Letter to the Editor

Synthetic magnetic resonance imaging predicts the prognostic evaluation of rectal cancer

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We read with interest the article by Ma *et al.* (1) published in the journal of *Quantitative Imaging in Medicine and Surgery*. The authors conducted a prospective, single-centre study involving eighty-seven patients who had pathologically confirmed rectal cancer and underwent synthetic magnetic resonance imaging (SyMRI) before therapy. Ma *et al.* found that T2 and proton density (PD) values obtained by SyMRI decreased significantly among patients with poor differentiation and lymph node metastasis and concluded that T2 and PD. values were noninvasively prognostic factors of rectal cancer. We appreciate their efforts to provide insights into the noninvasive evaluation of patients with rectal cancer. However, some points merit further discussion.

Firstly, the article included important prognostic indicators such as mrT, mrN stage and tumour differentiation. However, many other critical prognostic factors which surgeons are greatly concerned about were still not included, like mesorectal fascia (MRF) status, lateral lymph node, and histological type. MRF is an essential structure in rectal cancer, defined as the fine linear structure enveloping the mesorectal compartment harbouring the rectum perirectal fat. If it is violated, the further use of total mesorectal excision and neoadjuvant radiotherapy might be needed (2,3). Besides, the incidence of lateral pelvic lymph node metastasis has been estimated to range from 11% to 22% in patients with T3/4 rectal cancer below the peritoneal reflection, which is significantly associated with the surgery of lateral lymph node dissection (LLND) (4). Though this article included the mrN stage, the complement of lateral lymph node assessment could make this study more clinically significant.

Furthermore, histological type, including adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma, etc., is a routine item in biopsy and postoperative pathology reports and affects prognosis and treatment options. It is also worth mentioning that perineural invasion is an essential prognostic factor. Though this article said it collected these pathological characteristics, it did not represent the results and explored them further in the following analysis. This study could have improved if it included the above factors.

Secondly, the receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic efficacy of T2 and PD values in tumour differentiation and the mrN stage. However, several clinically relevant influencing factors exist, and univariate analysis cannot rule out potential confounding. Multivariate analysis, such as logistic regression, is recommended to improve the outcomes' credibility.

Thirdly, this study used the mrN stage as the outcome when exploring the diagnostic performance of SyMRI, which was not so appropriate as they were both MRI features. If the mrN stage can be obtained directly from imaging, it is not so necessary to calculate parameters

derived from SyMRI to predict the mrN stage.

Moreover, studies have shown that 20% to 34% of patients with colorectal cancer (CRC) present with synchronous liver metastases (5). Different locations and metastases of primary rectal cancer lesions directly affect treatment goals, surgical approaches, and patient prognosis (5-7). However, essential clinical characteristics in this study, including distant metastatic status and location of rectal cancer, were not included, which will affect the applicability of the conclusions.

Lastly, neoadjuvant therapy is one of the effective treatments for patients with cancer (8), especially among patients with low-risk, intermediate-advanced rectal cancer (9). However, only a portion of the patients is effective (10). The prediction of efficacy is a current clinical difficulty that needs to be solved urgently. In this article, 79.3% (69/87) of the patients received neoadjuvant therapy, but the predictive value of T2 and PD values in the efficacy of neoadjuvant treatment was not explored. If this study carries out further related research, It would be more clinically meaningful.

In summary, we appreciate the authors for their important and promising study. It highlights the noninvasively diagnostic value of SyMRI in patients with rectal cancer and the necessity of higher quality research in the future.

Supplementary file: Reply: 'Synthetic magnetic resonance imaging predicts the prognostic evaluation of rectal cancer'.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Reply: 'Synthetic magnetic resonance imaging predicts the prognostic evaluation of rectal cancer'

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Keywords: Synthetic MRI; rectal cancer; prognostic factors

Thank you very much for your letter. We have read the manuscript title 'Letter to the editor: Synthetic magnetic resonance imaging predicts rectal cancer'. Thanks for the readers' comments. Point by point response to the readers' comments are listed below.

Firstly, our study included other important prognostic factors such as T stage , N stage, circumferential resection margin (CRM) and extramural venous invasion (EMVI) according to the "DISTANCE" criteria (1). The sample size is relatively small in our study, many prognostic factors included may affect the statistical results. In the future, we will expand the sample size and include more prognostic factors such as mesorectal fascia status (MRF) and location of the lesion for research. Patients with only a pathological type of rectal adenocarcinoma were included in our study, consistent with other study (2). Adenocarcinoma is the most common pathological type of rectal cancer, including well-differentiated, moderately differentiated, and poorly differentiated, as one of our inclusion criteria. Maybe other histological types can be studied separately. Besides, our purpose is mainly to explore whether quantitative parameters can distinguish positive lymph nodes from negative lymph nodes including the mesorectal and lateral lymph nodes, etc., according to the eighth edition of the American Joint Committee on Cancer tumor-node-metastasis staging system.

Secondly, our study aimed to investigate each parameter's diagnostic performance in different prognostic factors. So, referring to other related literature (3), we chose the most common statistical method to deriving an "optimal" cutoff. In *Fig. 5* in our study (4), we evaluated the diagnostic performance of the combined parameters by multivariate logistic regression analysis. This will provide a preliminary basis for our subsequent research such as radiomics or deep learning. Although it is a significant difference in the mean for transverse relaxation time (T2) and proton density (PD) in magnetic resonance(mr)N stage and differentiation, it maybe exist the overlapping between T2 and PD parameters, which may make the test less useful in clinical practice; we have mentioned it in our limitation (4).

Thirdly, although mrN stage is not yet the gold standard, thus causing false positives or false positives with biased results inevitably, the determination of N stage is based on the magnetic resonance imaging (MRI) features recommended by the guidelines (5). What is more, on the one hand, some patients can obtain pathology through surgical resection within T1-2 stage; on the other hand, most patients with T3 stage or lymph node metastasis suspected will undergo neoadjuvant therapy directly without pathological results before treatments. Exploring the value of synthetic MRI (SyMRI) through mrN stage can be a preliminary exploration for the follow up studies such as the prediction of neoadjuvant efficacy evaluation. Also, we will expand the sample size in the follow-up study and explore the relationship between pathologically confirmed lymph node status and imaging parameters.

Besides, we aimed to explore the correlation between the quantitative parameters derived from SyMRI and clinical stage according to the "DISTANCE" criteria and RC differentiation. We can investigate the correlation between distant metastatic

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status and rectal cancer itself in the follow up study.

Lastly, the value of neoadjuvant therapy efficacy prediction is clinically significant indeed (6). We have explored the diagnostic performance of quantitative SyMRI parameters in predicting the complete or sustained complete clinical response in patients with rectal cancer receiving neoadjuvant chemoradiotherapy. The paper has been written and under review.

In summary, we appreciate the readers for their important comments. In the future, we will further investigate the application of quantitative SyMRI parameters in rectal cancer.

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