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Rectal perfusion parameters normalised to tumour-free rectal wall can predict response to neoadjuvant chemoradiotherapy

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AIMS: To evaluate absolute changes in quantitative and semi-quantitative perfusion parameters using a newer approach of comparing these parameters with tumour-free normal rectal wall (i.e., relative/normalised change) in predicting complete pathological response to chemoradiotherapy.

MATERIALS AND METHODS: Perfusion parameters measured before and after treatment of 10 patients with histopathologically proven rectal cancer that showed complete treatment response (Group 1) were compared with 10 patients with residual tumour on histopathology following treatment (Group 2). Quantitative perfusion MRI parameters (Ktrans: volume transfer coefficient reflecting vascular permeability, Kep: flux rate constant, Ve: extracellular volume ratio reflecting vascular permeability, integral of area under the curve (IAUC); Toft model) were quantified by manually delineating a region of interest in the upper, mid and lower third of the tumour (1 cm^2), in addition similar parameters were obtained from the normal rectal wall at least 1 cm away from the potential resection margin, absolute as well as relative perfusion values normalised to that of the normal rectal wall were evaluated. The differences in absolute and normalised qualitative parameters were compared within each group using paired *t*-tests and between each group using analysis of variance (ANOVA).

RESULTS: Wash-in, wash-out, positive enhancement integral (PEI), Ktrans, IAUC in the complete pathological responders when compared to the adjacent normal rectal wall showed ratios approaching 1, suggesting that rectal perfusion is similar to the adjacent normal rectal wall in complete pathological responders. The difference in the normalised values in the responders and non-responders was statistically significant.

CONCLUSION: Perfusion parameters can be used in predicting response to treatment, when normalised to the adjacent normal rectal wall.

Introduction

There are differences in rectal cancer treatment between countries and between institutions; however, as per revised guidelines provided by American Society of Colon and Rectal Surgeons (ASCRS) standards committee, early-stage/

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low risk disease (T1–2, N0) is treated with surgical intervention alone while locally advanced/intermediate risk disease (T1–3 N1, T3) requires a multidisciplinary approach, which includes neoadjuvant radiation with or without chemotherapy. High-risk/metastatic disease (any T N2, T3MRF positive, or T4) has to be treated with chemoradiotherapy (CRT) and surgery. Post-CRT, there is shrinkage of tumour cells with nuclear changes of non-viability.[1–3]

It is also known that some patients show a good response to chemoradiotherapy, while others do not. Morphological magnetic resonance imaging (MRI) has been used to triage patients according to T-staging and involvement of the colorectal resection margin; however, despite observed changes in tumour size and reduction in overall extent, there is no definite finding that can differentiate between complete/partial responders and non-responders.[4–8] It is also known that some tumours show good treatment response at the cellular and vascular levels without definite changes in the size.

Perfusion-based MRI parameters are promising tools for the functional evaluation of tumour micro-circulation, neoangiogenesis, and response to treatment. Vascular characteristics within the tumour have a major influence on chemoradiosensitivity and dynamic contrast-enhanced (DCE [perfusion]) MRI may be used to assess this haemodynamic information, which makes it a useful predictor of treatment response.

Charting of the DCE MRI data uses a compartmental model in which there is a tissue compartment and a vascular compartment; the so-called “Tofts model”, which is used to measure Ktrans (volume transfer coefficient reflecting vascular permeability) and Ve (extracellular volume ratio reflecting vascular permeability).[7–12] The differences in enhancement curve shape, and the time to peak (TTP) enhancement, both are important; the initial slope depends on Ktrans, and is independent of Ve, the final peak value depends on Ve, and larger Ve tumours take longer to reach their peak. The wash-in, wash-out, TTP, and positive enhancement integral (PEI) are the semi-quantitative parameters based on contrast enhancement versus time curves in the tissue.[9,12–14]

A large decrease in Ktrans is said to be associated with a good therapeutic response to CRT; however, the published literature is divided with no discrete single or range of values. Some authors have also promulgated change in Ve as a marker of response to CRT. There is heterogeneity in the published literature with no discrete defined cut-off value to predict or analyse tumour response.[14–17]

The hypothesis of the present study was that instead of absolute values, if the parameters were normalised to the non-involved rectal wall, it would be possible to detect whether there is favourable response following CRT in terms of down-staging or complete resolution. This is a retrospective pilot study to evaluate the above-mentioned hypothesis.

Material and methods

In this institutional review board-approved study, perfusion parameters of pre- and post-treatment imaging of histopathologically proven patients (n=10) with rectal cancer who had complete response and complete absence of tumour on histopathology following treatment (group 1) were evaluated retrospectively of over a 2-year period (January 2014 to December 2015). These patients were compared with 10 patients with residual tumour on histopathology following treatment (group 2). Two radiologists reviewed the MRI images separately and had no knowledge of the postoperative biopsy result. Informed consent was obtained from all patients.

The two groups were matched for T stage of tumour. Patients undergoing post-treatment imaging were included only if histopathology correlation was available. Patients with T4 disease and those without followash-up imaging or biopsy results were excluded.

The treatment protocol consisted of neoadjuvant CRT with oxaliplatin/capecitabine and 5-fluorouracil. Semi-quantitative perfusion MRI parameters (Ktrans, Ve, IAUC; Toft model) were quantified by manually delineating a region of interest in the upper, mid and lower third of tumour at least 1 cm^2 (because of the morphology of the tumour, freehand ROIs were drawn in three representative parts of the tumour. The anatomical location of the ROI was matched between pre- and post-CRT studies by fusing the two images as well as visual inspection of the pre- and post-CRT images side by side). In addition similar parameters were obtained from the normal rectal wall at least 1 cm away from the potential resection margin. Absolute as well as normalised values (ratio of perfusion parameter in tumour to normal rectal wall) to the perfusion in the normal rectal wall were evaluated. Semi-quantitative perfusion parameters were also assessed (wash-in, wash-out, TTP, PEI, iAUC). All the images were anonymised and analysed using a Tissue 4D post-processing workstation (Syngo Via, Siemens, Erlangen, Germany) for post-processing. Colour-coded perfusion maps were co-registered on the anatomical T2-weighted images for ROI measurement.

Imaging protocol included three orthogonal (axial/coronal/sagittal) high-resolution T2-weighted turbo spin-echo (TSE) scans. DCE MRI was performed using a free-breathing T1-weighted three-dimensional (3D) spoiled gradient echo fat lowash-angle shot (flash) sequence with fat suppression on the sagittal plane. The protocol for the T1 map included a T1-weighted sequence with flip angles of 2° and 15°. Dynamic T1-weighted images were obtained with temporal resolution of 1.5–1.6 seconds, at the same field of view and matrix as those of the T1 map protocol. Gadoterate meglumine (Dotarem, Guerbet, Villepinte, France) 0.2 ml/kg (0.1 mmol/kg) intravenous bolus was infused at rate of 2 ml/s with a saline chase of 20 ml. After CRT, all patients underwent complete surgical resection and the surgical specimen served as the reference standard. Differences in pre- and post-treatment absolute and normalised values within each group, as well as between the two groups, were compared. Differences in absolute and normalised quantitative/semi-quantitative parameters were compared within each group using paired t-test and between each group using analysis of variance (ANOVA). A p-value of 0.05 was considered statistically significant.

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