

MAJOR PAPER

Quantitative T2 Mapping to Discriminate Mucinous from Nonmucinous Adenocarcinoma in Rectal Cancer: Comparison with Diffusion-weighted Imaging

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Purpose: Mucinous adenocarcinoma (MA) is associated with worse clinicopathological characteristics and a poorer prognosis than non-MA. Moreover, MA is related to worse tumor regression grade and tumor downstaging than non-MA. This study investigated whether lesions in MA and non-MA can be quantitatively assessed by T2 mapping technique and compared with the diffusion-weighted imaging (DWI).

Methods: High-resolution MRI, DWI, and T2 mapping were performed on 81 patients diagnosed with rectal cancer via biopsy. Afterward, T2 and apparent diffusion coefficient (ADC) values were manually measured by a senior and a junior radiologist independently. By examining surgical specimens, the patients with MA and non-MA were identified. Inter-observer reproducibility was tested, and T2 and ADC values were compared using Mann–Whitney U test. Finally, receiver operating characteristic (ROC) curves were drawn to determine the cut-off value.

Results: Of the 81 patients, 11 patients with MA were confirmed by pathology. The inter-observer reproducibility of T2 and ADC values showed an excellent intraclass correlation coefficient (ICC) of 0.993 and 0.913, respectively. MA had higher T2 (87.9 ± 5.11 ms) ($P = 0.000$) and ADC (2.03×10^{-3} mm²/s) ($P = 0.000$) values than non-MA (66.6 ± 6.86 ms and 1.17×10^{-3} mm²/s, respectively). The area under the ROC curves (AUC) of the T2 and ADC values were 0.999 (95% confidence interval [CI]: 0.953–1) and 0.979 (95% CI: 0.920–0.998), respectively. When the cutoff value in T2 mapping was 80 ms, the Youden index was the largest, sensitivity was 100%, and specificity was 97%.

Conclusion: As a stable quantitative sequence, T2 mapping of MRI is useful in differentiating MA from non-MA. Compared to ADC values, T2 values are also diagnostically effective and non-inferior to ADC values.

Keywords: rectal cancer, mucinous adenocarcinoma, magnetic resonance imaging, T2 mapping, diffusion-weighted imaging

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Introduction

Mucinous adenocarcinoma (MA) is diagnosed when over 50% of the tumor comprises a mucinous pattern upon histological examination.¹ MA of the rectum, which accounts for 5%–10% of all adenocarcinomas of the rectum,² is associated with worse clinicopathological characteristics and a poorer prognosis with an increased risk of metastasis, and poorer survival rates than non-MA.^{3,4} In terms of treatment, MA is related to worse tumor regression grade and tumor downstaging than non-MA.^{4,5} The reason why MA is prone to resistance to chemotherapy is partly that the genetic origins of MA are predominantly associated with v-Raf murine sarcoma viral oncogene homologue B (BRAF), microsatellite

instability (MSI), and CpG island methylator phenotype (CIMP) pathways.⁶ Therefore, the treatment strategy for MA could be preoperatively differentiated from non-MA.⁷

In the past decade, high-resolution MRI has been widely used in preoperative evaluation of rectal cancer.^{8,9} However, distinguishing MA from non-MA by the subjective judgment of radiologists is difficult. As a helpful and highly reproducible functional sequence of MRI, diffusion-weighted imaging (DWI) is widely employed in clinical imaging of rectal cancer.^{10,11} Apparent diffusion coefficient (ADC) values can be used to identify tumor necrosis or solid tumor; ADC values are higher in necrosis and mucus than in the solid composition of rectal cancer.^{12–14} In theory, ADC values can also be utilized to identify MA from non-MA because the mucus component has high ADC values. However, DWI not only has a low spatial resolution but is also very susceptible to image artifacts because it is based on echo-planar imaging pulse sequences. As another quantitative measurement, T2 mapping has the potential to objectively quantify different tissues according to T2 values. T2 mapping not only shows high spatial resolution but is also less prone to motion artifacts because it is based on spin-echo sequences. T2 mapping is widely utilized to identify myocardial edema and fibrosis,^{15,16} and it has the potential to distinguish benign and malignant tumors in mammary glands.¹⁷ We hypothesized that T2 mapping can potentially distinguish MA from non-MA based on T2 values of tumors.

In this study, we investigated the feasibility and reproducibility of T2 mapping and DWI in distinguishing MA and non-MA preoperatively. To the best of our knowledge, this is the first study to evaluate the use of T2 values for the characterization of MA in patients with rectal cancer.

Materials and Methods

Patients

This retrospective study was approved by the institutional review board, and informed consent was waived. A total of 81 consecutive patients who were diagnosed with rectal cancer and had undergone surgical resection from November 2017 to March 2020 were initially enrolled. The inclusion criteria were as follows: (1) histologically confirmed rectal cancer by surgery with the maximum diameter of the tumors in the gross specimen was greater than 1 cm; (2) DWI and T2 mapping were included in MRI 2 weeks before operation; and (3) the boundaries of the tumors and surrounding tissues were shown very clearly without any overlapping artifacts on DWI and T2 mapping that the ROI of tumors can be clearly delineated. The exclusion criteria were as follows: (1) patients who received treatment (radiotherapy or chemotherapy) before MR examination and (2) diagnosed with specific pathological types of rectal cancer except for mucinous and tubular adenocarcinoma, including signet ring cell carcinoma,

adenosquamous carcinoma, and squamous cell carcinoma. The workflow of this study is displayed in Fig. 1.

MRI protocol

A 3.0-Tesla (T) MR system (Discovery MR750w; GE Healthcare, Chicago, IL, USA) with a 16-channel phased-array body coil was used for image acquisition. All patients were scanned in the supine position with a feet-first orientation. Before rectal preparation, the patients were fasted and orally administered with polyethylene glycol electrolyte solution for 6–8 hours. Unless contraindicated, 20 mg of raceanisodamine hydrochloride (Minsheng Pharmaceutical Group, Hangzhou, China) was slowly injected intramuscularly into the buttocks to prevent bowel peristalsis 10–15 min before the examination. Axial, sagittal, and coronal high-resolution T2-weighted images, as well as axial DWI, were obtained. The oblique axial planes were orthogonal to the tumor base on the high-resolution T2-weighted imaging (T2WI). FOV settings included tumors and all lymph nodes in the mesentery and fascia. Coronal T2 maps were scanned with reference to the high-resolution T2-weighted images and DWI ($b = 1000 \text{ s/mm}^2$). The parameters for all MRI protocols are enumerated in Table 1.

Image measurements

T2 and the ADC map were automatically post-processed on a workstation (ADW 4.6; GE Healthcare). An image in the T2 mapping was selected to place an ROI at least 10 mm^2 on the tumor at the slice with the largest axial diameter of the tumor. The ADC value of the tumor was measured on the ADC map with reference to axis T2-weighted image by following the same method. T2 and ADC values were independently measured by two radiologists. Clinical parameters, including sex, age, and TNM staging, were also recorded.

Statistical analysis

χ^2 -test or Fisher's exact test was used to compare the clinical characteristics of the two groups of patients (MA and non-MA) where appropriate. Intra-class correlation coefficient (ICC) with two-way effects was used to evaluate inter-observer agreement for T2 and ADC measurements. The strength of inter-observer agreement was defined as poor (< 0.00), slight ($0.00–0.20$), fair ($0.21–0.40$), moderate ($0.41–0.60$), substantial ($0.61–0.80$), and almost perfect (> 0.80). The Student's t-test was used to compare the T2 and ADC values of the MA and non-MA groups. A receiver operating characteristic (ROC) curve analysis was performed on the T2 and ADC values to obtain the optimal cut-off value. Areas under the ROC curves (AUCs) were calculated to determine the diagnostic performance of the T2 and ADC values, whereas a De-long test was conducted to compare the differences among the curves. All statistical analyses were performed using MedCalc (version 11.3.8.0; MedCalc Software, Ostend, Belgium) and SPSS software (version 22.0; IBM, Armonk, NY, USA). A P value less than 0.05 was considered to be statistically significant.

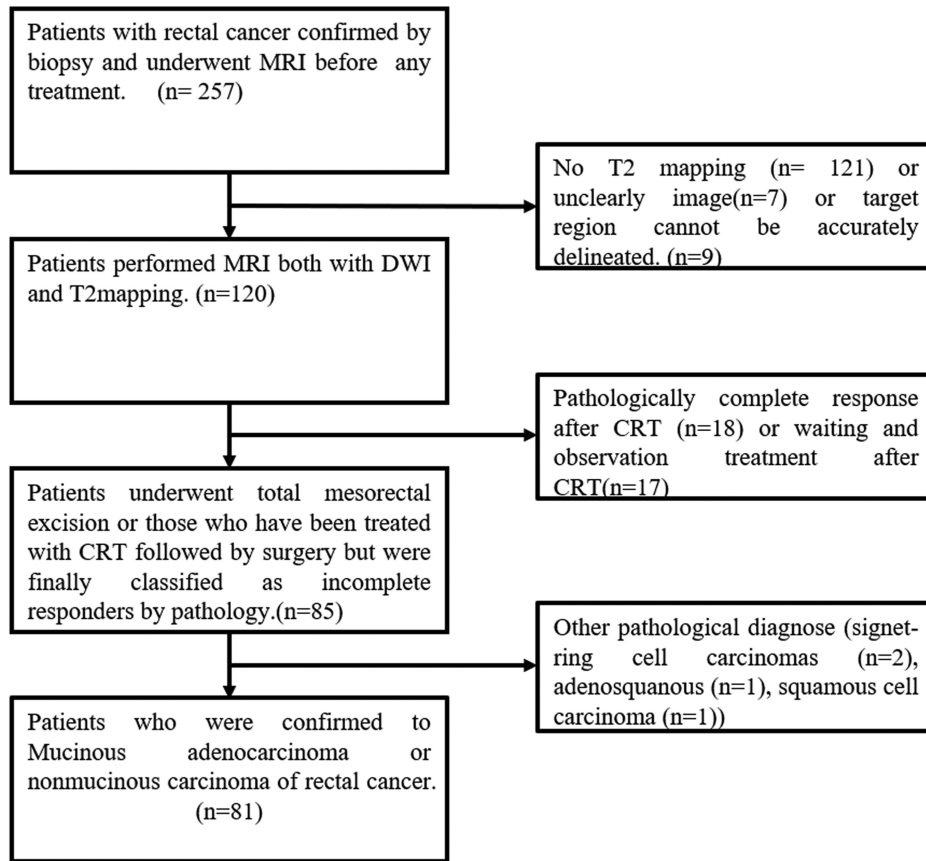


Fig. 1 Illustration of the workflow of this study. CRT, chemoradiotherapy; DWI, diffusion-weighted imaging.

Table 1 MR sequence parameters

Parameters		T2WI		DWI	T2 mapping
Oreitation	Sagittal	Axial	Coronal	Axial	Coronal
Sequence	Spin-echo	Spin-echo	Spin-echo	EPI	Multiecho spin-echo
TR (ms)	6222	5367	5367	3648	2000
TE (ms)	107	107	107	70	8.1–64.6 ($\Delta = 8.1$ ms)
FOV (mm)	260	180	180	360	320–340
Slice thickness (mm)	4.0	3.0	3.0	5.0	3.0
b value (s/mm ²)	-	-	-	0, 800	-
No. of slices	20	30–37	30	21	19
Acquisition time (min:s)	3:50	3:10–3:50	2:36	1:03	4:03

DWI, diffusion-weighted imaging; T2WI, T2-weight imaging; EPI, echo planar images.

Results

Clinical and histopathologic findings

Among the 81 patients, 11 were diagnosed with MA and 70 with non-MA based on the pathological results. Clinical

data, including gender, age, T stage, N stage, and smoking history, were statistically analyzed. Results showed that patients with MA had higher T and N stages than the patients with non-MA (Table 2).

Table 2 Clinical characteristic of patients

Characteristic	non-MA n(%)	MA n(%)	P value
Number	70	11	
Gender (%)			0.457
male	49 (70)	7 (63.6)	
Female	21 (30)	4 (36.4)	
Age, year, mean + SD (range)	52 ± 8 (15–67)	48 ± 10 (25–72)	0.021
Smoking history (%)			0.585
Smoker	18 (25.7)	3 (27.3)	
Non-smoker	52 (74.3)	8 (72.7)	
Histologic t stage (%)			0.243
T1-T2	24 (34.3)	2 (18.2)	
T3-T4	46 (65.7)	9 (81.8)	
Histologic n stage (%)			0.029
N0	44 (62.9)	3 (27.3)	
N1–2	26 (37.1)	8 (72.7)	

MA, mucinous adenocarcinoma; SD, standard deviation.

Table 3 Inter-observer agreement of T2 value and ADC for the patients

	Reader 1 (the senior radiologist)	Reader 2 (the junior radiologist)	Inter-observer consistency test
T2 value (ms)	69.5 ± 9.89	70.1 ± 10.20	0.998
ADC (×10 ⁻³ mm ² /s)	1.29 ± 0.39	1.32 ± 0.57	0.985

ADC, apparent diffusion coefficient.

Inter-observer agreement

The ICCs of the T2 mapping and ADC displayed excellent inter-observer agreement. The measured values for all patients are summarized in Table 3. Finally, the results of the senior radiologist were used for further analyses because the inter-observer agreement for the T2 mapping and ADC values were excellent.

Diagnostic efficiency and comparison

The patients with MA (Fig. 2) had higher T2 (87.9 ± 5.11 ms) ($P = 0.000$) and ADC (2.03×10^{-3} mm²/s) ($P = 0.000$) values than the patients with non-MA (Fig. 3; 66.6 ± 6.86 ms and 1.17×10^{-3} mm²/s, respectively) (Table 4). The AUCs derived from the ROC curves of both the T2 and ADC values exhibited excellent diagnostic performance for discriminating MA from non-MA (Fig. 4). Pairwise comparison of the two ROC curves showed that the significance level was 0.675. When 80

ms was used as the cut-off T2 value, the sensitivity and specificity were 100% and 97%, respectively.

Discussion

The present work proposed a newly developed T2 mapping sequence for quantitatively distinguishing MA and non-MA of rectal cancer preoperatively. Compared with the patients with non-MA, the patients with MA had higher T2 and ADC values. The diagnostic efficacy and inter-observer consistency were as high as ADC values. As an objective and highly scorable index, T2 mapping can be used to diagnose MA in rectal cancer prior to surgery.

Unlike the T2-weighted image, T2 mapping has the potential to objectively quantify the T2 values of tissues. The T2 values of patients with MA were higher than those of patients with non-MA likely because of the large amounts of water molecules in MA, especially extracellular water. Several studies convincingly demonstrated that the T2 transverse relaxation times of inflamed or edematous muscles are longer than those of normal muscles.^{18,19} Reports in the literature on the use of T2 mapping in diagnosing tumors are few. An *in vitro* study found a difference between the T2 relaxation times of benign and malignant breast lesions, which could be employed to differentiate them.²⁰ Another study established that quantitative T2 values are suitable for distinguishing prostate cancer from normal gland tissues or benign prostatic hyperplasia nodes.²¹ Previous work demonstrated that 3-T high-spatial-resolution quantitative T2 mapping is useful for distinguishing colorectal wall layers and differentiating tumor and fibrotic tissues *ex vivo*.²² The present study is the first report to measure the T2 value of rectal adenocarcinoma *in vivo*. Therefore, T2 mapping has a broad application prospect in tumor diagnosis.

DWI and ADC measurements are useful for differentiating MA and non-MA. Mucinous carcinomas have higher ADCs than tubular adenocarcinomas.¹³ The mean ADC for mucinous carcinomas in anal canal cancer is reportedly $1.49 \pm 0.34 \times 10^{-3}$ mm²/s, whereas that for tubular adenocarcinomas is $0.80 \pm 0.15 \times 10^{-3}$ mm². Non-MA, with tubular adenocarcinomas as the dominant pathologic type of colorectal cancer, has high solid tumor cell proliferation and high cellular density. By contrast, MA consists of large amounts of extracellular mucin and a few cancer cell columns, creating a meshwork in the mucinous pool. Its cellular density is far lower than that of tubular adenocarcinoma.⁴ Therefore, the ADC values of MA are higher than those of non-MA.

In rectal cancer, the ADC values were found to have a significant positive correlation with the T2 values. Similar to those of the ADC values, the inter-observer consistency and diagnostic efficiency of the T2 values in distinguishing MA from non-MA were excellent. Compared with ADC mapping, T2 mapping has several advantages. First, T2 mapping had a relatively high resolution of 0.8 mm × 0.8 mm by fast spin echo (FSE) sequence. By comparison, the resolution of DWI was

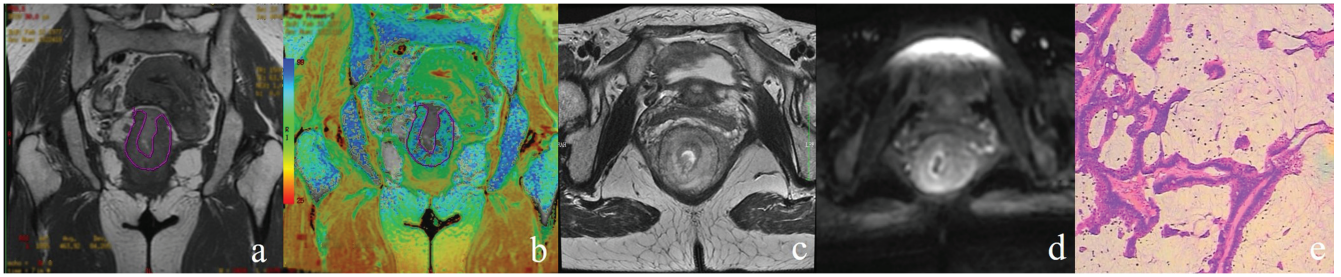


Fig. 2 Coronal T2 mapping (a and b) and axial T2-weighted image (c) of the same section as DWI (d) of the rectum from a 41-year-old woman with mucinous adenocarcinoma; The tumor in the middle level of the rectum was shown on T2 mapping (a) with a T2 value of 85 ms on the color-coded image (b). The resolution of the images on original T2 mapping (a) and on axial T2-weighted image (c) were significantly better than DWI (d). Pathology reveals mucinous adenocarcinoma with a large amount of extracellular mucin and cancer cell columns. Its cellularity is far lower than that of tubular adenocarcinoma (e) (hematoxylin–eosin stain, original magnification 40×). DWI, diffusion-weighted imaging.

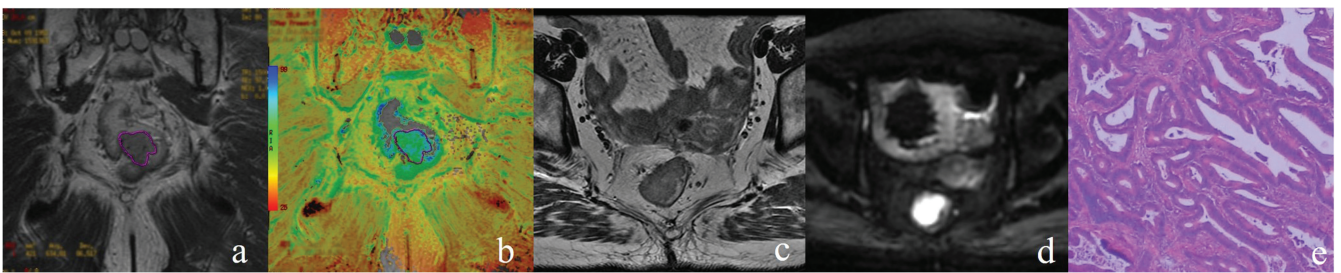


Fig. 3 Coronal T2 mapping (a and b) and axial T2-weighted image (c) of the same section as DWI (d) of the rectum from a 68-year-old woman with non-mucinous adenocarcinoma; The tumor in the middle level of the rectum was shown on original T2 mapping (a) with a T2 value of 72 ms on the color-coded image (b). The resolutions of T2 mapping and T2-weighted image were higher than DWI. Pathology reveals tubular adenocarcinoma (e)(hematoxylin–eosin stain, original magnification 40×). DWI, diffusion-weighted imaging.

Table 4 Comparison of ADC and T2 values for MA and non-MA

	MA (n = 11)	non-MA (n = 70)	t values, P values
ADC ($\times 10^{-3}$ mm ² /s)	2.03 ± 0.27	1.17 ± 0.26	-9.937, 0.000
T2 values (ms)	87.9 ± 5.11	66.6 ± 6.86	-9.873, 0.000

ADC, apparent diffusion coefficient; MA, mucinous adenocarcinoma.

2.8 mm × 2.8 mm by echo planar imaging (EPI) sequence. Therefore, when the ROIs were placed, T2 mapping clearly showed the tumor boundary. For DWI, the ROIs were drawn by comparing the T2-weighted (T2W) images of the same section. Second, DWIs were scanned with an EPI sequence, which was easily affected by the inhomogeneity of the magnetic field. By contrast, T2 mapping was gathered by spin echo (SE) sequence, which was barely influenced by magnetic field inhomogeneity. Moreover, T2 mapping, as a quantitative MRI method with higher reproducibility than previous weighted MRI, may provide more information than DWI in the application of rectal cancer, such as the determination of benign and malignant lymph nodes.²³

This study has several limitations. First, the patient cohort and the number of studied MA and non-MA cases were

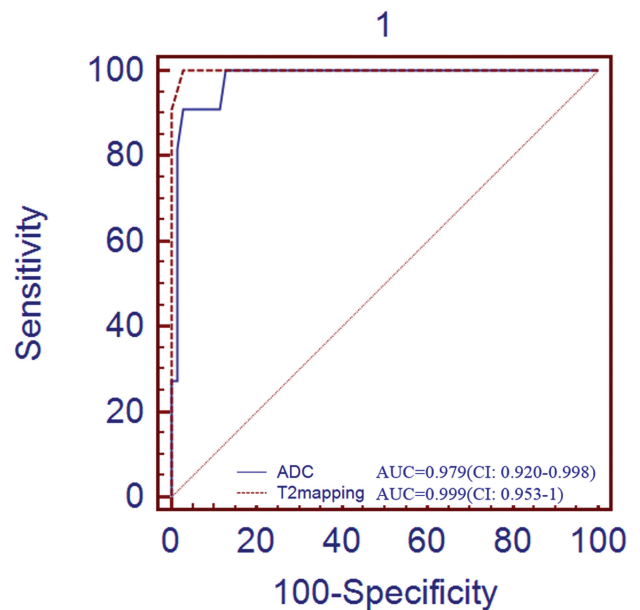


Fig. 4 Receiver operating characteristic curves for the diagnostic performance in the diagnosis of mucinous adenocarcinoma for T2 mapping and diffusion-weighted imaging. ADC, apparent diffusion coefficient; AUC, area under the curve.

relatively small. Secondly, only a basic T2 mapping sequence was used; evaluation of the entire tumor areas, especially when the tumor size was large, was time-consuming. Compared with that of DWI, the acquisition time of T2 mapping might be too long when applied to clinical practice. With the application of compressive sensing technology in T2 mapping, the acquisition time may be shortened to about 3 min.²⁴ Third, high-resolution T2 mapping was not attempted. A recent study observed that T2 maps could distinctly resolve the normal colorectal wall into eight layers, corresponding to the histologic layers *ex vivo*.²² Therefore, we believe that displaying more details of rectal cancer is possible. Finally, our data acquisition may be somewhat biased because T2 values are measured in the coronal, while ADC values are measured in the axial.

Conclusion

Our study demonstrated that T2 mapping, as a quantitative and accurate method, can be used as a noninvasive biological marker to distinguish the MA from non-MA of rectal cancer.

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Conflicts of Interest

Weiqiang Dou is an employee of GE Healthcare, China. The other authors declare that they have no conflicts of interest.

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