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COMMENTARY

MRI for evaluation of treatment response in rectal cancer

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ABSTRACT

MRI plays an increasingly pivotal role in the clinical staging of rectal cancer in the baseline and post-treatment settings. An accurate evaluation of response to neoadjuvant treatment is crucial because of its major influence on patient management and quality of life. However, evaluation of treatment response is challenging for both imaging and clinical assessments owing to treatment-related inflammation and fibrosis. At one end of the spectrum are clinical yT4 rectal cancers, wherein precise post-treatment MRI evaluation of tumour spread is particularly important for avoiding unnecessary exenterative surgery. At the other extreme, for tumours with clinical near-complete response or clinical complete response to neoadjuvant treatment, less invasive treatment may be suitable instead of the standard surgical approach such as, for example, a “Watch and Wait” approach or perhaps local excision. Ideally, the goal of post-treatment MRI evaluation would be to identify these subgroups of patients so that they might be spared unnecessary surgical intervention. It is known that post-chemoradiation therapy restaging using conventional MR sequences is less accurate than baseline staging, particularly in confirming T0 disease, largely owing to the difficulty in distinguishing fibrosis, oedema and normal mucosa from small foci of residual tumour. However, there is a growing utilization of multiparametric MRI, which has superseded other types of evaluations and requires review and periodic re-evaluation. This commentary discusses the current status of multiparametric MRI in the post-treatment setting and the challenges facing imaging in general in the accurate determination of treatment response.

INTRODUCTION

Rectal cancer is a distinct subset of colorectal cancer that requires a highly dedicated multidisciplinary approach including subspecialty surgical, medical and radio-therapeutic expertise to ensure the preservation of sphincter, bladder and sexual function, all of which hinge upon tailored imaging interpreted by subspecialized oncologic radiologists. Rectal cancer poses a significant clinical burden, with almost 40,000 new cases in the USA and >14,000 cases in the UK in 2015.^{1,2} In spite of the overall decreasing incidence and mortality of colorectal cancer, the incidence in young patients, notably, is rising, with an anticipated 124% increase among 20–34-year olds by 2030.³ There is an increasingly pivotal role for pelvic MRI in the clinical staging evaluation of tumour size, location, TNM stage and relationships to the sphincter apparatus, anterior peritoneal reflection and circumferential resection margin. In our own practice and in that of others, MRI has largely replaced endorectal ultrasound and contributed value to patient management in the baseline and post-treatment settings. Evaluation of treatment response is challenging for both imaging and clinical assessments owing to treatment-related inflammation and fibrosis. However, the growing utilization of MRI, in particular,

unique sequences that may interrogate tumour biology (“multiparametric”) in the post-treatment setting, has superseded other types of evaluations and requires review and periodic re-evaluation. This commentary discusses the current status of multiparametric MRI in the post-treatment setting and the challenges facing imaging in general in the accurate determination of treatment response.

Role of MRI in evaluating response to chemoradiation therapy

An accurate imaging evaluation of response to neoadjuvant treatment is crucial because of its major influence on patient management and quality of life. At one end of the spectrum are clinical yT4 rectal cancers, wherein precise post-treatment MRI evaluation of tumour spread is particularly important for avoiding unnecessary exenterative surgery. At the other extreme, for tumours with clinical near-complete response or clinical complete response (cCR) to neoadjuvant treatment, less invasive treatment may be suitable instead of the standard surgical approach such as, for example, a “Watch and Wait” approach or perhaps local excision. Complete pathological response (no viable tumour cells in rectal tissue specimens and no tumour-bearing nodes), is present in 8–34% of patients with rectal cancer

treated with neoadjuvant therapy.⁴ Ideally, the goal of post-treatment MRI evaluation would be to identify these subgroups of patients so that they might be spared unnecessary surgical intervention. Various international experts have described their experience with close non-operative surveillance of complete clinical responders, but the single optimal method to accurately confirm complete response remains elusive. Biopsy has been associated with an 11% negative-predictive value and reports of persistent mucosal ulceration at endoscopy in 66% patients with complete pathologic response limit reliance on endoscopy.^{5,6} It is known that post-chemoradiation therapy (CRT) restaging using MRI is less accurate than baseline staging, particularly in confirming T0 disease, largely owing to the difficulty in distinguishing fibrosis, oedema and normal mucosa from small foci of residual tumour; and consequently, radiologists tend to overstage. A large meta-analysis revealed a mean sensitivity of 50% and a specificity of 91% to detect residual tumour using standard T_2 weighted sequences during restaging MRI post-CRT, with sensitivity markedly improved after the addition of diffusion-weighted imaging (DWI), but at no real cost to specificity.⁷ Much research continues into optimizing the role of multiparametric MRI including morphologic, volumetric and functional imaging, with the goal to provide a more accurate evaluation of tumour response. Another line of investigation uses fludeoxyglucose positron emission tomography/CT to interrogate differing rates of glucose metabolism between responder and non-responder tumours at various times during treatment, indicating some predictive value at earlier stages in treatment. Although beyond the focus of this commentary, the reader is referred to this important body of research.⁸

Qualitative assessment of T_2 hypointensity in the tumour bed, which is felt to represent scar/fibrosis, has a reported accuracy of only 70% in identifying near-complete response, limited by a low sensitivity, and a low negative-predictive value of only 66.7%.^{9,10} Further stratifying this qualitative assessment and attempting to approximate tumour regression grade used at histopathological examination, an MR tumour regression grade system has been devised. In highly expert hands, MR tumour regression grade is claimed to prognostically stratify good and poor responders by the relative amounts of residual intermediate signal intensity (tumour) vs hypointense signal (fibrosis).¹¹ Combining morphology with $\geq 70\%$ tumour volume reduction may increase the accuracy in predicting response (complete or partial) to 86.8%.⁹ Other groups have validated that a $\geq 70\%$ volume reduction can be significantly associated with histologic tumour regression and greater disease-free survival.¹² Nonetheless, limitations of T_2 volumetry include excessive time consumption and lack of seamless assimilation into daily workflow. In addition, T_2 weighted imaging alone, by either qualitative assessment or three-dimensional volumetric analysis, is insufficient to guide clinical decision-making in the selection of patients with clinical complete response eligible for a non-operative approach.^{10,13}

"Functional" MRI sequences that interrogate dynamic processes occurring at the cellular level, in particular DWI and perfusion-weighted imaging, provide enhanced information about tumour biology. DWI assessment, which renders an image of protons

immobilized by tightly packed tumour cell environments, has a high specificity and high negative-predictive value for the detection of complete response and is therefore considered particularly useful for highlighting the presence of residual tumour in incomplete responders.^{10,14,15} It thus has an emerging role in deselecting individuals otherwise chosen for non-operative management on the basis of endoscopy. However, the limited positive-predictive value of DWI-MRI precludes confident identification of complete responders, which remains a major challenge.^{7,14} The role of quantitative assessment of tumour response by measuring tumour apparent diffusion coefficient (ADC) value is still undefined, since some groups have found mean ADC values to be significantly higher in responders, while other groups have found no difference compared with non-responders.^{10,13,14} Furthermore, several extraneous factors influence ADC values including imaging acquisition parameters, region-of-interest number, size and placement, mathematical assumptions and rectal air causing susceptibility artefacts, limiting implementation of any generalizable ADC cut-off values.¹⁴ Post-CRT DWI volumetry has compared favourably with post-CRT T_2 volumetry, proving a better predictor of complete response, with a higher specificity and an area under the curve of 0.93 vs 0.70, confirming the greater biospecificity of DWI signal compared with the non-specific T_2 weighted signal in the tumour bed.^{13,16}

Dynamic contrast-enhanced MR imaging (DCE-MRI), another functional MRI sequence, evaluates tumour vessel permeability and blood flow, generating various perfusion parameters which are then applied to a pharmacokinetic model. Investigators have found K^{trans} , a measure of capillary permeability, to be the most useful parameter thus far. Some groups have found that pre-CRT K^{trans} significantly differentiates responders (elimination of leaky vessels) from non-responders (persistent leaky neo-vasculature), while others have found differences in K^{trans} pre-/post-treatment or post-treatment K^{trans} alone to be helpful.¹⁷⁻¹⁹ Other investigators have focused on semi-quantitative, non-pharmacokinetic model-based assessments such as signal intensity time curve shape characteristics to facilitate incorporation into daily workflow.^{20,21} Differing contrast agents, temporal resolution and imaging parameters limit comparison of these multiple studies, especially since imaging parameters and pharmacokinetic modelling have yet to be standardized. As such, DCE-MRI remains an active area of ongoing research.

Characterization of lymph nodes remains a daunting challenge. Encouragingly, recent publications indicate that lymph node size, in spite of being a limited predictor pre-treatment, is a more reliable predictor of malignancy post-treatment, with 6-14% of nodes ≤ 5 mm containing metastases, particularly if a complete response is noted in the tumour bed at MRI.^{22,23} Morphologic criteria may again be applied, and when combined with size > 5 mm, have a sensitivity of 71% and specificity of 93% for metastatic disease.²⁴ DWI has not been found to be helpful in distinguishing benign from malignant nodes.²⁴

Most practical current approach

A recently published study offers a pragmatic approach to post-CRT evaluation by using a combination of digital rectal

examination, endoscopy and MRI (combined T_2 and qualitative DWI evaluation). In this small study, which awaits further validation, the authors could reportedly identify 98% of complete responders, missing only 2%.⁴ However, even when there was all-modality agreement on the presence of residual tumour, the authors found that a 15% chance of complete clinical response remains. This innovative study is highly clinically relevant and practical in that it combines the strengths of the endoscopic luminal evaluation and the supplementary information provided by MRI for mural/extramural tumour extent. A minor limitation is their use of a recurrence-free interval of 12 months as a surrogate end point for a CR, whereas recent experiences have shown that 70% of tumour regrowth occurred within 13 months of completing chemoradiation²⁵ and we look forward to updated survival data. A further development which may inform the design of future such studies is the emerging evidence that postponing MRI restaging from 6–8 to 10–12 weeks after completion of neoadjuvant CRT reveals more patients with complete response to therapy.²⁶

While various MRI sequences are undergoing active investigation, our centre has found that combined T_2 morphology and qualitative/volumetric DWI evaluation form the cornerstone of clinically applicable daily rectal MRI interpretation, in spite of a prolonged learning curve. We concur with others that discussion of discordant, unusual or challenging cases at our weekly multidisciplinary team conference proves invaluable in reaching consensus on the best treatment approach for these patients. We also believe that this exchange of ideas and new information is the key to providing the most appropriate tailored patient care in this emerging era of organ-preserving, quality of life-maintaining, non-operative management of rectal cancer.

Looking towards the future

While the role of imaging in the post-treatment evaluation of rectal cancer continues to evolve, the radiology community faces

significant challenges. In spite of technological advances in our field, various vendors are used and there is enormous variability in image quality and technical parameters utilized, particularly for the more modern and emerging biofunctional techniques like DWI-MRI and DCE-MRI, to the extent that results from a scan performed on one vendor's scanner may not translate well or be easily reproduced on another vendor's scanner, limiting intrapatient, interpatient and interinstitutional comparisons. Much like the digital imaging and communications in medicine standard that was developed years ago, greater standardization in MRI performance is desperately needed so as not to impair patient care. Secondly, published studies of advances in techniques and interpretation for rectal cancer MRI currently originate from only a few centres of extreme expertise with virtually unparalleled reader experience compared with the community or even with the average academic centre. Therein, reproducibility suffers. Insufficient information is provided on learning curves to allow reliable early adoption of these advances. Finally, experience by the authors and their colleagues as central imaging reviewers for national and international multicentre clinically driven trials has shown that there is a high degree of heterogeneity, not only in interpretation expertise, but also in dedication to and quality of MRI for rectal cancer, and that this strongly needed validation and reproducibility information (which can only be accomplished through multicentre trials) may currently be out of our reach as a result of the lack of standardization as discussed above. We therefore offer some suggestions and action items including the need for: (1) standardization of scanning techniques and protocols, (2) ensuring availability of appropriate expertise by promotion of excellence among centres and (3) performance of high-quality prospective multicentre imaging studies with imaging goals as primary objectives. In sum, greater efforts on a national and international level are needed to face these challenges accordingly in order to provide the optimal imaging and treatment strategy tailored to every individual patient with rectal cancer.

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