



T stage prediction of colorectal tumor based on multiparametric functional images

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Background: Recent studies have shown radiomics parameters of functional imaging have predictive values in many diseases. This study was to investigate the value of radiomics parameters of both computed tomography (CT) and magnetic resonance imaging (MRI) in predicting T stage of colorectal cancer (CRC).

Methods: Imaging findings of CT and MRI (both cT1-W and T2-W) and clinical information were collected from 29 patients. A total of 330 radiomics parameters were computed from manually annotated medical images, and a lasso regression model with 10-fold cross validation was employed to predict the T stage with radiomics parameters.

Results: The lasso regression model showed good performance with area under the curve (AUC) of 0.85. A total of three parameters from MRI were used in this model, while no CT findings were included in this model. The 3 selected parameters were from first-order parameters' group, which include energy and totalenergy from both cT1-W and T2-W. These parameters indicate the magnitude of pixels in the medical images.

Conclusions: This study indicates that some radiomics parameters of functional images have predictive values in T staging of CRC. Also, MRI may be more valuable than CT based on the image findings with lasso regression.

Keywords: Colorectal tumor; T staging; multiparametric functional imaging; regression

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Introduction

Numerous studies have shown that the differentiation of malignant tumor is an important prognostic factor (1). In the tumor staging [including colorectal cancer (CRC)], a two-tiered classification system of histologic grade (low grade = well and moderate differentiation; high grade = poor differentiation) is recommended because it has favorable reproducibility and prognostic significance. In addition, there is evidence showing that the risk to relapse is higher for high-grade CRC after tumor resection, which results in poor prognosis (2). It has been shown that pre-operative

radiotherapy and/or chemoradiotherapy may improve the local control and disease-free survival in high-risk CRC patients (1). However, neoadjuvant therapies may still cause serious side effects (1). Thus, the differentiation of high-grade CRC from low-grade CRC will be beneficial to maximize the benefit and avoid unnecessary side effects of pre-operatively excessive treatment, helpful to identify patients with high risk for recurrence before treatment and crucial for the individualized therapy, which hence improves outcomes.

The histologic grade determined by pathologic assessment of biopsy samples may offer some information

of tumor differentiation. However, most tumors are spatially heterogeneous, and there may be discrepancy in the histologic grade between biopsy samples and surgical specimens (1,3). As an invasive examination, colonoscopic biopsy also has complications such as bleeding, colonic perforation and abdominal pain (1).

Great progress has been achieved in the non-invasive diagnostic imaging techniques for CRC in the past decades. Computed tomography (CT) and magnetic resonance imaging (MRI) have been widely used in the preoperative staging of CRC (4-7). Nevertheless, the sensitivity and specificity of them are largely dependent on the classical colorectal morphologic evaluation. In a study of Kim *et al.* (3), the characteristic CT findings on contrast-enhanced CT were employed to discriminate poorly differentiated CRC from well or moderately differentiated CRC, and their results showed the sensitivity and specificity were 88% and 70%, respectively, but the subjective assessment of these features has a low reproducibility due to the significant intra- and interobserver variability.

Thus, it is imperative to develop functional primary local staging assessment method with advanced sequences, rather than the method relying only on the morphologic features. A radiomics signature has been developed to assist the differentiation of high-grade from low-grade CRC before treatment and studies have confirmed it as a complementary approach. The radiomics signature, as a non-invasive and quantitative tool to predict the histologic grade before surgery, plays a vital role in the individualized therapy and the improvement of outcomes in CRC patients. Huang *et al.* (1) reported the colonoscopic biopsy has limited value in the evaluation of histologic grade of CRC, because the overall accuracy was only 0.447, which was significantly lower than that of radiomics signature (0.775 in training dataset and 0.743 in validation dataset). In addition, some studies have revealed that the combined analysis of multiple features as a radiomics signature may be helpful for the evaluation of correlation between radiomics signature and histologic grade of CRC. Huang *et al.* (1) developed a radiomics signature and confirmed it was a complementary tool that helps to differentiate high-grade from low-grade CRC preoperatively which is beneficial for the personalized treatment. However, MRI was not included in their study. MRI has been widely accepted as a tool for the pre-treatment evaluation of CRC, especially in the local staging. The key sequences for T staging are high resolution T2-weighted turbo spin-echo (TSE) images

acquired in different planes, planned according to the axis and orientation of the tumor. Generally, MRI has a high sensitivity for local staging of the primary tumor, especially when T staging is considered. MRI has the potential to evaluate and predict circumferential resection margin (CRM) and extramural invasion (including venous invasion) with a high accuracy. In addition, studies have shown that it is a reproducible technique because its specificity is as high as 92% in predicting the negative CRM, the depth of invasion beyond muscularis propria and the relationship of the tumor with the CRM (7-10). In a study of Sun *et al.* (11), results showed pre-treatment T2WI radiomics could be used to characterize the histopathological features of rectal cancer, which suggests that tumor-derived radiological features may be employed for T staging.

In addition, the contrast-enhanced CT has also been frequently used in the management of CRC, and thus CT-based radiomics signature has better popularization and application in differentiating high-grade from low-grade CRC.

To the best of our knowledge, no study has been conducted to investigate the correlation between radiomics signature and histologic grade of CRC based on both CT and MRI findings. This study was undertaken to develop and validate a tumor stage prediction model based on the findings from functional imaging including CT and MRI (including cT1-W and T2-W images). Lasso regression model with 10-fold cross-validation was employed on the set of image parameters to predict the T stage of CRC.

Methods

Patients and data acquisition

Clinical records and functional images of 41 patients were retrieved in this study under the ethical board approval of Shuguang hospital affiliated to Shanghai Traditional Chinese Medical University from June 2018 to April 2019. Patients' written consent were not needed because this study is a retrospective study, and both CT and MRI were performed as regular examinations in our institution. This study aims to investigate the association between the parameters of functional images and T stage. Thus the T stage of the involved patients must be confirmed based on pathology diagnosis. To study the parameters of both MRI and CT images, the contrast-enhanced CT images, MR cT1-w and MR T2-w images of each patient must be available. Based on the two criteria, 29 were selected out of the 41 patients in this study. Among them, 6 was confirmed

Table 1 Characteristics of patients—CT, MR

Characteristics	Early-stage CRC	Late-stage CRC
Age (year)	66.67±6.80	70.83±7.43
Male	5 (5/29)	1 (1/1)
Female	1 (1/29)	7 (7/29)
Tumor pathologic types	Chorionic tubular adenoma with intraepithelial neoplasia 2 (2/29) Adenocarcinoma 1 (1/29) Adenocarcinoma 3 (3/29)	T3: Adenocarcinoma 21 (21/29); Mucinous adenocarcinoma 1 (1/29); Signet ring cell carcinoma 1 (1/29) T4: 0
Size of tumor (mm)		
Long diameter	42.57±12.43	62.69±34.22
Short diameter	20.6±7.27	24.96±14.19

MR, magnetic resonance; CT, computed tomography; CRC, colorectal cancer.

with early-stage tumor (T stage: Tis, 1 and 2), and 23 were confirmed with late-stage tumor (T stage: 3, 4). The characteristics of the patients are shown in *Table 1*.

Both the patients' CT scans and MRI scans were performed on the same day. All the patients CT scans were performed with a DECT scanner (SOMATOM Force; Siemens Healthineers, Forchheim, Germany), and all the MRI scans were performed on a 3.0-T system (uMR 780, united-imaging healthcare, China). A set of preparations were performed before the examinations. All patients were instructed to undergo the enema with water (about 500–1,000 mL) on the night before the DECT examination. On the day of the DECT examination, the patient's colon or rectum was not distended. The per-colonic or rectal contrast was setup according to the tumor location. In order to minimize the artifacts caused by respiratory motion, all the patients were asked to breathe quietly during their perfusion CT (PCT) examination.

In order to select the scan range for the PCT scan, a non-contrast scan of the entire abdominal cavity was performed at first, which covers the region from the lung base to the lower margin of the symphysis pubis. A VPCT scan was followed afterwards. Contrast injection was performed 5 seconds' prior to the VPCT scan, which includes a 33 mL of a nonionic iodinated contrast agent (350 mg/mL, Bonorex[®] 350; Central Medical Service) and a 33 mL saline flush via an antecubital vein. The scan coverage for PCT was setup to be 17.6 cm. The cycle time was 1.5 seconds. And a total of 26 scans were acquired during 40 seconds' scanning. The detector collimation of the PCT was 48×1.2 mm. The gantry rotation time was

0.32 seconds with a tube current-time product of 60 mAs at 80 kVp. A 3 mm increment was used to reconstruct the PCT images with a 5 mm thickness. DECT scan was performed after acquiring the PCT images. An additional contrast was injected 30 seconds before DECT scan, which include 1.2 mL of per kilogram of body weight and a 25 mL saline flush via an antecubital vein. The contrast was injected at a 3 mL/s flow rate. The tube voltage of 100 and Sn150 kVps and respective ref. tube current time products of 180 and 90 mAs were used. The detector collimation of the DECT scan was setup to be 128×0.6 mm. And gantry rotation time was 0.5 seconds. The image reconstruction was performed with 1.5 mm thickness at 1 mm increments.

After the acquisition of CT images, MRI was performed on the same day. Prior to the MRI scan, a 20 mg of phloroglucinol was injected to each patient intramuscularly, in order to minimize intestinal peristalsis. The patients didn't perform colorectal distension or antispasmodic medication. Routine 3 mm MRI scan was performed with no inter-slice gap, which include oblique sagittal and axial T2-weighted (T2-w), axial T1-weighted (T1-w) and contrast-enhanced T1-weighted (cT1-w) images. A 3D dynamic sequence was used to perform DCE-MRI. High spatial and temporal resolution was achieved with time-resolved technique based on inter-leaved stochastic trajectories (3D-QUICK). After DCE-MRI, gadopentetate dimeglumine (0.1 mmol/kg body weight, at a rate of 3.0 mL/s) and saline flush (25 mL) were injected to the patients. Thereafter, the axial images were obtained in 25 dynamic phases with 3 mm thickness, as well as the post-contrast coronal 3D T1W images with 3.0 mm thickness at

Table 2 MRI parameters

Parameter	Fast (Turbo) Spin Echo, T2 Weighted		Fast (Turbo) Spin Echo, T1 Weighted	Contrast-enhanced T1-weighted (cT1-w)
	Sagittal (LFOV)	Axial (LFOV)	Axial (LFOV)	Axial (LFOV)
Repetition time (TR), ms	4,062	3,948	766	3.47
Echo time (TE), ms	141	130	12	1.51
Flip angle (FA), °	110	110	150	10
Field of view (FOV), mm	240	220	250	350
Thickness/gap, mm	3/10	3/10	3/10	3/0
No. slices	25	28	28	54
Matrix	352*316	352*316	304*258	320*288
Acquisition time, min	2.35	3.50	2.30	5.17

MRI, magnetic resonance imaging.

10 mm interval. The details of involved parameters in the colorectal MR protocol and image acquisition process are presented in *Table 2*.

Parameters

In order to compute the image parameters from the tumor region, on each slice of the functional images, the tumor region was manually labelled by experienced radiologists using a free software named ITK-snap (9). Examples of the labelled regions are shown in *Figure 1*. Each tumor was labelled on multiple slices of the functional image.

Radiomics parameters were extracted from 3D volumes constructed from the labelled tumor region in each slice in many previous studies. However, the colorectal tumor has irregular shapes, which varies largely among slices and often occupies many slices in one image. Thus we believe that computing parameters from 3D volume will introduce additional variations and noises due to the 3D volume reconstruction from 2D regions. Instead, in this study, parameters were computed from slices without forming 3D volumes. The parameters were averaged over all slices of each patient and used for further analysis. The maximal values and the minimal values were removed from the averaging. Therefore, in order to compute the average values, the patients' images must contain at least 3 slices. From each of the CT contrast-enhanced image, MR cT1-w image and T2-w image, 110 image parameters were computed using an open-source Python package PyRadiomics (12). Therefore, a total of 330 image parameters were obtained for each patient.

Analysis

A classical regression analysis method named least absolute shrinkage and selection operation (Lasso) regression was used to build a prediction model of tumor T staging based on the pairs of image parameters and patients' T stages. A 10-fold cross-validation was applied. The regression method automatically assign non-zero weights to part of the parameters during the model training. Thus only parameters with meanings for the model were selected. The model was trained on the pairs of the computed image parameters and the patients' T stage.

Results

The patients were divided into non-metastatic group and metastatic group based on their tumor stages. Non-metastatic group refers to the early stage patients, and metastatic group refers to the late stage patients. The parameters were computed from the labelled tumor regions and averaged over slices for each patient. As at least 3 slices were needed for the computation of the average value, 3 patients were excluded due to that the number of labelled slices were fewer than 3. A total of 26 patients were analyzed. Among them, 4 were with early-stage CRC and 22 were with late-stage CRC.

Based on 10-fold cross-validation, three parameters with non-zeros coefficients were selected by the lasso regression model (see *Table 3*). It can be seen that all the selected parameters are first-order parameters. Among them, two are parameters of MR cT1-w images, the other one is

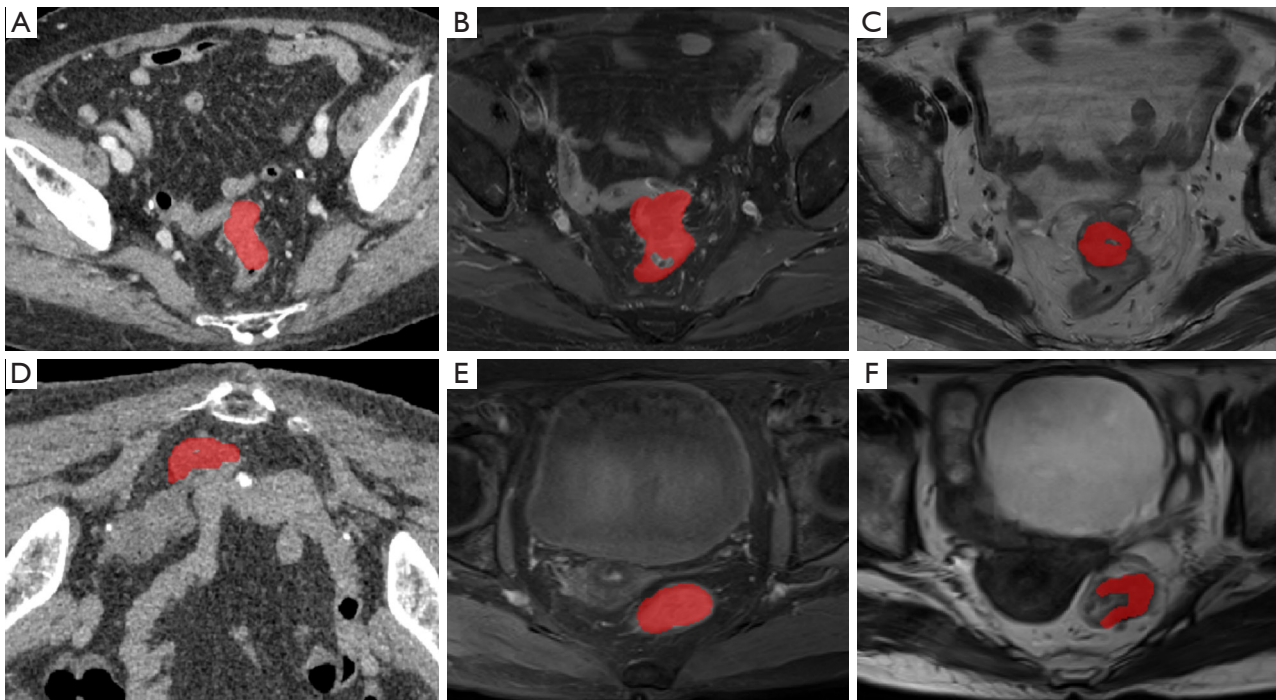


Figure 1 Example of labelled tumor regions. (A) Example of metastical tumor in CT image; (B) example of metastical tumor in MR T1 contrast image; (C) example of metastical tumor in MR T2 image; (D) example of benign tumor in CT image; (E) example of benign tumor in MR T1 contrast image; (F) example of benign tumor in MR T2 image. MR, magnetic resonance; CT, computed tomography.

Table 3 Selected image parameters with non-zero coefficients based on lasso regression

CT image parameters	T1 contrast image parameters		T2 image parameters
	First-order: energy	First-order: total energy	First-order: total energy

parameters of MR T2-images. None of the parameters of CT images is selected. The AUC obtained by the lasso regression model is 0.85 (see *Figure 2*).

Discussion

CT and MRI are the two main image resources for preoperative diagnosis of patients with colorectal tumor, which are often involved in their routine examinations. Previous studies have shown the predictive values of either CT or MRI on colorectal tumor (13-18). However, no study had used both of them. This study aimed to investigate the predictive values

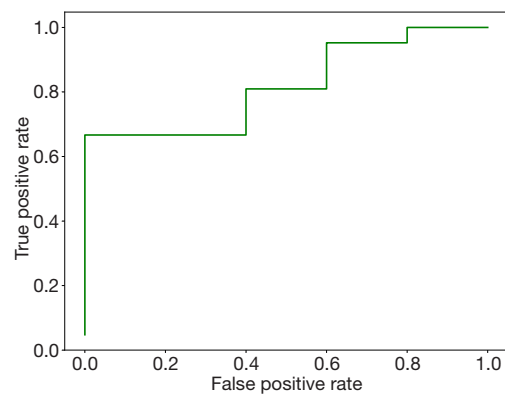


Figure 2 ROC curve of the Lasso regression model (AUC =0.85). ROC, receiver operating characteristic curve; AUC, area under the curve.

of the Radiomics parameters of both CT and MR images in colorectal tumor T staging. A total of 330 image parameters were computed from CT image, MR cT1-W image and MR T2-W image for each patient with confirmed T stage based on pathology. A prediction model was constructed based on the pairs of the parameters and the T stage using classical lasso

regression with 10-fold cross-validation.

It can be seen from *Figure 2* that the AUC of the prediction model is 0.85, which demonstrate the potential predictive value of the radiomics parameters. The selected parameter consists of one energy parameters and two total energy parameters. Based on definition (19), first-order statistics describe the distribution of the image intensities. Both energy and total energy measure the magnitude of the pixels in the image. Larger values imply a greater sum of the squares of the pixel values. This demonstrates that the magnitude of the pixels in the MR images have the potential to be used in colorectal tumor staging.

Moreover, it can be concluded that all the three selected parameters are first-order parameters from MR images (see *Table 3*), while no parameter is selected from CT image. This indicate that MR images may have more value than CT images in tumor staging prediction using modern computer-aided method. In the present clinical process, CT is a more widely applied technique than MRI in the pre-operative tumor staging due to the low cost and fast speed. In this study, by comparing CT with MRI, it reveals that MRI may be more valuable than CT. In clinical practices, many factors must be considered during pre-operative diagnosis and planning, for example the cost, scan time, radiation and predictive value. Thus, whether CT or MRI is to be used is related to the on-site situations.

Conclusions

This study investigated the predictive value of both CT and MR images in the evaluation of colorectal cancer staging. A lasso regression model was used to construct the prediction model based on Radiomics parameters of functional images. Based on the results, it is demonstrated that three parameters of MR (cT1-w and T2-w) images may have predictive value in the colorectal tumor staging evaluation. The number of patients included in our study is limited, therefore, CT and MR images of each patient are needed for evaluation. Our further study will focus on collecting more patients' data and validate the proposed model.

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Footnote

Conflicts of Interest: The authors have completed the

ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.11.41>). The authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study had been approved by the Ethics Committee of Affiliated Shuguang Hospital, Shanghai TCM University (2019-687-42). Patients' written consent were not needed because this study is a retrospective study.

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