Pathological correlation with diffusion restriction on diffusion-weighted imaging in patients with pathological complete response after neoadjuvant chemoradiation therapy for locally advanced rectal cancer: preliminary results

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Objective: The objective of this study was to assess causative pathological factors associated with diffusion restriction on diffusion-weighted imaging (DWI) in patients who achieved pathological complete response (pCR) after treatment with neoadjuvant chemoradiation therapy (CRT) for locally advanced rectal cancer.

Methods: In total, 43 patients with locally advanced rectal cancer ($\geq T3$ or lymph node positive) who underwent neoadjuvant CRT, subsequent surgery and ultimately achieved pCR were enrolled. All patients underwent pre- and post-CRT 3.0 T rectal MRI with DWI. Two radiologists blinded to pathological staging reviewed pre- and post-CRT 3.0T rectal MRI for the presence of diffusion restriction in the corresponding tumour areas on post-CRT DWI, with a third radiologist arbitrating any disagreement. The consensus of these findings was then correlated with pathological data such as intramural mucin and the degree of proctitis and mural fibrosis seen on surgical specimen. Additionally, the pre-CRT tumour volume was measured to define the effect of this variable on the degree of radiation proctitis and fibrosis, as well as the presence of intramural mucin.

Results: Diffusion restriction occurred in 18 subjects (41.9%), while 25 subjects remained diffusion restriction-free (58.1%). The diffusion restriction group tended to have more severe proctitis and mural fibrosis when compared with non-diffusion restriction group ($p < 0.001$). Intramural mucin was also more common in the diffusion restriction group ($p = 0.052$). Higher pre-CRT tumour volumes were significantly predictive of the degree of proctitis ($p = 0.0247$) and fibrosis ($p = 0.0445$), but not the presence of intramural mucin ($p = 0.0944$). Proctitis and mural fibrosis severity were also identified as independent pathological risk factors for diffusion restriction on multivariate analysis ($p = 0.0073$ and 0.0011 , respectively).

Conclusion: Both radiation-induced proctitis and fibrosis were significant and independent predictors of diffusion restriction in patients achieving pCR after treatment with neoadjuvant CRT for locally advanced rectal cancer, and pre-CRT tumour volume significantly affects both variables.

Received 27 June 2011
Revised 16 August 2011
Accepted 14 September 2011

DOI: 10.1259/bjr/24557556

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Currently, surgery following neoadjuvant chemoradiation therapy (CRT) is considered the gold standard for the treatment of locally advanced rectal cancer, with pathological complete response (pCR) and partial response rates to neoadjuvant CRT approaching 25% and 60%, respectively [1–5]. These outcomes allow for improved resectability, better local control, decreased overall recurrence rates and longer disease-free survival [1–5].

The use of non-invasive MRI for the preoperative prediction of pCR and the post-CRT identification of

viable rectal cancer tumours is critical in the planning of the optimal therapeutic approach for each patient. Specifically, this modality is particularly beneficial to complete responders, who benefit from less extensive resections—such as sphincter-saving approaches in the case of deep-seated tumours—or less aggressive resections in initially advanced tumours [4]. However, the reliable differentiation of active tumour tissue from radiation-induced fibrosis using conventional MRI remains challenging [6–8].

Recently, data from several clinical studies have indicated that diffusion-weighted imaging (DWI) has better sensitivity (82–91%) and diagnostic accuracy (82–85%) in predicting the pCR among patients with locally advanced rectal cancer treated with neoadjuvant CRT when compared with conventional MRI [9, 10].

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However, these results also suggest that the misdiagnosis of pCR status post neoadjuvant CRT still occurs in these patients [10]. To the best of our knowledge, the causes of diffusion restriction on DWI have never been described among patients with locally advanced rectal cancer who achieved pCR after neoadjuvant CRT.

Accordingly, this study attempts to assess the causative pathological factors responsible for diffusion restriction on DWI in patients with locally advanced rectal cancer who achieved pCR after neoadjuvant CRT.

Methods and materials

Patients

Institutional review board approval was obtained, and written informed consent was waived because of the retrospective nature of the analysis. We enrolled 253 consecutive patients in the present study between October 2008 and October 2010. All subjects met the following criteria: (1) histopathologically proven locally advanced rectal cancer ($\geq T3$ or positive regional lymph nodes at the time of initial MRI); (2) neoadjuvant CRT; (3) pre- and post-CRT 3.0 T rectal MRI with DWI; and (4) post-CRT surgical resection of the tumours. Of the 253 subjects enrolled, 43 (17%) were found to have achieved pCR on surgical specimen obtained by either low anterior resection ($n=41$) or abdominoperineal excision of rectum ($n=2$), with a mean interval time of 60.0 ± 10.9 days (range: 43–101 days) from final CRT treatment to surgery. When stratified by gender, these individuals comprised 15 women and 28 men (age range: 32–85 years; mean age: 55 years).

Neoadjuvant chemoradiation therapy

All patients underwent normofractionated pelvic radiation 5 days per week for 5 weeks, with a total dose of 45 Gy and a daily fraction of 1.8 Gy. Additionally, chemotherapy was administered concurrently with the radiotherapy on an outpatient basis, which consisted of bolus infusions of 5-fluorouracil (500 mg m^{-2}) on days 1–3 and 23–25.

Standard of reference and histopathological examination

A gastrointestinal pathologist (with 10 years of clinical experience) who was unaware of all imaging findings retrospectively reviewed the haematoxylin and eosin (H&E)-stained slides for all 43 subjects, with all specimens obtained by surgical bowel resection. The pathological findings were assessed using the following parameters: the maximum mural thickness of the corresponding lesion, the presence of intramural mucin, and the degree of inflammation and mural fibrosis. The degree of inflammation was graded as follows: none, absent or sparse inflammatory cells; mild, occasional inflammatory cells in the mucosa; moderate, prominent aggregates of inflammatory cells in the mucosa and submucosa; and severe, compact inflammatory cell

aggregates from the mucosa to the proper muscle. Additionally, the degree of mural fibrosis was graded as follows: none, the total absence of fibrosis; mild, mucosal fibrosis; moderate, mucosal and submucosal fibrosis; and severe, fibrosis involving the tissue from the mucosa to the proper muscle with comorbid muscle fiber dissection.

MRI examination

A 3.0 T whole-body system (Intera Achieva 3 T; Philips Medical Systems, Best, Netherlands) and a dedicated cardiac sensitivity-encoding (SENSE) coil (16 channel) were used for this study. To reduce colonic motility, 20 mg of scopolamine butylbromide (Buscopan; Boehringer Ingelheim, Ingelheim, Germany) was injected intramuscularly 30 min prior to MRI. All patients were asked to undergo rectal cleansing by rectal suppository 2 to 3 h prior to MRI examination. In the MRI room, ultrasound transmission gel was applied using a balloon-tipped rectal tube, so that the rectum was filled until the patient reported a sensation of rectal fullness [11]. The rectal tube was then removed after rectal ultrasound transmission gel instillation.

Initially, sagittal localising images were obtained to facilitate axial and coronal image selection using a T_2 weighted turbo-spin echo sequence (repetition time/echo time, TR/TE: 2500–5000/100 ms; echo train length: 6; slice thickness: 3 mm; gap: 1 mm; matrix: 256×256 ; field of view: 36 cm; signals acquired: 2; SENSE factor: 2; sequence duration: 3–5 min). The oblique axial and coronal T_2 weighted turbo-spin echo images (TR/TE: 2500–5000/100 ms; echo train length: 6; slice thickness: 3 mm; gap: 3 mm; matrix: 312×312 ; field of view: 36 cm; signals acquired: 4; SENSE factor: 2; sequence duration: 3–4 min) were obtained orthogonally and parallel to the long axis of the rectal cancer. Finally, an axial T_1 weighted turbo-field echo sequence (TR/TE: 656/10 ms; echo train length: 5; slice thickness: 3 mm; gap: 1 mm; signals acquired: 4; matrix: 256×256 ; field of view: 36 cm; sequence duration: 4–5 min) was acquired. All sequences were obtained without fat saturation.

Immediately after conventional rectal MRI was performed, diffusion-weighted MRI images were obtained in an oblique axial plane using the single-shot echo planar imaging technique with the following scan parameters: TR/TE: 2800/70 ms; slice thickness: 3 mm; interslice gap: 1 mm; matrix: $104/100$; field of view: 36 cm; SENSE factor: 4; and number of signal acquired: 2. Diffusion-encoding gradients were applied as bipolar pairs along the three orthogonal directions of the motion-probing gradients at b -values of 0, 100 and 1000 s mm^{-2} . Apparent diffusion coefficient (ADC) maps were also automatically constructed on a pixel-by-pixel basis (0 and 1000 s mm^{-2}), with all DWI acquisition times $<110 \text{ s}$.

Imaging analysis

After reviewing the pre- and post-CRT rectal MRI with DWI for each of the subjects, two gastrointestinal radiologists (with 3 and 7 years of clinical experience in interpreting rectal MRI) who were blinded to all surgical

and pathological results assessed the presence (diffusion restriction group) or absence (no diffusion restriction group) of diffusion restriction at corresponding tumour on post-CRT MRI. Here, diffusion restriction was defined as the presence of high signal intensity on DWI (b -value, 1000 s mm^{-2}) and low signal intensity on the ADC map in the corresponding tumour compared with that of normal rectal wall (Figures 1 and 2). In cases of disagreement between the two reviewers, a third radiologist (with 10 years of clinical experience in interpreting rectal MRI) reviewed and interpreted the disputed MRI images, breaking the tie.

For quantitative analysis, the third radiologist assessed the ADC values in the corresponding tumour on post-CRT ADC map in correlation with pre- and post-CRT T_2 weighted images. A circular or ovoid region of interest (ROI) with an area of at least 4 mm^2 (larger than 2 mm in minimum diameter) was placed within the three portions of the tumour to obtain average ADC values. The interval time between chemoradiation and post-CRT MRI, and between post-CRT MRI and surgery in each patient was recorded because tumour regression is progressed after CRT, and those interval times could have an effect on signal intensity of tumour on DWI [5]. Pre-CRT tumour volumes were also measured on the assumption that pre-CRT tumour volume could be an

important determining factor of the extent of radiation proctitis and fibrosis, and/or intramural mucin. During all pre-CRT MRI studies, cross-sectional tumour area was measured on axial T_2 weighted images by manually tracing the lesion boundaries of the ROI. Lesion volumes were displayed automatically in a three-dimensional format and calculated by adding the individual cross-sectional lesion volumes (derived by multiplying the cross-sectional lesion area by the section thickness) for the entire lesion using the Advantage Workstation, v. 4.4 (General Electric Medical Systems, New York, NY).

Statistical analysis

All statistical analyses were performed using statistical software (SAS 9.1; SAS Institute, Cary, NC). In quantitative comparisons between the diffusion restriction and non-diffusion restriction groups, the Mann-Whitney U -test was used for the following variables: pre-CRT tumour volume, interval time from final CRT treatment and post-CRT MRI, interval time from post-CRT MRI and surgery, ADC values and maximum mural thickness of the corresponding tumour. Conversely, Fisher's exact test was used for qualitative intergroup analyses of the

Figure 1. 39-year-old male with pathologically proven middle rectal cancer (ypT0N0, pathological complete response). The pre-chemoradiation therapy (CRT) tumour volume was 21.6 cm^3 . (a) Pre-CRT T_2 weighted axial MRI shows an ulceroinfiltrative mass with perirectal fat infiltration between the 3 and 12 o'clock positions (arrow). An enlarged perirectal lymph node is also present (arrowhead). (b) Post-CRT T_2 weighted axial MRI shows a decrease in tumour size (arrow) and a perirectal lymph node (arrowhead). (c) Post-CRT axial diffusion-weighted MRI (b -value, 1000 s mm^{-2}) shows residual hyperintense signal in the corresponding tumour (arrow) and perirectal lymph node (arrowhead). (d) Post-CRT apparent diffusion coefficient (ADC) mapping shows residual hypointense signal with ADC_{1000} value of $0.85 \times 10^{-3}\text{ mm}^2\text{ s}^{-1}$ in the corresponding tumour (arrow). (e) On histopathological photomicrography, there are thickened eosinophilic submucosa (asterisks) and dissecting fibrosis (thin arrows), and inflammation involving mucosa to proper muscle (thick arrows; haematoxylin and eosin stain, $\times 40$).

Figure 2. 66-year-old female with pathologically proven distal rectal cancer (ypT0N0, pathological complete response). The pre-chemoradiation therapy (CRT) tumour volume was 1.9 cm^3 . (a) Pre-CRT T_2 weighted axial MRI shows a focal irregular wall thickening (arrow) between the 1 and 3 o'clock positions. (b) Post-CRT T_2 weighted axial MRI shows no wall thickening, with only a diffuse hypointense wall (arrow) noted between the 1 and 2 o'clock positions. (c) Post-CRT axial diffusion-weighted MRI (b -value, 1000 s mm^{-2}) shows no residual hyperintense signal in the corresponding tumour (arrow), in comparison with normal rectal wall (white arrow). (d) Post-CRT apparent diffusion coefficient (ADC) mapping shows no residual hypointense signal with ADC_{1000} value of $1.37 \times 10^{-3}\text{ mm}^2\text{ s}^{-1}$ in the corresponding tumour (arrow). On pathology, there is neither remarkable fibrosis nor inflammation.

following variables: the presence of intramural mucin, the degree of proctitis and the degree of mural fibrosis. To define the effect of pre-CRT tumour volume on the resulting proctitis, mural fibrosis and intramural mucin, an ordinal logistic regression analysis was performed. A multivariate analysis using a logistic regression model was also used to identify independent pathological factors associated with diffusion restriction in patients who achieved pCR after neoadjuvant CRT for locally advanced rectal cancer. In all cases, p -values <0.05 were defined as statistically significant differences for all statistical comparisons.

Results

Out of the 43 cases in which pCR was achieved, 18 (41.9%) developed diffusion restriction, while the remaining 25 cases (58.1%) were placed into the non-diffusion restriction group. When compared, no statistically significant differences between groups were identified in the following variables: mean interval times from final

CRT treatment to post-CRT MRI (42.5 ± 6.7 days *vs* 46.0 ± 11.6 days; $p=0.276$), and from post-CRT MRI to surgery (14.5 ± 2.8 days *vs* 15.7 ± 7.9 days; $p=0.700$). The ADC values were significantly different between the diffusion restriction group (range: $0.56\text{--}1.25 \times 10^{-3}\text{ mm}^2\text{ s}^{-1}$; mean: $1.01 \pm 0.19 \times 10^{-3}\text{ mm}^2\text{ s}^{-1}$) and non-diffusion restriction group (range: $0.82\text{--}1.80 \times 10^{-3}\text{ mm}^2\text{ s}^{-1}$; mean: $1.26 \pm 0.29 \times 10^{-3}\text{ mm}^2\text{ s}^{-1}$; $p=0.019$).

Table 1 summarises the results pertaining to the pre-CRT tumour volume and other pathological data for the two groups. The mean pre-CRT tumour volume in the diffusion restriction group (Figure 1) was significantly larger than in the non-diffusion restriction group ($p<0.001$; Figure 2). Statistically significant differences in the degree of proctitis and mural fibrosis also occurred between the two groups ($p<0.001$): the majority of individuals in the diffusion restriction group developed moderate to severe proctitis (15 of 18, 84%) and mural fibrosis (14 of 18, 78%), while most subjects in the non-diffusion restriction group demonstrated either none or only mild proctitis (18 of 25, 72%) or mural fibrosis (23 of 25, 92%). Although intramural mucin was more common

Table 1. Comparison of demographic characteristics between the complete response groups with or without diffusion restriction

Variables	Diffusion restriction group (n=18)	Non-diffusion restriction group (n=25)	p-value
<i>Continuous variables (mean $\pm$ SD)</i>			
Pre-CRT tumour volume	14.7 $\pm$ 6.8 cm ³	6.3 $\pm$ 5.4 cm ³	<0.001
Maximum mural thickness on pathology	6.7 $\pm$ 2.2 mm	5.5 $\pm$ 1.5 mm	0.100
<i>Categorical variables</i>			
Proctitis			<0.001
No	0 (0)	3 (12)	
Mild	3 (16)	15 (60)	
Moderate	5 (28)	7 (28)	
Severe	10 (56)	0 (0)	
Mural fibrosis			<0.001
No	2 (11)	9 (36)	
Mild	2 (11)	14 (56)	
Moderate	1 (6)	0 (0)	
Severe	13 (72)	2 (8)	
Intramural mucin			0.052
No	12 (67)	23 (92)	
Yes	6 (33)	2 (8)	

CRT, chemoradiation therapy; SD, standard deviation.

Data in parentheses are percentages.

Diffusion restriction is defined as the presence of high signal intensity on DWI (b -value, 1000 s mm⁻²) and low signal intensity on the afferent diffusion coefficient map in the corresponding tumour compared with the normal rectal wall.

in the diffusion restriction group (6 of 18, 33%) than in the non-diffusion restriction group (2 of 25, 8%), this difference did not reach statistical significance ($p=0.052$). While higher pre-CRT tumour volumes correlated significantly with higher degrees of proctitis ($p=0.0247$) and fibrosis ($p=0.0445$), such a relationship did not occur with the presence of intramural mucin ($p=0.0944$). Similarly, the maximum mural thickness of the corresponding tumour did not vary significantly between the diffusion restriction and non-diffusion restriction groups. In multivariate analysis, both proctitis [odds ratio (OR): 0.074; 95% confidence interval (CI): 0.011, 0.495; $p=0.0073$] and mural fibrosis (OR: 0.032; 95% CI: 0.004, 0.254; $p=0.0011$) severity were identified as independent factors associated with diffusion restriction.

Discussion

In patients treated with neoadjuvant CRT for locally advanced rectal cancer, long course radiotherapy (45–50.4 Gy in 25–28 fractions) often provokes florid inflammation and fibrosis, resulting in considerable difficulties in reliably differentiating active tumour from post-treatment fibrosis on conventional MRI [6–8]. Recent data from Kim et al [10] indicate that the diagnostic accuracy in evaluating CR significantly increases when DWI is performed concurrently with conventional MRI. However, as our results demonstrate, diffuse restriction in the corresponding tumour frequently occurs with DWI in patients who achieved pCR after treatment with neoadjuvant CRT for locally advanced rectal cancer (18 of 43, 41.9%).

DWI derives its image contrast on the basis of differences in the molecular diffusion, which is the thermally induced Brownian motion of water molecules. The apparent diffusion of water protons can be restricted by highly cellular tissue (e.g. tumour tissues), intracellular

oedema, increased viscosity, tortuous extracellular space (e.g. fibrosis with or without granulation tissue) and increased densities associated with hydrophobic cellular membranes [12]. Consequently, in patients treated with neoadjuvant CRT for locally advanced rectal cancer, tumour regression, as well as benign iatrogenic processes such as proctitis and fibrosis, may result in diffusion restriction during the imaging of the corresponding tumour.

In their recent report, Kim et al suggest that several factors limit the capacity of DWI to evaluate tumour response in patients with locally advanced rectal cancer status post neoadjuvant CRT: inactive mucin pools, microscopic residual tumour cell nests and the low spatial resolution of DWI with high b -values of 1000 mm² s⁻¹ [10]. Our results indicate that the severity of proctitis and fibrosis both represent significant pathological factors causing diffusion restriction in patients who achieved pCR after treatment with neoadjuvant chemotherapy for locally advanced rectal cancer ($p<0.001$) and quantitatively, the mean ADC value ($1.01 \pm 0.19 \times 10^{-3}$ mm² s⁻¹) of the diffusion restriction group was significantly lower than that ($1.26 \pm 0.29 \times 10^{-3}$ mm² s⁻¹) of non-diffusion restriction group. In addition, pre-CRT tumour volume was significantly correlated with the severity of both proctitis and fibrosis ($p=0.0247$ and $p=0.0445$, respectively). As the pre-CRT tumour volume goes up, the extent of tumour necrosis should be increased to achieve pCR, which might aggravate inflammation and fibrosis. The presence of intramural mucin was not a significant pathological risk factor for diffusion restriction ($p<0.052$) among these patients. The results presented here are consistent with several previous reports [13–15]. Specifically, data from Woodhams et al suggest that mucinous carcinomas were associated with significantly higher mean ADCs than benign lesions and other malignant tumours [13]. This study also demonstrates that while low DWI signal intensity often

represents mucin-rich compartments with low cellularity, high DWI signal intensity can indicate compartments with high cellularity or fibrous stroma. Notably, the diagnostic role of DWI in fibrosis has also been studied in patients with liver fibrosis. In one such study, Taouli et al [14] found that the ADC values for patients with moderate to advanced liver cirrhosis were significantly lower among individuals with relatively less severe liver cirrhosis. Similarly, Oto et al [15] found that DWI could be used to detect bowel inflammation in patients with Crohn's disease, where the ADC values were significantly lower in inflamed bowel segments than in comparable unaffected regions. Moreover, in a study by Wolff et al [16], pCR has been significantly associated with neoadjuvant CRT that results in acute high-grade organ toxicity, such as proctitis and enteritis, with the authors proposing that both tumour and normal tissue probably behave similarly in response to treatment. Such changes in benign non-cancerous tissue and malignant tissue before and after radiotherapy has been further described in a recent prostate cancer study [17]. In this study, ADC values for the peripheral and transition zones significantly decreased in benign non-cancerous tissue after radiotherapy. Additionally, while the ADC values varied significantly between the tumours and benign tissue before treatment, no such difference was observed after radiotherapy, suggesting that the histological changes induced by radiation, such as acinar distortion and atrophy, stromal fibrosis with granulation tissue formation and decreases in extracellular space secondary to inflammatory cellular oedema, may result in decreased ADC values.

Here, no significant differences were observed between the diffusion restriction and non-diffusion restriction groups in the mean interval times from final CRT treatment to post-CRT MRI ($p=0.276$) or post-CRT MRI to surgery ($p=0.700$). Hence, the timing of the post-CRT MRI might not affect the degree of proctitis seen on DWI. Also, while longer intervals between radiotherapy and surgery may help abate the amount of proctitis present on imaging, the potential effects of residual tumour growth and development of radiation-induced fibrosis progression during this time period must be considered [18]. In patients with longer courses of radiotherapy (45–50.4 Gy), CRT to surgery intervals of 4 to 8 weeks are accepted as standard practice in many centres [18]. As such, we contend that highly sophisticated and prospective studies that precisely correlate MRI with histopathological findings are necessary to discriminate the diffusion restriction associated with active tumour tissue from benign non-cancerous tissue reflected on post-CRT MRI in patients with locally advanced rectal cancer after treatment with neoadjuvant CRT.

The current study has several identifiable limitations. First, the retrospective nature of the study design inherently limits the precision of matching the MRI with the histopathological findings, despite the use of standardised histological examination procedures and detailed pathology reviews by experienced pathologists. Second, given the retrospective nature of the study and inadequate medical records, it was not possible to obtain accurate clinical correlation of patients' symptoms in cases of acute high-grade organ toxicity—such as

proctitis—with diffusion restriction in patients who achieved pCR after treatment with neoadjuvant CRT for locally advanced rectal cancer.

In conclusion, diffuse restriction commonly occurs in post-CRT DWI among patients achieving pCR after treatment with neoadjuvant CRT for locally advanced rectal cancer, and may result from radiation proctitis and mural fibrosis.

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