T staging with functional and radiomics parameters of computed tomography in colorectal cancer patients

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Abstract
Preoperative T staging is closely related to operation planning and prognosis of colorectal cancer (CRC). This study aimed to re-investigate the value of computed tomography (CT) in T stage evaluation of CRC patients with both functional and radiomics parameters.

The functional and radiomics parameters of CT images and the clinical information were collected from 32 CRC patients. The radiomics parameters were measured based on manually labelled 5-mm circles using software Syngo. The radiomics parameters were computed based on labelled tumor regions using Python software package.

A total of 125 parameters were collected and analyzed by using decision tree analysis. The decision tree analysis identified 6 rules. Based on the rules, the shape elongation, flow extraction of nodule and blood volume of tumor region were found to be of significance and could define a high-risk group and a low-risk group.

This study shows the combination of functional parameters and radiomics parameters of CT is helpful for the diagnosis and T staging of CRC.

Abbreviations: BV = blood volume, BVD = blood volume, CRC = colorectal cancer, CT = computed tomography, DCE = dynamic contrast material-enhanced, DECT = dual energy CT, FED = flow extraction, MVD = micro-vessel density, PCT = perfusion CT.

Keywords: colorectal cancer, computed tomography, functional parameter, T staging, texture parameter

1. Introduction

Increasing attention has been paid to the assessment of tumor hallmarks and the microenvironment of colorectal cancer (CRC) with noninvasive imaging techniques. Medical imaging is a major noninvasive tool in the assessment of many diseases. It has also been commonly used in the TNM staging in patients with CRC as well as the clinical management of CRC.

As a quick examination of the chest and abdomen, computed tomography (CT) is commonly employed for the staging of local and distance lesions. In clinical practice, it is used as a routine procedure in many hospitals in the preoperative assessment of patients with CRC. Although it has been widely used, conventional structural imaging techniques have limitations in the assessment of tumors in recent studies.[1,2] For example, in

the adenoma-carcinoma sequence of CRC, angiogenesis has been recognized as a key feature in the early development of cancers. Therefore, some studies have employed histologic markers of angiogenesis such as micro-vessel density (MVD) and vascular endothelial growth factor as important prognostic factors of CRC. However, conventional imaging fails to quantify the angiogenesis.

In recent years, along with the transition of function imaging techniques, for example, dynamic contrast material-enhanced (DCE) imaging, into clinical practice, important new insights have been introduced into tumor phenotype.[3] For example, perfusion CT (PCT) has been employed to quantify the tissue vascularity and angiogenesis via tracking the contrast agents in the absence of tissue biopsy. To date, few studies have been undertaken to investigate CRC with PCT. Goh et al[4] found that

some PCT parameters such as blood volume (BV) and permeability surface-area product were positively related to MVD. However, the relationship between PCT-related parameters (eg, blood flow and permeability) and MVD remains controversial in the CRC.[4,5] Studies about the role of PCT in tumor characterization indicate PCT-related parameters are related to the degree of tumor differentiation and the tumor grade. In the study of Xu et al,[6] results showed the blood flow and time to peak on PCT were related to the tumor grade. The study of Sun et al[7] revealed that the mean blood flow was significantly different among well, moderately, and poorly differentiated tumors. Although DCE imaging technique has shown great value, they are not widely applied in clinical practice because there are different technical approaches, the measurements of parameters are complex, and the reproducibility of these parameters is poor.

In clinical process, medical images are perceived with simple visual inspection by radiologists, in which case, size, shape and intensity (eg, mean CT HU value) were the parameters that can commonly be observed. In recent years, many other parameters have been identified from medical images with computer-aided methods, which is named as radiomics parameters.[8] In the evaluation of CRC, some preliminary studies have shown the potential values of radiomics parameters (such as imaging texture features, spatial distribution and heterogeneity of voxel intensities). In the T-staging, radiomics features of CT[9] and MRI using T2WI[10] and ADC map[11] have been investigated in previous studies and have shown to be useful. In a study of Huang et al,[12] radiomics signatures were identified from CT images and used for the preoperative discrimination of high-grade CRC from low-grade one. Their results showed the effectiveness of the radiomics signature with large area under the curve. In their study, only the portal venous phase CT images were used in the identification of radiomics signature, while none of the DCE parameters were involved.

To date, no study has investigated the role of both CT perfusion and texture parameters in the evaluation of histologic grade of CRC. The present study aimed to re-explore the potential values of both functional parameters and radiomics parameters from CT in CRC staging.

2. Materials and methods

2.1. Patients

This study is a retrospective study, and was approved by Shuguang Hospital, and thus written consent was not required. The CT images and clinical records were collected from 41 patients between June 2018 and April 2019 in Shuguang hospital. A total of 32 patients in whom the T stage of CRC was confirmed during the surgery and by the postoperative pathology were included for further analysis. Among them, 7 patients had no metastasis, and the remaining 25 patients were diagnosed with metastatic tumor. The characteristics of these patients are shown in Table 1. Metastatic tumor is defined as the tumor with T stage ≥3 based on surgical and pathological examinations, and nonmetastatic tumor as the tumor with T stage <3.

All patients received a dual energy CT (DECT) (SOMATOM Force; Siemens Healthineers, Forchheim, Germany) scanning. Each patient was received an enema with 500 to 1000 mL of water 12 hours before the examination. No distention was performed in the colon or rectum before the CT acquisition. The per-colonic or rectal contrast was set up according to the

Characteristics of CT images in patients.

Characteristics	Nonmetastatic CRC	Metastatic CRC
Age (yr)	65.14 ± 7.40	69.88 ± 8.45
Gender		
Male	5 (5/32)	18 (18/32)
Female	2 (2/32)	7 (7/32)
Pathologic type		
Chorionic tubular adenoma with intraepithelial neoplasia	2 (2/32)	
Adenocarcinoma	2 (2/32)	23 (23/32)
Adenocarcinoma	3 (3/32)	
Mucinous adenocarcinoma		1 (1/32)
Signet ring cell carcinoma		1 (1/32)
Stage		
T3		25
T4		0
Tumor size (mm)		
Long diameter	37.63 ± 17.31	61.73 ± 32.98
Short diameter	19.0 ± 7.87	25.10 ± 13.67

CRC = colorectal cancer, CT = computed tomography.

location of the tumor. During the PCT, patients were asked to breathe as quietly as possible, aiming to reduce the artifacts caused by respiratory motion. The scan range of the PCT was determined based on a noncontrast scan performed from the lung base to the lower margin of the symphysis pubis in the abdominal cavity. After the previous step, a 350 mg/mL nonionic iodinated contrast agent (33 mL, Bonorex 350; Central Medical Service) was injected to the patient at a rate of 6.5 mL/s, followed by injection with 33 mL of normal saline. Both the injections were performed via the antecubital vein. Five seconds after injection, VPCT scanning was initiated, during and images were collected for 40 seconds with a cycle time of 1.5 seconds. This generated 26 scans covering 17.6 cm for PCT scan. The detector collimation was 48 × 1.2 mm. The gantry rotation time was 0.32 seconds and the tube current-time product was 60 mAs at 80 kVp. The collected images were reconstructed with the thickness at 5 mm and a 3-mm increment.

DECT was performed after the acquisition of PCT data set. For each patient, an additional contrast (1.2 mL/kg body weight) was injected at 3 mL/s, followed by a flush with 25 mL of normal saline at the same rate via the antecubital vein. Thirty seconds after the injection, DECT scanning was started. The tube voltage was set at 100 and Sn150 kVps and the respective ref. tube current time products were set up to be 180 mAs and 90 mAs. The detector collimation was 128 × 0.6 mm and the gantry rotation time was 0.5 seconds. The reconstruction was performed at 1.5 mm in thickness and with 1 mm increment.

2.2. Parameters

This study investigated both functional parameters and texture parameters of CT images. A total of 125 parameters were computed from the labelled CT images of each patient, including 18 functional parameters and 107 radiomics parameters. The functional parameters include 6 types: iodine content, blood volume (BVD), mean transit time, time to drain, time to peak, and flow extraction (FED or permeability). They were measured using Syngo by drawing 5-mm circles on the tumor region, lymph nodule region and normal tissue region with the CT Perfusion software package (Fig. 1).

Figure 1. Labelled ROIs of tumors, nodules, and normal tissues. The circles were 5 mm in diameter and manually labelled by radiologists. (A) Tumors; (B) nodules; (C) normal tissues.

Tumor regions were manually labelled by experienced radiologists using a free software ITK snap for the computation of radiomics parameters.[13] Tumor regions were labelled on multiple slices in each CT image. Examples of labelled tumor regions are shown in Figure 2. It indicated that their shapes varied significantly. Based on an open source software named pyRadiomics,[8] a set of 107 radiomics parameters were computed for each tumor region. The averaged parameters of multiple tumor regions in each CT image were used for analysis. Based on the experiment, 3 patients were excluded from analysis because their functional parameters were incomplete. A total of 29 patients were included, including 6 patients with nonmetastatic CRC, and 23 with metastatic CRC.

2.3. Methods

A decision tree method with Gini impurity criteria was used to identify the rules between the computed parameters and the tumor T stages in this study. The decision tree method was implemented using free Python data mining and analysis package scikit-learn. Decision tree method is often used as a classification method, which can group data according to its attributes and class. Different to other classification method, decision tree method is superior because rules can be identified based on learned classification model. In this study, the functional parameters and the radiomics parameters were the attributes of the patients, and the class was the tumor T stages.

3. Results

Based on the decision tree analysis, 6 rules of tumor metastasis were identified (Table 2). Among them, 3 were rules in the

metastasis group, and the remaining 3 were rules in the nonmetastasis group. The ratios of the patients' number (n/N) are shown in Table 2, where n refers to the number of patients that satisfy the rule, and N refers to the number of patients in either metastasis group or nonmetastasis group.

A total of 4 parameters were selected out of 125 parameters to define the 6 rules. Among them, 2 were radiomics parameters and the remaining 2 were functional parameters. The 2 radiomics parameters were shape: elongation and glrlm: run length nonuniformity. The 2 functional parameters were the FED value of the nodule and the BVD value of the tumor. Results showed that both radiomics parameters and functional parameters were needed in the tumor metastasis grouping using the decision tree method.

As shown in Table 2, the first rule in both metastasis group and nonmetastasis group had the highest ratios of patients' number (metastasis: 20/23 = 87.0%, nonmetastasis: 4/6 = 66.7%), and both were defined by 3 parameters. The numbers of selected patients by the first rule in the metastasis group and the nonmetastatic group accounted for a large proportion in the metastasis and nonmetastatic group, respectively, which demonstrates that they are common characteristics. As compared to the other 4 rules, which were found in small numbers of patients, the first 2 rules were of greater importance.

For the first rule in the metastasis group, 20 of 23 metastatic patients had following common characteristics: shape: elongation >0.468, FED: nodule > 6.595, and BVD: tumor > 5.01. For the first rule in the nonmetastatic group, the common characteristics were shape: elongation > 0.587 and FED: nodule ≤ 6.595. The shape: elongation describes the relationship between 2 largest principal components in the labelled region,[8] which refers to the ratio between 2 largest principal components of the
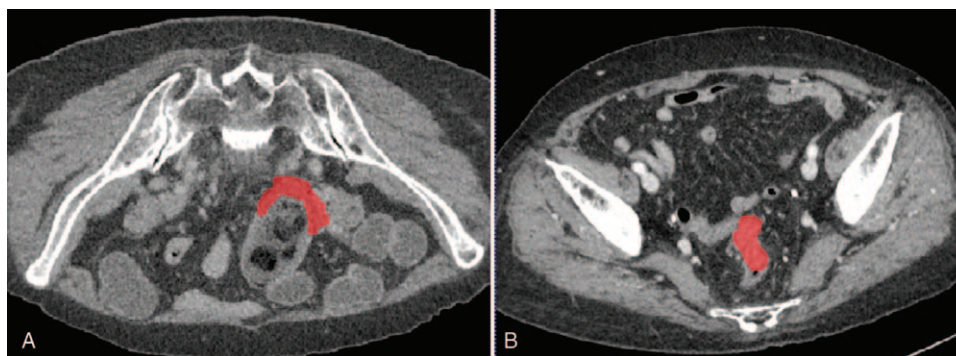

Figure 2. Representative labelled tumor regions on CT images. (A) Nonmetastatic tumor; (B) Metastatic tumor. CT = computed tomography.

Rules of tumor metastasis.

Items	n/N	Radiomics parameters		Functional parameters	
		Shape: elongation	glrlm: RunLengthNonUniformity	FED: nodule	BVD: tumor
Metastasis	20/23	>0.468		>6.595	>5.01
	1/23	≤0.468	≤138.876	>6.595	>5.01
	2/23	≤0.587		≤6.595	
Nonmetastasis	4/6	>0.587		≤6.595	
	1/6	≤0.468	>138.876	>6.595	>5.01
	1/6			>6.595	≤5.01

BVD = blood volume, FED = flow extraction, glrlm = gray level run length matrix, n = number of patients in the group that follow the rules, N = the total number of patients in the metastasis or nonmetastasis group.

tumor region in this study. This parameter was involved in the first rule of both metastatic group and nonmetastatic group, which indicates that the shape of the tumor is related to the metastasis. Besides shape: elongation, 2 functional parameters were involved: the FED of the nodule and the BVD of the tumor. The FED value of the nodule in the metastatic group was larger than in the nonmetastatic group.

In summary, based on 3 parameters: shape: elongation, FED: nodule, BVD: tumor, a high-risk group (the first rule in the metastatic group) and a low-risk group (the first rule in the nonmetastatic group) could be identified. Thus, the 3 parameters could be used to assist T staging of CRC.

4. Discussion

As a quick imaging method, CT has been the first choice for the preoperative staging of CRC in clinical practice.[14] Although it is widely applied, clinically-used features of CT images for tumor evaluation appear to be very subjective due to the intra- and interobserver variability. With the assist of modern computer engineering methods, the high-throughput quantitative parameters (namely radiomics parameters) can be extracted from tumor images.[15–17] In the assessment of CRC differentiation, some radiomics parameters have demonstrated potentials in previous studies and they can be used to assist the individualized management of CRC.[9,18,19]

In the present study, results showed that among all the radiomics parameters used in this study, shape: elongation and glrlm: run length nonuniformity were of greater value than other parameters. They are difficult to be observed and described by naked eyes. This demonstrates the potential value of radiomics parameters. Comparing to traditionally-used clinical parameters, radiomics parameters can describe subtler changes within the tumor region in the CT images.

In recent years, the PCT perfusion parameters have drawn lots of attention since PCT has been applied in clinical practice. Studies have shown that the PCT perfusion parameters can be applied to assess the tumor response to certain treatment. In a study of neoadjuvant chemotherapy, the blood flow, BVD, and permeability changed significantly in the rectal cancer patients after chemotherapy.[20] In the present study, we investigated the role of CT perfusion in the assessment of histologic grade of CRC. In our study, based on the first rule, the FED of the nodule in the metastasis group was larger than in the nonmetastasis group. Our results showed the metastatic lymph node is often related to rich blood supply, which thereafter increases the estimated perfusion.

This study investigated the application radiomics parameters together with functional parameters in the evaluation of CRC staging. The findings of this study indicate that the combination of functional parameters and radiomics parameters may be valuable in the evaluation of CRC. Although the sample size was small, they are of great value because they may provide evidence for the T staging of CRC and assist the diagnosis and treatment of CRC. As they are both quantitative parameters, embedded software may be developed to generate one-click application in the future, which makes the investigation promising in practical application.

5. Conclusions

This study investigates the predictive value of radiomics parameters and functional parameters from CT. A decision tree method is used to generate a set of rules for tumor metastasis classification. Based on the 6 rules generated, 3 parameters with significance can be used to define the high-risk group and the low-risk group. Among these parameters, 1 is the radiomics texture parameter, and the remaining 2 are the functional parameters. This shows that the combination of functional parameters and texture parameters may have the potential in the classification of tumor metastasis based on CT images.

Author contributions

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