Magnetic Resonance Texture Analysis in Identifying Complete Pathological Response to Neoadjuvant Treatment in Locally Advanced Rectal Cancer

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Abstract

Background:A certain proportion of patients with locally advanced rectal cancer (LARC) experience complete response (CR) after undergoing neoadjuvant chemoradiotherapy (NCRT). These patients might be suitable for a conservative "watch & wait" approach, avoiding high-morbidity surgery. Texture analysis is a new modality that can assess heterogeneity in medical images by statistically analysing grey-level intensities within it. This study hypothesises that texture analysis on magnetic resonance images can identify patients with CR.

Objective: This study aims to determine whether MRI texture analysis (MRTA) as a quantitative imaging biomarker can accurately identify patients with CR.

Design: Retrospective Diagnostic accuracy study.

Settings: Colchester General Hospital, January 2003 - 2014.

Patients:All patients diagnosed with LARC who underwent long-course NCRT, had a post-treatment MRI scan, and underwent surgery are included.

Intervention: Texture analysis extracted from T2-weighted MR images of the rectal cancer.

Main-outcome-measures: Textural features that are able to identify CR were identified by Mann-Whitney U test. Their diagnostic accuracy in identifying CR was determined by area under curve (AUC) of Receiver Operator Characteristics (ROC) curve. Cut-off values were determined by Youden's index. Pathology was the standard of reference.

Results:114 patients with first post-treatment MRI scans (6.2 weeks after completion of NCRT) were included. 68 patients had a second post-treatment scan (10.4 weeks). With no filtration, Mean (p=0.033), standard deviation (p=0.048), entropy (p=0.007), and skewness (p=0.000) from first post-treatment scans; and standard deviation (p=0.042), entropy (p-0.014), mean of positive pixels (p=0.032), and skewness (0.000) from second post-treatment scans were all able to identify CR. AUC ranged from 0.750 to 0.88.

Limitations:MRTA is a new modality, therefore further studies are necessary to standardise methodology of extraction of texture features, timing of scans, and MRI acquisition parameters.

Conclusions:MRTA is a potentially significant imaging biomarker that can accurately identify patients who have experienced CR, who might be suitable for a non-surgical approach.

Introduction

Management of locally advanced rectal cancer (LARC) with curative intent involves neoadjuvant chemo-radiotherapy (NCRT) followed by surgical resection of the rectum. Neoadjuvant treatment is offered in order to downstage the tumour, improve operability, and clear the surgical resection margins [1]. Around 20% of patients who undergo neoadjuvant therapy experience complete response (CR), with no cancer cells left in the irradiated rectum. Multiple studies have shown that patients who experience CR live longer with better quality of life [2,3]. It is therefore argued that those patients are unnecessarily exposed to surgical resection of the rectum, with high morbidity and mortality.

However, there is currently no reliable accurate modality that can pre-operatively identify those patients who have experienced CR after NCRT, as standard morphological imaging in the form of Magnetic Resonance Imaging (MRI) or endorectal ultrasound (ERUS) has shown to suffer suboptimal accuracies in assessing response to treatment [4], and specifically in identifying patients with CR. This is due to the failure of morphological imaging in differentiating post-treatment oedema and fibrosis from remnant tumour mass. Therefore, functional imaging and quantitative imaging biomarkers are being assessed as potential adjunct modalities for assessing response to treatment.

Malignant tumours exhibit higher extracellular, intracellular, and genetic heterogeneity [5]. This is due to variations in cellular proliferation, necrosis, haemorrhagic and myxoid changes in the extracellular matrix, and angiogenesis. Tumour biopsy specimens, in addition to being invasive, reveal only a minority of these variations within the lesion [6]. Histopathological assessment of the resected lesion as a whole can only be done post-operatively. It has therefore become essential to obtain information on tumour heterogeneity from non-invasive medical imaging.

Texture analysis is a quantitative imaging biomarker that assesses tumour heterogeneity by measuring the distribution of gray-scale intensities on a pixel-by-pixel basis. It provides a measure of uniformity and coarseness within the lesion from medical images, which aid in identifying underlying patterns and pathologies [7]. The statistical method of texture analysis studies the histogram distribution of different grey-level intensities as a function of the number of pixels bearing that intensity. It assesses heterogeneity in medical images by measuring different statistical parameters from this histogram distribution. Texture analysis has been shown to be an effective modality in identifying pathologies in breast, nasopharyngeal, and brain cancers [8-10]. It has shown to be effective in discriminating benign from cancerous nasopharyngeal lesions, in classifying soft-tissue tumours, and in monitoring response to treatments in breast and oesophageal cancers. It has also shown to exhibit a prognostic potential in predicting survival in patients with CRC [11].

This study aims to determine whether MRI texture analysis (MRTA) as a quantitative imaging biomarker can accurately identify patients with complete response. Those patients can then avoid exposure to a high risk surgical procedure, and adhere to a 'watch and wait' protocol instead.

Materials and Methods

Patients with suspected rectal cancer normally undergo a MRI scan prior to being discussed at MDT. Those staged as having locally advanced disease are normally offered a 5-week course of NCRT. Tumours with threatened resection margins, defined as tumour closer than 1mm to the mesorectum are considered LARC, and are also offered NCRT. Patients then undergo a restaging MRI 6 weeks after completion of treatment. Surgery is offered 4 weeks later.

Eligibility criteria

All patients diagnosed with locally advanced rectal adenocarcinomas between January 2003 and July 2014 in Colchester General Hospital who underwent neoadjuvant treatment and had undergone at least one post-treatment MRI scan are included.

Patients who did not receive long course NCRT or who did not have an MRI after treatment are excluded. Patients who had a local excision procedure in the form of endoscopic mucosal resection are also excluded, as the histopathological assessment fails to provide tumour regression grading or lymphatic assessment. Mucinous tumours or those that underwent mucinous degradation of their rectal adenocarcinomas were excluded from the analysis, as mucinous cancers represent a separate entity pathologically. Also, the pools of high-intensity mucin renders the texture analysis futile.

Neoadjuvant treatment

Established local institutional protocol states that patients diagnosed with LARC are offered long course chemo-radiotherapy consisting of 45–50.4 Gy in 25–28 fractions over 5 weeks, with concomitant chemotherapy consisting of 240 mg/m^2/day oral Tegafur–uracil on days 1–28, given with leucovorin 90 mg/day.

MRI protocol

Our institution protocol states that post-treatment restaging MRI scans are performed at 6 weeks after completion of the neoadjuvant treatment. A subgroup of patients underwent a second post-treatment MRI 4 weeks later. Imaging protocol included an initial localizing scan followed by a sagittal T2-weighted fast spin-echo (FSE) sequence scan. An axial T2-weighted FSE was used to image the whole pelvis from the iliac crest to the symphysis pubis to identify the pelvic side wall and nodal disease. An oblique axial T2-weighted FSE high-resolution sequence was performed with slices positioned perpendicular to the long axis of

the rectum to enable accurate tumour staging. Finally, an oblique coronal T2-weighted FSE high resolution sequence was performed in patients with a low rectal tumour. The slices were positioned along the long axis of the anal canal to show the relationship of the levator ani muscles to the tumour to demonstrate the degree of margin for resection. All sequences used a matrix of 256/256. Parameters for the scans are summarized in table 1 below.

Two radiologists (DB and AM) blinded to clinical outcomes, pathological outcomes, and to textural features, staged all pre-treatment and post-treatment MRI scans. They however had access to previous MRI staging and reports. Tumour regression grades on post-treatment MRI scans (mrTRG) were assessed as per the technique devised by the MERCURY study group[12], which corresponds to the pathological tumour regression grade (TRG) devised by Dworak et al. [13], summarized in table 2 below. Note that the numbering of mrTRG and pathological TRG have been modified to match each other.

Histopathological assessment

Histopathological assessment of resected specimens provides the standard of reference against which MRI staging was compared. Our in-house pathologist at our institution (JL) restaged all resected specimens for this study. Histopathological reports contained the standard data-set of histopathology results such as T (ypT) and N stages (ypN). Information on the differentiation and whether the circumferential resection margin is involved or threatened is also reported. TRG was assessed as developed by Dworak et al. (Dworak, Keilholz and Hoffmann, 1997).

MRI Texture analysis (MRTA)

MR texture analysis (MRTA) process included firstly identifying the axial slice on the T2-weighted MR images that traverses the mid-section of the tumour with the largest cross-sectional area. Choosing the MRI slice was performed under the supervision of GI radiology

specialist with seven years' experience (AA). The region of interest (ROI) is then manually drawn to enclose the tumour. The ROI was drawn under the supervision of an imaging scientist (BG) with nine years' experience in texture analysis. The ROI included the medium intensity tumour tissue, with the low intensity bowel lumen and muscularis propria excluded from the ROI. MRTA of the selected ROIs was performed using proprietary commercially available TexRAD research software (version 3.3, TexRAD Ltd www.texrad.com - part of Feedback Plc, Cambridge, UK). Figure 1 shows an example of a ROI drawn enclosing an ulcerating rectal cancer on the MRTA software (TexRAD).

MRTA firstly involved an image filtration step, where a Laplacian of gaussian (LoG) band-pass filter (which is similar to a non-orthogonal Wavelet) is employed. This step extracts and enhances objects/features corresponding to a specific spatial scale filter (SSF), which ranges from SSF=2mm (fine) to SSF=6mm (coarse) in radius, with SSF=3mm-5mm in radius corresponding to medium texture coarseness. Each SSF value can be considered as the width at which structures in the image will be highlighted and enhanced, while structures less than this width will be blurred. Second step comprised texture quantification using statistical based histogram-analysis which results in parameters such as mean gray-level intensity, standard-deviation, entropy, mean of positive pixels (MPP), kurtosis and skewness. The total number of pixels in the ROI is also counted. Textural parameters from non-filtered ROI's were also extracted.

Statistical analysis

Categorical variables extracted from MRI scans included tumour radiological T-stage, N-stage, extramural venous invasion (EMVI) status and circumferential resection margins (CRM) status. Tumour regression grade (mrTRG) is also extracted on post-treatment scans. Pathological T-staging, N-staging, and pathological TRG are also obtained as categorical

variables, they are considered the reference standard. MRTA metrics are obtained as continuous variables.

All patients were categorized by their pathological response into CR, comprising TRG 5, and non-CR, comprising TRG 1 to TRG 4. The ability of the MRTA parameters with no filtration and at each individual SSF value in differentiating between CR and non-CR was assessed using Mann-Whitney U test. The diagnostic accuracy of MRTA parameters (which showed statistical significance on Mann-Whitney U test) in identifying CR was then assessed using Receiver operating characteristic (ROC) analysis where the area under the ROC curve (AUC), along with the sensitivity and specificity which were determined at the optimal cut-off. The optimal cut-off value was identified using Youden's index [14].

Results

One hundred and fourteen patients were identified who had a diagnosis of LARC and underwent NCRT, and subsequently underwent surgical removal of the rectum. All 114 patients underwent a first post-treatment MRI scan (designated MRI2) on average 6.2 weeks after completion of NCRT (median: 6.1; range: 3.0 – 11.7). A subset of sixty-eight patients underwent a second post-treatment scan (designated MRI3) on average 10.4 weeks after completion of NCRT (median: 10.4; range: 4.0 – 15.1). A further subset of nine patients were diagnosed to have CR and joined a non-operative approach. Those were excluded from any further analyses as there are no pathological results available. Overall, pathological CR was found in 24 patients (21.05%).

Identifying complete responders

Textural parameters with no filtration

When analysing the textural features without applying any filtration, independent Mann-Whitney U test showed that textural features extracted from the first post-treatment

MRI scans performed at an average of 6.2 weeks after completion of NCRT, namely mean, Standard Deviation, entropy, and skewness, were all statistically able to identify complete responders. Textural parameters derived from the second post-treatment MRI scans performed on an average of 10.4 weeks after completion of NCRT, were also significantly able to identify patients with CR. Standard deviation, entropy, skewness, and mean of positive pixels, were all able to significantly identify CR. Table 3 below summarizes the MRTA parameters extracted from the first and second post-treatment scans and their p-values derived from Mann-Whitney U test.

Textural parameters with filtration

Independent Mann-Whitney U test showed that only skewness of the textural features extracted from the first post-treatment MRI scans was significantly able to identify complete responders on SSF sizes of 4mm, 5mm, and 6mm, with a p-value of 0.007, 0.008, and 0.036 respectively.

Also from the second post-treatment MRI scans skewness at SSF value 3mm and 4mm, were significantly able to identify patients with CR with p-values of 0.016 and 0.014 respectively. Table 4 shows different means and standard deviation of Skewness at different SSF values in identifying CR. P-values were derived from Mann-Whitney U test. Figure 2 below shows the box and whiskers plots of the significant skewness values in table 4.

ROC analysis

Figure 3 A and B below shows the ROC curve for the above significant results. All parameters are plotted on the same curve except for skewness. This separation was necessary as the value of skewness seems to be inversely related to sensitivity, i.e. higher skewness value is associated with CR; whereas for the remaining parameters higher values are associated with poor responders.

Accuracy of MRTA parameters ranged from 59.4% for skewness derived from the second post-treatment scan on a medium coarseness filtration (SSF value of 4mm), to 88% from entropy derived from the second post-treatment scan without filtration. Table 5 below summarises the significant parameters, the AUC, their p-values, and the optimal cut-off in identifying CR calculated by Youden's indices.

Discussion

This study aimed to assess whether textural features derived by statistical methods from pre- and post-treatment MRI scans are able to identify patients with CR. This study showed that textural features extracted from the first post treatment MRI and second MRI scan performed at an average of 6.1 weeks and 10.4 weeks respectively, were significantly able to identify those with a CR. AUC from the ROC analyses showed a maximum accuracy of 88% with entropy derived from the histogram of the second post-treatment scans.

Two recent studies evaluated the role of texture analysis in assessing response to chemo-radiation in LARC. Jalil et al. [15] retrospectively assessed whether textural features extracted from MRI scans were able to predict survival. Fifty-six patients with LARC who underwent NCRT were included. They showed that of all textural features, MPP derived from of pre-treatment scans (p=0.008), and skewness from the post-treatment scans (p=0.034) were the only variables that could predict overall survival. Kurtosis of post-treatment scans (p=0.009) and entropy of post treatment scans (p=0.002) were able to predict disease-free survival and relapse-free survival respectively. In their study, they firstly did not correlate textural features with histological response, which would make more clinical sense. Their results also showed some of their textural features, such as MPP and entropy from post-treatment scans, were better predictors of overall survival than pCR and the presence EMVI, which had lower p values. Both parameters that were able to predict survival in their study,

namely MPP and entropy from post-treatment scans, were also able to histologically identify patients with CR in this study.

Another study assessed the role of texture analysis of MRI in assessing response to chemo-radiation in LARC. De Cecco et al. [7] prospectively recruited 15 patients with LARC who underwent NCRT, they extracted textural features from pre-treatment MRI and from mid-treatment MRI, which was performed at day 21 of the forty-day NCRT. Six of those patients experienced pCR. They also assessed the relative change in textural features by measuring the absolute gradient between pre- and mid-treatment parameters. They found that pre-treatment kurtosis was significantly lower in those with pCR than in those with less than complete response (p=0.01), and that mid-treatment kurtosis was significantly higher in pCR than in partial responders or non-responders (p=0.045). They also showed that change in kurtosis from pre-treatment to mid-treatment was also significantly higher in pCR than in non-pCR (p=0.038). The AUC from ROC analysis was impressively 0.907, and at the cut-off value of 0.19 resulted in sensitivity and specificity for CR prediction of 100% and 77.8%, respectively.

Texture parameters have therefore shown in multiple studies to carry important clinical significance in terms of predicting survival and in predicting pathological outcomes. However, the lack of concordance in the specific textural features that are able to identify CR among published studies is possibly due to the lack of a unified methodology in extracting those features in this relatively new modality. Furthermore, there seems to be a large difference in the sequence of MR images used to extract the features, in timing of the scans, and indeed on the software used to extract textural features. Certainly, further prospective studies are required in order to understand the role and significance of texture analysis in assessing response to NCRT in LARC and in other cancers.

Conclusions

This study shows that textural features extracted from post-treatment scans in patients with LARC can in fact identify patients with CR, with an accuracy that is comparable, if not better than, conventional MRI staging. Texture analysis can provide a reliable imaging biomarker that can aid in identifying patients who have likely experienced CR who can benefit from either a less invasive surgical approach or deferring surgery altogether as a non-surgical "watch and wait" approach.

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