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MRI radiomics analysis for predicting preoperative synchronous distant metastasis in patients with rectal cancer

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Abstract

Objectives To investigate the value of MRI radiomics based on T2-weighted (T2W) images in predicting preoperative synchronous distant metastasis (SDM) in patients with rectal cancer.

Methods This retrospective study enrolled 177 patients with histopathology-confirmed rectal adenocarcinoma (123 patients in the training cohort and 54 in the validation cohort). A total of 385 radiomics features were extracted from pretreatment T2W images. Five steps, including univariate statistical tests and a random forest algorithm, were performed to select the best preforming features for predicting SDM. Multivariate logistic regression analysis was conducted to build the clinical and clinical-radiomics combined models in the training cohort. The predictive performance was validated by receiver operating characteristics curve (ROC) analysis and clinical utility implementing a nomogram and decision curve analysis.

Results Fifty-nine patients (33.3%) were confirmed to have SDM. Six radiomics features and four clinical characteristics were selected for predicting SDM. The clinical-radiomics combined model performed better than the clinical model in both the training and validation datasets. A threshold of 0.44 yielded an area under the ROC (AUC) value of 0.827 (95% confidence interval (CI), 0.6963–0.9580), a sensitivity of 72.2%, a specificity of 94.4%, and an accuracy of 87.0% in the validation cohort for the combined model. A clinical-radiomics nomogram and decision curve analysis confirmed the clinical utility of the combined model.

Conclusions Our proposed clinical-radiomics combined model could be utilized as a noninvasive biomarker for identifying patients at high risk of SDM, which could aid in tailoring treatment strategies.

Key Points

- *T2WI-based radiomics analysis helps predict synchronous distant metastasis (SDM) of rectal cancer.*
- *The clinical-radiomics combined model could be utilized as a noninvasive biomarker for predicting SDM.*
- *Personalized treatment can be carried out with greater confidence based on the risk stratification for SDM in rectal cancer.*

Keywords Rectal neoplasm · Magnetic resonance imaging · Radiomics · Metastasis

Huanhuan Liu and Caiyuan Zhang contributed equally to this work.

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Abbreviations

AUC	Area under the curve
CA199	Carbohydrate antigen 199
CEA	Carcinoembryonic antigen
DKI	Diffusion kurtosis imaging
DWI	Diffusion-weighted imaging
GLCM	Gray-level co-occurrence matrix
GLRLM	Gray-level run-length matrix
ICC	Intraclass correlation coefficient
LN	Lymph node
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver operating characteristic curve

SDM Synchronous distant metastasis
VOI Volume of interest

Introduction

Local recurrence rate of rectal cancer has been significantly reduced to 5–10% following the introduction of total mesorectal excision and neoadjuvant radiochemotherapy [1, 2]. However, distant metastasis remains a problem. Most rectal cancer deaths can be attributed to metastasis [3]. Approximately 20 to 30% of rectal cancer patients have metastatic lesions at the time of diagnosis [4, 5]. The three most common metastatic sites are the liver, lung, and bone [6]. For localized colorectal liver or lung metastases, resection has been considered the treatment of choice for improving long-term survival. The 5-year survival rates for patients treated with surgical resection of colorectal liver or lung metastasis can be enhanced to 58.0% or 56.2%, respectively [7, 8]. Therefore, preoperative identification of rectal cancer patients with a high risk of synchronous distant metastasis (SDM) is crucial for personalized treatment strategies. Strategies such as further imaging examinations including liver contrast-enhanced MR or FDG PET-CT imaging for the detection of additional metastatic lesions, intensified systemic therapy, and metastasectomy should be considered for high-risk patients with rectal cancer [9].

However, there are few published studies about predicting SDM of rectal cancer [6, 9, 10], and no consensus exists on the matter. Gaitanidis et al [6] recently demonstrated the feasibility of predictive nomograms for evaluating the probability of synchronous liver, lung, and bone distant disease in 46,785 rectal cancer patients. The results were promising with clinical and pathologic features in the proposed nomograms, yet the pathologic information is available only after surgery, which cannot be used to guide preoperative treatment strategy. Accordingly, development of preoperative noninvasive biomarkers to predict SDM is warranted. MR imaging (MRI) was the noninvasive imaging modality of choice for preoperative rectal cancer staging. It can also provide more than just morphological information, as images are data more than pictures [11]. To the best of our knowledge, there is no reported study about the feasibility of MRI radiomics in predicting SDM in patients with rectal cancer.

Radiomics, which involve high-throughput extraction of a large number of quantitative features from medical images, has recently received growing attention [12–14]. Predictive models or nomograms developed with radiomics signature or clinical-radiomics data could perform as imaging biomarkers for oncologic diagnosis and treatment guidance, thus supporting the personalized treatment. The potential benefit of radiomics had been highlighted in different clinical applications concerning cancer detection, phenotypic subtype classification, treatment response assessment, and so on [15–27]. With regard to rectal cancer, the application of radiomics mainly focused on the treatment response to chemoradiotherapy [23, 26–28].

In the present study, we aimed to assess the value of MRI radiomics based on T2-weighted (T2W) images in preoperatively identifying rectal cancer patients at high risk of SDM, and to develop a prediction clinical-radiomics combined model that can aid in improving decision-making and guiding individualized treatment.

Materials and methods

Patients

This retrospective study was approved by the Institutional Ethics Committee of Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, and the informed consent requirement was waived. Data of consecutive 531 patients with rectal adenocarcinoma confirmed by endoscopic biopsy between November 2015 and August 2017 in our institution were reviewed. Patients who underwent high-resolution pretreatment rectal MRI and unenhanced chest CT as well as contrast-enhanced abdominal CT examinations were enrolled ($n = 225$). Clinical data including age, gender, pretreatment carcinoembryonic antigen (CEA) data, pretreatment carbohydrate antigen 199 (CA199) data, tumor diameter, tumor location, MR-predicted T staging (mrT), and MR-predicted N staging (mrN) were collected. Forty-eight patients were excluded according to the criteria shown in Fig. 1. The final recruited patients were randomly allocated to the primary and validation cohorts in a ratio of 7:3. Then qualitative and quantitative image evaluation was performed. The workflow of this study is displayed in Fig. 1.

Imaging acquisition

All patients underwent rectal MRI with a 3.0-T scanner (Ingenia, Philips Medical Systems) using a 32-channel phase-array body coil in the supine position. A 60-mL enema was rectally administered 1 h before MRI to better visualize the primary tumor. Rectal distension with air or water was not performed, and antispasmodic medication was not provided. The minimum sequences acquired were sagittal T2-weighted imaging (T2WI), oblique axial high-resolution T2WI, coronal T2WI, and oblique axial single-shot echo planar diffusion-weighted imaging (DWI) with two b-factors (0 and 1000 s/mm^2) sequences. The oblique axial T2W sequence was acquired perpendicular to the long axis of the rectal tumor. The parameters of oblique axial T2WI are provided in Appendix E1.

All patients also underwent unenhanced chest and contrast-enhanced abdominal CT imaging using a dual-source 64-

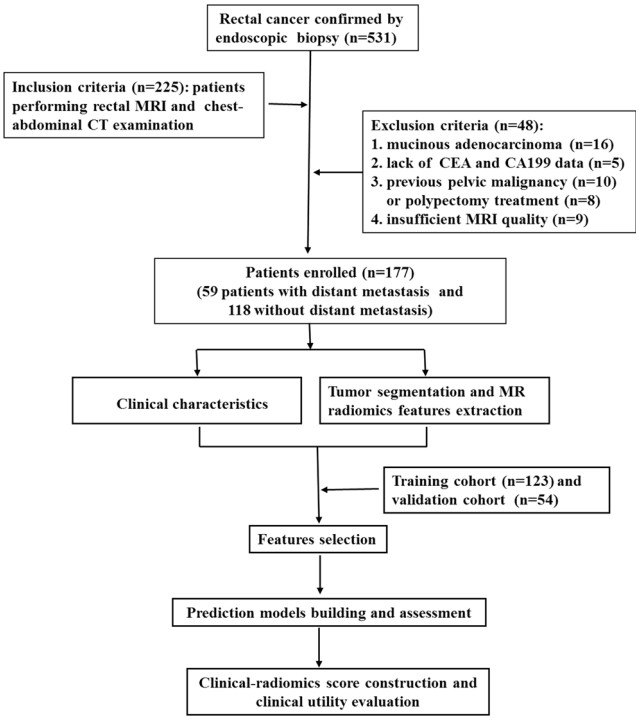

Fig. 1 Workflow of this study

MDCT (Somatom Definition Flash, Siemens Healthineers) scanner. The main parameters for chest and abdominal CT imaging are demonstrated in Appendix E2.

Qualitative image evaluation

All MR and CT images were retrieved from a picture archiving and communication system for further qualitative or quantitative analysis. Two radiologists (C.Y.Z and J.N.L, with 8 and 6 years of experience in gastrointestinal imaging, respectively) reviewed in consensus the pretreatment MR images of all patients and performed T and N staging as well as assessment of other pelvic tissues. Another two radiologists (L.J.W and R.L, with 6 and 5 years of experience in chest and abdominal diagnosis, respectively) analyzed in consensus the chest and abdominal CT images for distant metastasis assessment. All the radiologists were aware that the tumors were biopsy-proven rectal adenocarcinomas, but they were blinded to the histopathology staging information. When the observers could not reach a consensus, another experienced radiologist (D.B.W, with 30 years of experience in chest and abdominal diagnosis) was consulted for a final opinion. TN staging of rectal cancer was defined according to the 7th American Joint Committee (AJCC) TNM staging system. T3 tumor was further categorized into the early T3 tumor (T3a, extramural spread ≤ 5 mm) and advanced T3 tumor (extramural spread > 5 mm) due to the different prognosis [29]. Regional lymph node (LN) involvement was determined according to any criterion as follows: a short axis greater than 5 mm, mixed signal intensity, or irregular border [9].

Quantitative image evaluation

Image segmentation After the two radiologists who performed qualitative MR evaluation determined the tumor region on oblique axial T2W images in consensus with sagittal T2W, coronal T2W, and diffusion-weighted images as references, they independently and manually segmented the entire volume of interest (VOI) of the primary tumor via a free open-source software package (itk-SNAP, version 3.4.0, www.itksnap.org). The delineations included the surrounding chords and bundles, which were suspicion of tumor infiltration, and excluded the non-invaded rectal wall as well as the intestinal lumen. The delineation of rectal cancer is shown in Fig. 2.

Image feature extraction and selection A total of 385 radiomics features from the VOI were extracted automatically using in-house software (Analysis Kit, version 3.0.0, GE Healthcare). These radiomics features were divided into four groups: (1) gray-level histogram features; (2) shape features; (3) gray-level co-occurrence matrix (GLCM) features; and (4) gray-level run-length matrix (GLRLM) features. Detailed information about the extracted radiomics features is provided in Appendix E3. The interobserver reproducibility evaluation of radiomics feature extraction was performed using intraclass correlation coefficients (ICC), where an ICC of 0.81 to 1.00 showed almost perfect agreement, 0.61 to 0.80 as substantial agreement, and 0.41 to 0.60 as moderate agreement [26].

To reduce overfitting and select the most informative clinical and radiomics features to develop a prediction model, univariate statistical tests and a random forest algorithm comparing the metastasis and non-metastasis groups were performed in the primary cohort. First, the best-performing features based on the univariate statistical tests including analysis of variance (ANOVA), Kruskal-Wallis test, univariate logistic regression analysis, and Pearson correlation analysis with a Pearson correlation coefficient of 0.9 were selected. Second, a random forest algorithm was applied to select the most informative features that can contribute to the overall classification between the two groups in the primary dataset.

Development of the prediction model Multivariate logistic regression analysis using backward stepwise selection was applied to develop the clinical-radiomics combined model, incorporating the selected radiomics and clinical features. A clinical prediction model with the selected clinical characteristics alone was also built. The predictive performance of the clinical-radiomics combined model and clinical model in the training cohort was assessed by using the receiver operating characteristic curve (ROC) analysis, in which the areas under

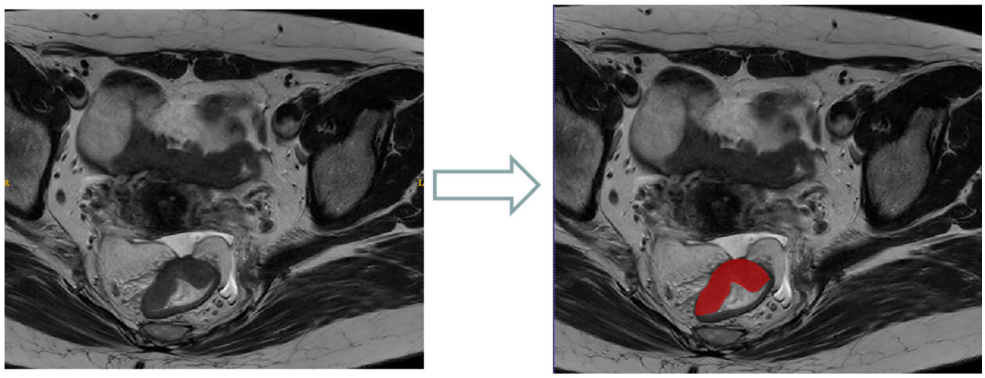

Fig. 2 Manual segmentation of rectal cancer

the curve (AUCs), sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and accuracies were established. The predictive performance of the models was further tested in the validation cohort.

Clinical-radiomics signature construction and clinical use A clinical-radiomics score was calculated for each patient using a linear combination of selected radiomics and clinical features in the validation cohort.

A clinical-radiomics nomogram was built in the training set. Decision curve analysis was implemented to evaluate the net benefits of the prediction models at different threshold probabilities in the training cohort.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD). Univariate associations of patient characteristics with the status of SDM were evaluated using independent two-sample *t* test and chi-squared test via SPSS 23.0 (IBM). The univariate statistical tests for selection of the radiomics and clinical features (one-way ANOVA, Kruskal-Wallis test, chi-squared test, univariate logistic regression, Pearson correlation analysis) and multivariate regression analysis for prediction model building were performed with R software (version 3.4.2, http://www.Rproject.org). $P < 0.05$ indicated a statistically significant difference.

Results

Patient characteristics

A total of 177 patients were recruited for analysis. Sixty patients underwent TME-based surgery after chemotherapy or chemoradiotherapy, and 102 patients without neoadjuvant treatment. The remaining 15 patients received only chemotherapy or chemoradiotherapy. The detailed patient characteristics are displayed in Table 1. There was no significant difference between the two groups in terms of gender, age, tumor location, and tumor diameter. CEA and CA199 levels were significantly higher in the metastasis group than in the non-metastasis group. Regarding the MR staging of rectal cancer, significant differences were observed for both mrT staging and mrN staging between the two groups.

Fifty-nine patients (33.3%) were confirmed to have SDM by either an imaging test or histopathological analysis. The metastatic locations were the liver ($n = 26$), lung ($n = 16$), bone ($n = 3$), peritoneum ($n = 2$), both the liver and lung ($n = 10$), both the liver and distant LNs ($n = 1$), and simultaneously the liver, lung, and peritoneum ($n = 1$). A total of 11 cases were confirmed by surgery and histopathology, and the other cases were diagnosed by radiologic features.

Features selection, development, and validation of prediction models

The inter-observer reproducibility of radiomics feature extraction was satisfactory with ICCs more than 0.80 for all extracted features.

After univariate statistical tests, 5 clinical and 7 radiomics features were selected. Finally, 10 features were included after applying a random forest algorithm: mrN staging, SphericalDisproportion, CA199, GLCMEntropy_angle90_offset7, GLCMEnergy_angle135 _offset7, Inertia_AllDirection_offset1_SD, CEA, SurfaceArea, GLCMEntropy_ angle0_offset4, and gender.

The clinical-radiomics combined and clinical models were built by applying multivariate logistic regression analysis. The AUC value of the combined model was 0.847, which was potentially higher than that of the clinical model with an AUC value of 0.792 in the training dataset, indicating that adding radiomics features could improve the predictive performance for SDM. A threshold value of 0.38 and 0.45 yielded an sensitivity, specificity, PPV, NPV, and accuracy of 75.6% (31/41), 75.6% (62/82), 60.8% (31/51), 86.1% (62/72), and 75.6% (93/123) for the clinical model, and 78.0% (32/41), 89.0% (73/82), 78.0% (32/41), 89.0% (73/82), and 85.4% (105/123) for the clinical-radiomics model, respectively.

Table 1 Characteristics of patients and associations with synchronous distant metastasis

Characteristics	Non-metastasis ($n = 118$)	Metastasis ($n = 59$)	p value
Median age, years (range)	64 (39–88)	64 (21–88)	0.889
Gender (%)			0.080
Male	68 (57.6)	42 (71.2)	
Female	50 (42.4)	17 (28.8)	
CEA, ng/ml			< 0.001
< 10	98 (83.1)	28 (47.5)	
≥ 10	20 (16.9)	31 (52.54)	
CA199, U/ml			< 0.001
< 30	104 (88.1)	33 (55.9)	
≥ 30	14 (11.9)	26 (44.1)	
Tumor diameter, mean ± SD, cm	4.20 ± 1.37	4.53 ± 1.16	0.112
Tumor location (%)			0.563
Proximal rectum	28 (23.7)	12 (20.3)	
Middle rectum	42 (35.6)	18 (30.5)	
Distal rectum	48 (40.7)	29 (49.2)	
mrT staging*			0.008
T1-2 and T3a	86 (72.9)	31 (52.5)	
Advanced T3	25 (21.2)	17 (28.8)	
T4	7 (5.9)	11 (18.6)	
mrN staging			< 0.001
N0	84 (71.2)	16 (27.1)	
N1–2	34 (28.8)	43 (72.9)	

CEA carcinoembryonic antigen, *CA199* carbohydrate antigen 199

$p < 0.05$ indicates a statistically significant difference

*T3 tumor was categorized into the early T3 tumor (T3a, extramural spread ≤ 5 mm) and advanced T3 tumor (extramural spread > 5 mm)

When the clinical and clinical-radiomics combined prediction models were applied to the validation cohort, the predictive performance was also satisfactory. The AUC of the clinical-radiomics combined model was 0.827, which also indicated a trend towards higher diagnostic efficiency in the combined model than in the clinical model, which had an AUC of 0.779. When the threshold value was 0.44, the sensitivity, specificity, PPV, NPV, and accuracy were 72.2% (13/18), 94.4% (34/36), 86.7% (13/15), 87.2% (34/39), and 87.0% (47/54), respectively for the clinical-radiomics combined model. A threshold value of 0.36 yielded a sensitivity, specificity, PPV, NPV, and accuracy of 77.8% (14/18), 77.8% (28/36), 63.6% (14/22), 87.5% (28/32), and 77.8% (42/54) for the clinical model. The ROC analysis results are displayed in Fig. 3.

Construction of the clinical-radiomics signature and its clinical utility

The 10 best-performing predictive features are demonstrated in Supplementary Fig. S1 according to the contributing weight. The distributions of the clinical-radiomics score for each patient in the validation cohort are shown in Fig. 4. The clinical-radiomics score could help stratify the metastasis patients and non-metastasis patients.

A clinical-radiomics nomogram was developed with the selected clinical and radiomics features (Fig. 5). Decision curve analysis revealed that if the threshold probability was more than 10%, using the clinical-radiomics combined prediction model was more beneficial than using the clinical model (Fig. 6).

Discussion

In the present study, we investigated the complementary value of T2WI-based radiomics in identifying high-risk patients for SDM. Our results revealed that the addition of radiomics features to the clinical model could achieve a better predictive performance for SDM in rectal cancer patients, with an improved AUC of 0.827 from 0.779 and a relatively high sensitivity, specificity, PPV, and NPV in the validation cohort. The high specificity and NPV indicated that this model was reliable and could eliminate more false-positive and false-negative patients. In contrast, the high PPV demonstrated that the clinical-radiomics model can satisfactorily assist in

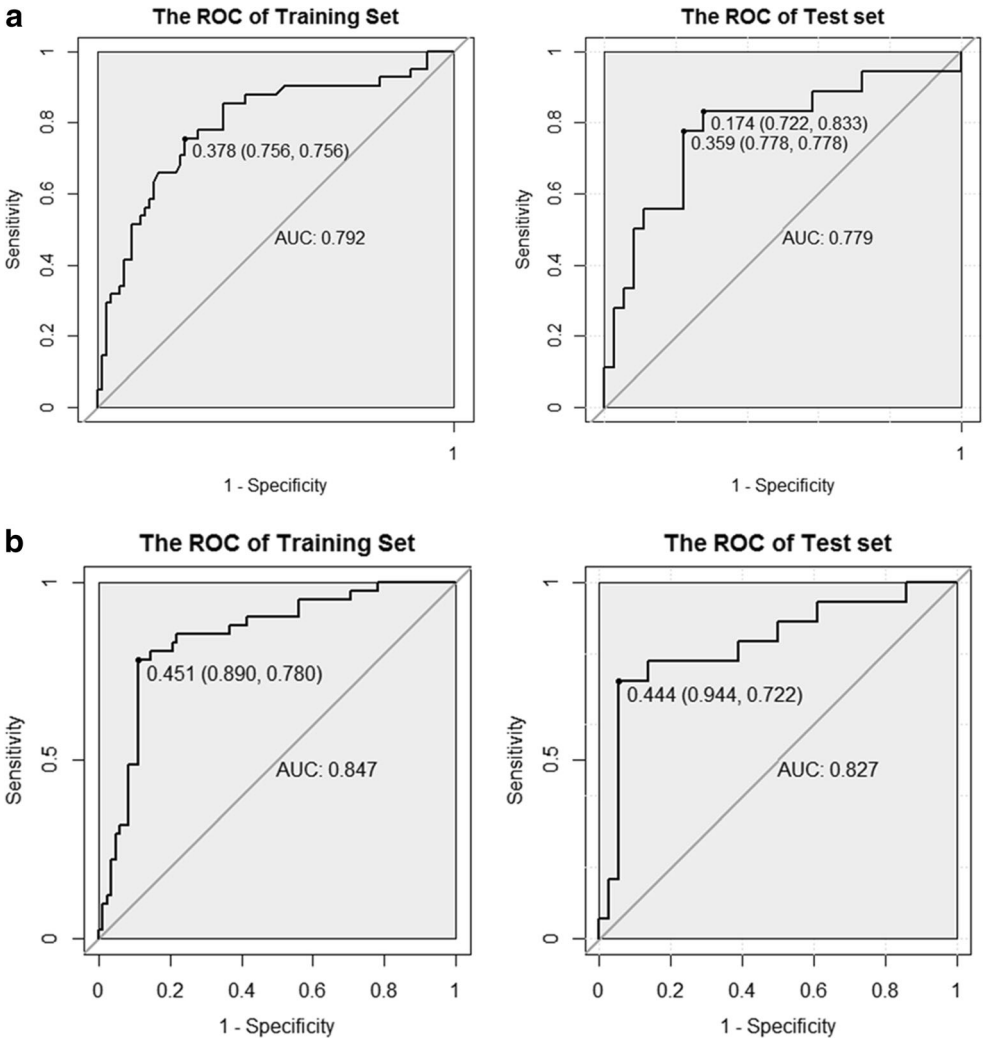

Fig. 3 Receiver operating characteristic curve (ROC) analysis for the clinical model (**a**) and clinical-radiomics combined model (**b**) in the training set and test set. The predictive performance of the combined model for preoperative synchronous distant metastasis of rectal cancer was better than that of the clinical model in both the training and test sets

identifying true high-risk patients of SDM. Those patients could be recommended to undergo more sensitive imaging examinations to detect additional metastatic lesions. The clinical-radiomics score could be used to stratify the high-risk and low-risk groups. Furthermore, we developed a clinical-radiomics nomogram as an individual and visualized tool to provide the estimated probability of SDM for a newly diagnosed rectal cancer patient. Decision curve analysis was also applied to confirm the clinical benefit.

Recently, few studies on rectal MRI have been conducted to seek noninvasive independent predictors of distant metastasis, in which features of MRI-detected extramural vascular

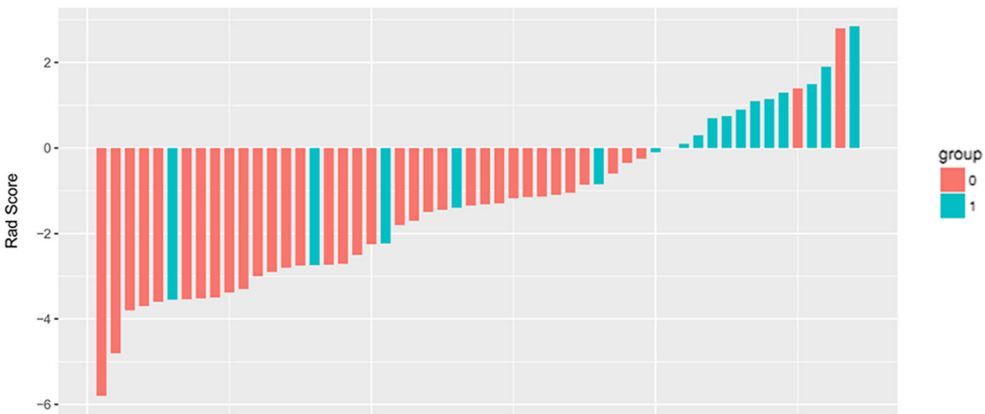

Fig. 4 Clinical-radiomics score for each patient in the validation cohort

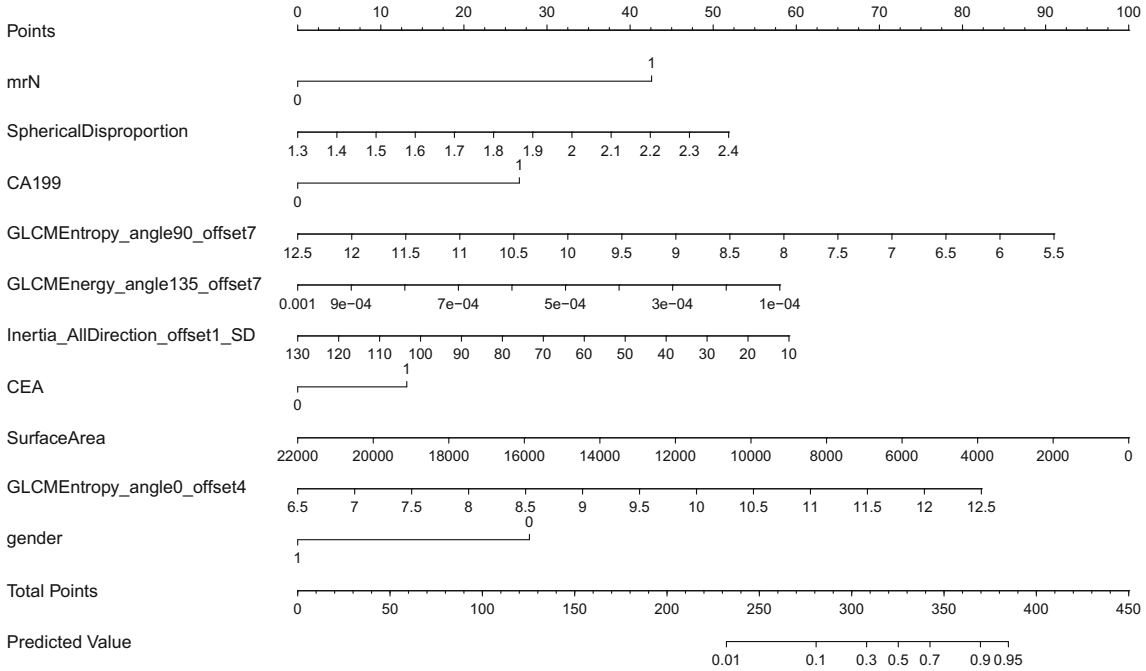

Fig. 5 The developed clinical-radiomics nomogram

invasion, high T staging, and positive regional LN metastasis were found to be potential predictors [9, 30]. In our prior study, we also confirmed that pretreatment LN involvement combined with elevated CEA levels could assist in recognizing high-risk patients for SDM [31]. However, these independent image predictors are subjective and qualitative parameters, which impair the clinical significance. Take the diagnosis of regional metastatic LN for example; it remains a major challenge with diagnostic accuracies ranging 43–85% [25]. Therefore, several studies had attempted to implement potential quantitative methods including DWI or diffusion kurtosis imaging (DKI) for predicting prognosis of rectal cancer. These studies [32, 33] found that DKI outperformed DWI in discriminating rectal cancer with distant metastasis from those without, and pathologic high- from low-grade rectal cancer, yet the predictive performance of LN involvement is still not satisfactory with an AUC of 0.726 [33].

Radiomics, integrating many high-dimensional imaging features used to quantify tumor heterogeneity, could facilitate oncologic diagnosis and prognosis prediction. The results of a recent study on applying radiomics analysis to predict LN metastasis in colorectal cancer with CT images was encouraging [34]. Huang et al [34] revealed that radiomics signature including 24 selected features could help predict LN-positive patients with a C-index of 0.773 in validation cohort and the proposed clinical-radiomics nomogram was useful for predicting LN involvement. Promising results of radiomics analysis were also revealed in identifying T stage and

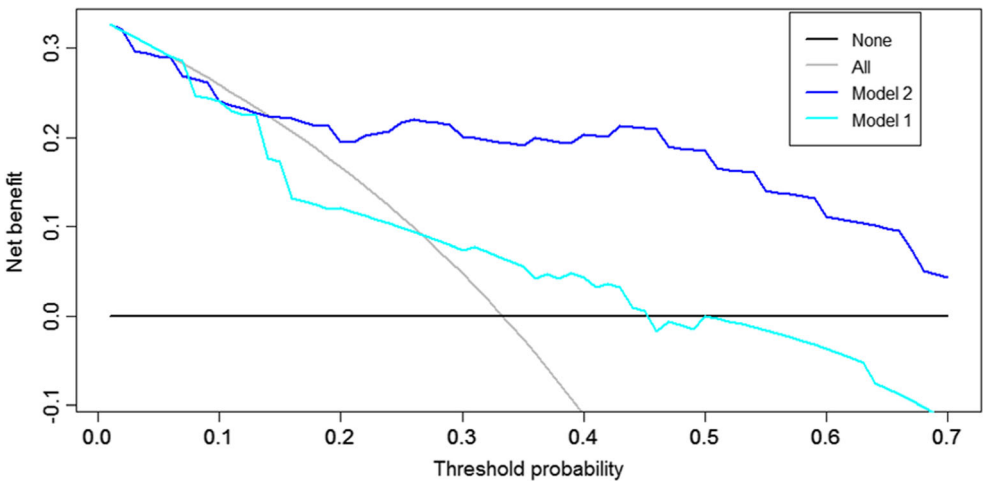

Fig. 6 Decision curve analysis for the clinical model (model 1) and clinical-radiomics combined model (model 2). The decision curve showed that if the threshold probability of a patient or a doctor is > 10%, using a clinical-radiomics combined model to predict preoperative synchronous distant metastasis of rectal cancer would be more beneficial than the clinical model

assessing neoadjuvant chemoradiation outcome with an AUC ranging 0.85–0.98 in previous studies [25–28]. In the present study, we investigate the added value of radiomics analysis to the clinical characteristics in predicting SDM, as TNM staging system of rectal cancer is still important and routinely used. Our results are also encouraging, especially for the higher specificity and PPV of clinical-radiomics model compared with the clinical model. The radiomics features in our study were calculated through the high-resolution axial T2W images alone because T2WI is the mandatory and key sequence in evaluation of primary rectal cancer [29]. On the other hand, variability in acquisition parameters from different sequences can be minimized. Our proposed clinical-radiomics prediction model confirmed the feasibility of T2WI-based radiomics analysis, providing a potential effective and easy-to-use model in clinical practice. Using our clinical-radiomics nomogram, an estimated probability of SDM could be calculated after referring to the selected T2WI-based radiomics features, MRI staging as well as other clinical information.

Our prediction model included clinical variables of positive mrN staging, elevated CA199, elevated CEA, and male gender. The results were consistent with the study conducted by Gaitanidis et al [6] whom reported that elevated CEA and positive mrN staging were associated with liver, lung, and bone metastasis, and male gender was an independent predictor of liver and bone metastasis. Regarding radiomics features, only shape features and texture features were included in our prediction model, reflecting the different growing patterns and the tumor heterogeneity of rectal cancer. Among the radiomics features, texture features accounted for most of them. Our study was similar to previous reports, demonstrating that texture features outperformed histogram-based or shape features in predicting tumor prognosis [17, 21]. The texture features reflecting interactions between neighboring pixels compared with histogram-based features dependent on a single pixel value is responsible for the phenomenon. Accordingly, it is not difficult to presume that intratumoral heterogeneity could be better captured through texture features.

Our study has several limitations. First, the sample size of patients with SDM was relatively small. A larger sample size and external validation will be required to confirm our prediction model in the future. Second, some unresectable distant metastasis lesions were proven by radiological features, lacking histopathological confirmation. Furthermore, more sensitive imaging modalities such as liver contrast-enhanced MRI or FDG PET-CT imaging are not performed in routine practice due to the limited resource and high cost. Hence, there is a possibility that some metastases were missed. Third, some reported poor prognostic factors of distant metastasis, such as extramural vascular invasion and mesorectal fascia involvement [10, 35] were not assessed in this study. For one thing, the discrimination between the tumor-invaded vessels and a benign desmoplastic reaction is difficult. For another, MR evaluation for mesorectal fascia involvement evaluation cannot be confirmed by histopathology due to the affection of neoadjuvant chemoradiotherapy. Finally, we performed only T2WI-based radiomics analysis to minimize variability in acquisition features. Another useful and routinely used sequence DWI reflecting tumor cellularity is not used in the radiomics analysis due to the insufficient image quality in some patients. We expect that the predictive value of radiomics analysis may be improved with the inclusion of DWI.

Conclusions

Our preliminary study demonstrated that T2WI-based radiomics analysis can improve the prediction of SDM. A proposed predictive clinical-radiomics combined model may provide useful information to help tailoring the initial staging and treatment strategy.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dengbin Wang, MD, PhD, the chief of department of radiology, Xinhua hospital affiliated to Shanghai Jiao Tong University School of Medicine.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Shaofeng Duan kindly provided statistical advice for the manuscript.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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