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Invited editorial re: "Response assessment after (chemo) radiotherapy for rectal cancer: Why are we missing complete responses with MRI and endoscopy?"

Accurate assessment of the treatment response to neoadjuvant chemoradiotherapy is critical in rectal cancer to help avoid overtreatment or undertreatment, define the optimal time to surgery, surgical procedure to perform, and identify appropriate patients for organ preservation. Between 10 and 25% of rectal cancer patients will experience a pathological complete response (pCR) following neoadjuvant chemoradiotherapy (nCRT) [1]. The identification of patients that will experience a complete clinical response (CR) to treatment and be appropriate for a "watch and wait" strategy remains challenging. van der Sande et al. [2] highlight the issue of the 'unrecognised' complete response, where patients have an incomplete CR at restaging, subsequently undergo surgical resection based on this reassessment, and have a pCR in the surgical histopathology. This overstaging of residual tumour can lead to a radical resection of the rectum in up to 30% of patients that may have been treated successfully with organ preservation [2,3]. We applaud the authors for their attempt to determine the features on Magnetic Resonance Imaging (MRI) and endoscopy that lead to the false diagnosis of residual tumour at restaging, in order to reduce the number of unrecognised complete responders. However, concerning the use of MRI after CRT for rectal cancers, there are some important take home points.

Reassessment after nCRT is not perfect by any method, but MRI with high resolution T2-weighted image (T2WI) sequences is the best standard for re-staging, with the MRI tumour regression grade (mrTRG) a proven predictive imaging biomarker for treatment response [4,5]. In several multicentre studies, it remains the best and most accurate option for re-staging [6]. van de Sande et al. advocate that the addition of diffusion-weighted imaging (DWI) to standard high resolution T2-weighted imaging (T2WI) can help to differentiate between scar tissue and residual tumour after nCRT and identify CR [6,7]. However, as their study has shown, the technique is not ready to be recommended for identification of CR. DWI has recognised limitations that may lead to suboptimal diagnostic performance. A good quality high resolution T2WI is necessary for interpretation alongside the DWI scan, and little evidence to date has shown incremental clinical benefit of adding DWI to mrTRG for this purpose. The evidence to date is mainly from single-center expert studies and prospective multicenter data are lacking, there is no standard for acquisition, reports for the quantitative diffusion parameter ADC in responsive and nonresponsive tumours are not standard across multiple MRI vendors, magnet field strengths and other factors, and the scans are prone to interpretation errors. This was the case in the present study, from an expert center, where more than half of CR patients had diffusion restriction indicative of residual tumour on restaging DWI. Therefore, as the authors have now shown, the addition of DWI does not improve the diagnostic performance compared with standard T2WI, and so cannot be recommended for identification of CR after CRT.

There are other problems with a study such as this. The authors' use of histopathology as the gold standard for comparison is also not ideal for several reasons. First, the pathologic T stage after CRT (ypT) does not predict outcomes as well as the mrTRG [8]. In addition, prognostic factors, such as persistent extramural venous invasion (EMVI), are difficult to interpret from the loss of architecture after CRT, and are often missed by pathologists. With the histopathology, the pCR is interpreted from a single moment at the time of resection, rather than as a function of time, where the ongoing regression can be observed, as with high resolution T2 weighted MRI monitoring [9]. Even the authors state they have changed their practice to an extended observation period in select patients to 8–10 weeks after neoadjuvant treatment, to allow for further regression to a CR [10]. Finally, the pathologists' assessment of TRG is poorly reproduced and does not correlate well with survival outcomes or the mrTRG, as the pathologist cannot know how well the tumour has regressed without knowledge of what the original tumour looked like [8].

In sum, the author's concluded that the presence of residual mucosal abnormalities at endoscopy, mixed signal intensity or irregular fibrosis at T2-weighted MRI, focal diffusion restriction at DWI MRI should not be regarded as unequivocal signs of residual tumour, and were proponents of DWI to the standard T2WI MRI to help identify discrepancies in treatment response. We caution accepting these results as conclusive. With their results in context, DWI is not appropriate for recommendation of benefits over T2WI. New techniques and sequences continue to emerge to address these limitations. Like the authors, we look forward to advances in imaging techniques, technology, in the future to help overcome the challenges in response assessment and better patient selection for organ preservation. In the meantime, the TRIGGER international prospective randomised Phase III trial is evaluating mrTRG as a biomarker for selecting patients for watch and wait (ClinicalTrials.gov: NCT02704520).

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Conflict of interest statement

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No conflicts of interests.

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