tumour on the resulting diffusion map. We established tumour size by consensus, as the product of the maximum cranio-caudal and transverse diameters.

We classified response to treatment in accordance with WHO criteria.3 Responders (n=7) were grouped as individuals showing a greater than 50% decrease in tumour size, and all others were termed non-responders (7). Details of treatment protocol are given elsewhere.4 We obtained ethics permission for the study, and all patients gave written consent.

We used the Shapiro-Wilk test to test the hypothesis that a given sample was from a normal population. Pearson’s correlation test was used to measure the linear association between two variables. We used a non-parametric test to assess significance between groups. We used the Mann-Whitney U test to measure the differences between mean ADC of responders and non-responders before and after chemoradiation and chemotherapy.

Figure 1: Correlation between mean tumour ADC before treatment and change in tumour size after end of chemotherapy (A) and chemoradiation (B)

Error bars indicate SEM.
We recorded a negative correlation between mean pretreatment ADC and tumour regression after chemotherapy ($r=-0.67, p=0.01$) and after chemoradiation ($r=-0.83, p=0.001$; figure 1). Mean percentage reduction in tumour size after chemotherapy was 32% (SD 26), and at the end of chemoradiation it was 40% (32). At presentation, mean tumoral ADC was $1.41 \times 10^{-5}$ cm$^2$/s (SD 0.41).

Behaviour of mean tumoral ADC of responders and non-responders during the course of treatment is shown in figure 2. The ADC of responders fell after chemotherapy and rose after chemoradiation. Non-responders maintained a high ADC throughout treatment. A significant difference between mean ADC of responders and non-responders was shown before ($p=0.03$) and after chemotherapy ($p=0.03$), but not after the end of chemoradiation ($p=0.20$).

We showed that mean pretreatment tumour water ADC is correlated with the degree of tumour response after chemotherapy and chemoradiation. Furthermore, responders seemed to have a lower ADC at presentation than non-responders. Lemaire and colleagues showed that an initially low ADC predicted tumour sensitivity to fluorouracil in female Wistar rats. In Lemaire’s study, high tumour ADC was correlated with a high necrotic fraction, mainly because of increased extracellular water. We therefore postulate that mean tumour ADC acts as a surrogate marker of tumour necrosis. The association we noted between high tumour ADC and poor response therefore accords with the known relation between necrosis and poor response to treatment in cancer.

A rise in ADC after the start of treatment has been reported to show an early response to treatment. Our findings show the opposite. Although we only studied 14 patients, the morphology of their rectal tumours might account for this drop in the ADC in responders after chemotherapy. A lower residual necrotic fraction might be expected if a necrotic luminal component sloughed off as a result of treatment. The remaining tumour would have a proportionately greater viable cell fraction and therefore a lower ADC. The subsequent rise in ADC of responders after chemoradiation might indicate radiation-induced inflammation.

Technical difficulties affecting measurements should be considered. Motion can affect ADC measurements, and the burst sequence we used does not compensate for motion or flow. However, we recorded no evidence of gross motion of patients on the basis of imaging sequences done either side of the diffusion study. Advantages of the burst sequence in freedom from susceptibility artifacts must be weighed against its long acquisition time, low signal-to-noise capacity, and absence of specificity in obtaining ADC values for lipids. Improved accuracy in ADC measurements is being investigated with alternative sequences. Finally, observer variation might have affected measures of tumour size and outline.

Our findings suggest that diffusion-weighted magnetic imaging could yield clinically important information for the prediction of rectal cancer prognosis. The approach needs validation and a prospective study of reproducibility to establish its clinical benefit in the management of patients with clinically advanced rectal cancer.

**Contributors**

A Dzik-Jurasz and M George had the idea for and initiated the study, and analysed data. A Dzik-Jurasz interpreted findings and wrote the report. M George recruited patients. C Domenig analysed data and, with J Wolber, tested the magnetic resonance sequence. S Doran suggested using the burst sequence to measure diffusion and oversaw technical aspects of the study. G Brown and A Padhani measured changes in tumour size with conventional MRI.

**Conflict of interest statement**

None declared.

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**References**


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