Morphology of the anterior mesorectum: a new predictor for local recurrence in patients with rectal cancer

Xiaojie Wang[1], Zhifang Zheng[1], Min Chen[2], Jing Lin[3], Xingrong Lu[1], Ying Huang[1], Shenghui Huang[1], Pan Chi[1]

[1]Department of Colorectal Surgery, Union Hospital, Fujian Medical University, Fuzhou, Fujian 350001, China;
[2]Department of Gynaecology and Obstetrics, Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian 350001, China;
[3]Integrated Information Section, Fujian Children's Hospital, Fuzhou, Fujian 350001, China.

Abstract

Background: Pre-operative assessment with high-resolution magnetic resonance imaging (MRI) is useful for assessing the risk of local recurrence (LR) and survival in rectal cancer. However, few studies have explored the clinical importance of the morphology of the anterior mesorectum, especially in patients with anterior cancer. Hence, the study aimed to investigate the impact of the morphology of the anterior mesorectum on LR in patients with primary rectal cancer.

Methods: A retrospective study was performed on 176 patients who underwent neoadjuvant treatment and curative-intent surgery. Patients were divided into two groups according to the morphology of the anterior mesorectum on sagittal MRI: (1) linear type: the anterior mesorectum was thin and linear; and (2) triangular type: the anterior mesorectum was thick and had a unique triangular shape. Clinicopathological and LR data were compared between patients with linear type anterior mesorectal morphology and patients with triangular type anterior mesorectal morphology.

Results: Morphometric analysis showed that 90 (51.1%) patients had linear type anterior mesorectal morphology, while 86 (48.9%) had triangular type anterior mesorectal morphology. Compared to triangular type anterior mesorectal morphology, linear type anterior mesorectal morphology was more common in females and was associated with a higher risk of circumferential resection margin involvement measured by MRI (35.6% [32/90] *vs.* 16.3% [14/86], $P = 0.004$) and a higher 5-year LR rate (12.2% *vs.* 3.5%, $P = 0.030$). In addition, the combination of linear type anterior mesorectal morphology and anterior tumors was confirmed as an independent risk factor for LR (odds ratio = 4.283, $P = 0.014$).

Conclusions: The classification established in this study was a simple way to describe morphological characteristics of the anterior mesorectum. The combination of linear type anterior mesorectal morphology and anterior tumors was an independent risk factor for LR and may act as a tool to assist with LR risk stratification and treatment selection.

Keywords: Local recurrence; Magnetic resonance imaging; Morphology of the anterior mesorectum; Rectal cancer

Introduction

Colorectal cancer is a substantial burden on healthcare systems and consumes considerable medical resources; much higher incidence and mortality were observed in countries with higher human development index.[1] In China, rectal cancer accounts for the largest proportion of colorectal cancer, and its treatment regimens are complex.[2] Local control, defined as an absence of tumor recurrence within the pelvic or perineal area,[3,4] has been considerably improved after the introduction of total mesorectal excision (TME) and neoadjuvant radiotherapy in the treatment of rectal cancer.[5,6] However, local recurrence (LR), with a range of 10% to 20% after surgery, remains a major problem.[7,8] It is well known that a tumor-involved circumferential resection margin (CRM) is a strong predictor of LR.[9] A previous study demonstrated that patients with an involved CRM, either from preoperative magnetic resonance imaging (MRI) or a pathological report, had a significantly higher risk of recurrence and cancer-related death.[10,11] Exploring other predictors of LR of rectal cancer, especially preoperative factors that can be evaluated by MRI, may be valuable for decisions regarding surgical strategies and intensive adjuvant therapies.

Preoperative assessment with high-resolution MRI is useful for assessing the risk of LR and survival.[12] For instance, CRM involvement on MRI is significantly associated with distant metastatic disease.[12] In addition to the application of MRI in tumor staging, the tumor

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002024

Xiaojie Wang, Zhifang Zheng, and Min Chen contributed equally to this work.

Correspondence to: Prof. Pan Chi, Department of Colorectal Surgery, Union Hospital, Fujian Medical University, 29 Xin-Quan Road, Fuzhou, Fujian 350001, China
E-Mail: chipan363@163.com;
Prof. Ying Huang, Department of Colorectal Surgery, Union Hospital, Fujian Medical University, 29 Xin-Quan Road, Fuzhou, Fujian 350001, China
E-Mail: hy9033sy@sina.com

Chinese Medical Journal 2022;135(20)

Received: 22-02-2022; **Online:** 22-07-2022 **Edited by:** Yanjie Yin and Xiuyuan Hao

volume measured based on pre-operative pelvic MRI may be considered an important predictor of LR.[13] Moreover, the amount of mesorectal fat, whether quantitatively measured by computed tomography (CT) or MRI, is an independent biomarker for predicting LR in patients undergoing curative-intent surgery for mid/lower rectal cancer.[14] Since the anterior portion of the mesorectum is smaller and thinner than the non-anterior portion, the risk of a positive CRM and LR may be higher for anterior cancers than for non-anterior cancers.[15] However, few studies have explored the clinical importance of the morphology of the anterior mesorectum, especially in patients with anterior cancer. We found that there are two types of anterior mesorectal morphology, one with trigonal fat and one that is thin; these two types could easily be distinguished with sagittal MRI in our preliminary observation. Hence, the study aimed to investigate the impact of morphology of the anterior mesorectum on LR in patients with primary rectal cancer. Furthermore, the relationships between the morphology of the anterior mesorectum and patient features were investigated.

Methods

Ethical approval

This study was approved by the Ethics Committee of Union Hospital, Fujian Medical University (No. 2021-KY134). All participants provided written informed consent.

Patients

By searching the electronic medical records from the Deepaint Colorectal Cancer Clinical Data Intelligent Processing and Analysis System at Union Hospital, Fujian Medical University, a total of 503 patients diagnosed with rectal cancer who underwent curative-intent surgery between January 2013 and December 2015 were identified. Among them, patients who met the following criteria were excluded: (1) patients diagnosed with stage IV of the disease ($n = 34$); (2) patients who did not receive neoadjuvant treatment ($n = 124$); (3) a lack of data regarding LR after a minimum of 3 years of follow-up ($n = 21$); and (4) a lack of preoperative MRI or MRI images available for download ($n = 41$). Pelvic recurrence that was evident was a regrowth of cancer in or around the tumor bed.[16] It is known that lateral pelvic lymph node metastases are not a major cause of LR[17] and are mainly due to the omission of dissection of the involved lateral pelvic nodes.[18] Since we aimed to examine the association between anterior mesorectal morphology and LR, patients with lateral lymph node metastasis ($n = 2$) and metachronous distant metastasis ($n = 105$) were also excluded.

As previously reported, all patients were evaluated by preoperative staging workups, both before and after neoadjuvant treatment, including digital rectal examinations, colonoscopy, chest radiography, endorectal ultrasound examination, abdominopelvic CT, and pelvic MRI.[19,20] All patients received 5-fluorouracil-based preoperative chemoradiotherapy (CRT). More specifically, preoperative radiotherapy was delivered to the whole pelvis at a dose of 45 Gy in 25 fractions (1.8 Gy per fraction), followed by a primary tumor boost of 5.4 Gy. Concurrent chemotherapy was administered with radiation using 2 to 5 cycles of XELOX (Capecitabine and Oxaliplatin) or FOLFOX (5-FU/Folinic acid/Oxaliplatin) regimens, depending on the tumor responses, toxic effects, and the availability of MRI machines. Standard TME was performed for patients with mid and low rectal cancers, and partial mesorectal excision with a distal margin of at least 5 cm was performed for high rectal cancers. Briefly, dissection anterior to Denonvilliers' fascia was our surgical strategy.

Tumor regression grading (TRG) was evaluated using the following 4-point scale[21]: TRG 0 (pathologic complete response [pCR]) indicated that there were no cancer cells; TRG 1 denoted cancer cells in <10% of the tumor mass; TRG 2 indicated that there were cancer cells in 10% to 50% of the tumor mass; and TRG 3 denoted that the cancer cells were in >50% of the tumor mass.

CRM involvement measured by MRI was defined when the minimum distance between the tumor and mesorectal fascia was ≤1 mm. The mesorectal fascia was regarded as a structure with good linearity enveloping the mesorectum that appeared hypointense on T2-weighted images.[22] Pathologic CRM involvement was defined when the minimum distance between the tumor and CRM was ≤1 mm.[9]

The anterior mesorectum morphology was evaluated using high-resolution MRI before CRT in the present study. The relation between MRI and mesorectal anatomy has been well defined in previous studies. As reported by Torkzad *et al*,[23] the morphological variations of the mesorectum were assessed by MRI, and a formula describing mesorectum morphology based on two simple measurements of the anteroposterior and left-to-right dimensions was established. Mesorectal morphometric assessment between the genders using MRI was reported by Boyle *et al*,[14] in which the most representative single slice was chosen and measurements of mesorectal morphology were performed on this image. In our current analysis, patients were divided into two groups according to the morphology of the anterior mesorectum on sagittal MRI: (1) linear type: the anterior mesorectum was thin and linear; and (2) triangular type: the anterior mesorectum was thick and had a unique triangular shape. The pubic symphysis was chosen as the bony landmark that could be readily identified on sagittal sequences, and then the section through the pubic symphysis was used for further analysis. The position of the peritoneal reflection was first located, then the type of anterior mesorectal morphology was evaluated [Figure 1A and 1B]. Importantly, the key feature of typical triangular shape was used to identify the triangular type.

As the purpose of this study was to examine the effect of anterior mesorectal morphology on LR, a circumferential tumor location may affect the results. Theoretically, patients with anterior cancer and linear type anterior mesorectal morphology were at higher risk of suffering from LR. Therefore, patients were then compared between those with both anterior cancer and linear type anterior mesorectal morphology [Group A, Figure 1C] and others

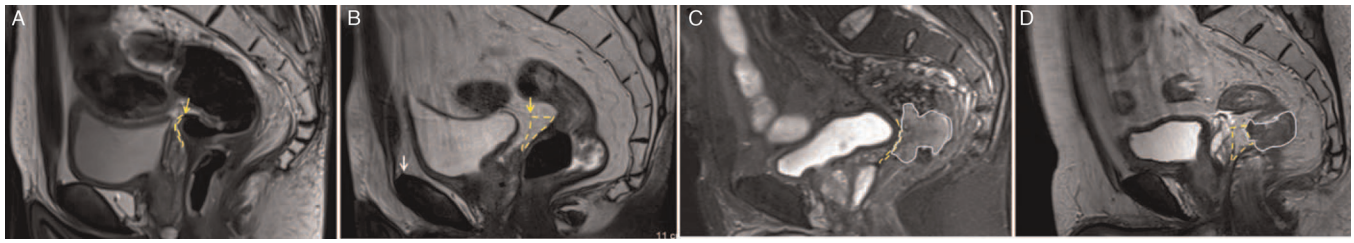

Figure 1: Patients were divided into two groups according to the morphology of the anterior mesorectum on sagittal MRI: (A) linear type: the anterior mesorectum was thin and linear (shown in yellow dotted box); and (B) triangular type: the anterior mesorectum was thick and had a unique triangular shape (shown in yellow dotted box). The pubic symphysis was chosen as the bony landmark (shown in white arrow) that could be readily identified on sagittal sequences, and then the section through the pubic symphysis was used to evaluate the types of anterior mesorectal morphology. The yellow arrow shows the position of the peritoneal reflection. (C) Representative picture of patient in Group A with linear type anterior mesorectal morphology and anterior tumor, defined as tumors in the anterior or circumferential quadrant. (D) Representative picture of patient with triangular type anterior mesorectal morphology and anterior tumor. MRI: Magnetic resonance imaging.

[Group B, one sample shown in Figure 1D]. The tumors were reclassified as anterior or non-anterior: tumors in the anterior or circumferential quadrant were classified as anterior tumors, and tumors in the lateral or posterior quadrant were classified as non-anterior tumors. The effect of the combination of anterior tumors and linear type anterior mesorectal morphology on LR was also evaluated.

Post-operative follow-up visits were scheduled every three months during the first two years and annually thereafter. At each visit, imaging assessments, including chest CT and abdominopelvic MRI, were performed. Colonoscopy was performed three months to one year after the initial surgery and then once every year thereafter. In addition, clinical follow-up was also obtained for each patient through outpatient visits or by telephone.

Statistical analysis

All statistical analyses were performed using SPSS software (ver. 17; SPSS Inc., Chicago, IL, USA). Categorical variables were compared using chi-squared and Fisher's exact tests. Continuous outcomes were compared using parametric (Student's t tests) and non-parametric (Mann–Whitney U, Kruskal–Wallis) tests, as appropriate. Intra- and inter-observer variations were evaluated using 50 randomly selected patients and Kappa values were calculated. In addition, the morphology of the anterior mesorectum was evaluated both before and after CRT for these 50 randomly selected patients to assess the effect of CRT on the morphology of the anterior mesorectum. LR rates were compared using the Kaplan–Meier method with a log-rank test. Univariate and multivariate analyses for LR were verified using a Cox proportional hazards model. The variable inflation factor (VIF) was utilized to assess collinearity. When the VIF was within the range from one to ten, there was no collinearity among the variables. All variables with significance ($P < 0.010$) by univariate analysis were included into a multivariate model to identify independent LR risk factors. The significance level was set at 5% for each analysis.

Results

Demographic data

Data from 176 patients (The mean age is 55.2 ± 11.1 years; the number of male and female is 112 and 64, respectively) were analyzed. The average tumor distance to the anal verge was 5.8 cm (standard deviation: 1.7 cm). There were 39 (22.2%) patients who achieved pCR; 63 (35.8%) were at stage I, 38 (21.6%) at stage II, and 36 (20.5%) at stage III. Regarding the circumferential tumor location, 125 (71.0%) were with anterior tumors, and 51 (29.0%) were with non-anterior tumors. In the morphometric analysis, 90 (51.1%) patients had linear type anterior mesorectal morphology, while 86 (48.9%) had triangular type anterior mesorectal morphology. Intra- and inter-observer variations were evaluated using 50 randomly selected patients and acceptable results were obtained (Kappa values: 0.827 and 0.786, respectively). In addition, no difference was observed in anterior mesorectum morphology type between patients before and after CRT (Kappa value: 0.955).

Factors related to anterior mesorectal morphology

The clinical and pathological characteristics of the patients with linear type or triangular type anterior mesorectal morphology are shown in Tables 1 and 2. Interestingly, females had a statistically higher rate of linear type anterior mesorectal morphology than males ($P = 0.023$). Linear type anterior mesorectal morphology was associated with a higher risk of CRM involvement measured by MRI compared to triangular type anterior mesorectal morphology (35.6% [32/90] *vs.* 16.3% [14/86], $P = 0.004$). The surgeons more often tended to use open approaches and abdominoperineal resection procedures for patients with linear type anterior meso-rectal morphology, but the difference did not reach statistical significance ($P = 0.086$ and $P = 0.072$). Regarding the pathological data, patients with linear type anterior mesorectal morphology had a more advanced N stage than patients with triangular type anterior mesorectal morphology ($P = 0.041$).

Recurrence analysis

The median duration of follow-up was 60 (interquartile range, 51–70) months. In 14 patients with LR, isolated LR developed in five patients and synchronously distant metastasis and LR developed in nine patients during the 5-year follow-up. For the anterior mesorectal morphology types of these 14 patients, 11 patients had a linear type and three patients had a triangular type. Of the 11 LR patients

Table 1: Clinical factors related to anterior mesorectum morphology.

Clinical factors	Linear type ($n = 90$)	Triangular type ($n = 86$)	*P* value
Gender			0.023
Male	50 (55.6)	62 (72.1)	
Female	40 (44.4)	24 (27.9)	
Age (years)	55.2 ± 10.9	55.1 ± 11.2	0.966
Circumferential location of tumor			0.102
Anterior	59 (65.6)	66 (76.7)	
Non-anterior	31 (34.4)	20 (23.3)	
Diabetes	15 (16.7)	7 (8.1)	0.087
Hypertension	18 (20.0)	23 (26.7)	0.290
Clinical T stage prior to CRT			0.083
cT2–3	47 (52.2)	56 (65.1)	
cT4	43 (47.8)	30 (34.9)	
Clinical N stage prior to CRT*			0.958
cN0	7 (9.2)	6 (9.0)	
cN+	69 (90.8)	61 (91.0)	
Circumferential margin involvement measured by MRI	32 (35.6)	14 (16.3)	0.004
Tumor distance to anal verge (cm)	5.5 ± 1.7	5.9 ± 1.6	0.155
Pre-CRT serum CEA (ng/mL)	3.45 (0.60–90.50)	3.15 (0.60–261.10)	0.831
Pre-CRT serum CA199 (U/mL)	15.08 (2.00–933.00)	11.30 (1.00–415.00)	0.226
Post-CRT serum CEA (ng/mL)	2.05 (0.40–50.50)	2.25 (0.20–24.50)	0.521
Post-CRT serum CA199 (U/mL)	10.96 (3.00–306.00)	10.80 (1.00–50.00)	0.811
Surgical access			0.086
Laparoscopy	67 (74.4)	73 (84.9)	
Open	23 (25.6)	13 (15.1)	
Surgical procedure			0.072
AR	79 (87.8)	82 (95.3)	
APR	11 (12.2)	4 (4.7)	

Data are presented as *n* (%), mean ± standard deviation or median (interquartile range). *With data missing for 33 cases (18.8%). APR: Abdominoperineal resection; AR: Anterior resection; CA199: Carbohydrate antigen 199; CEA: Carcino-embryonic antigen; cN: Clinical Node stage; CRT: Chemoradiotherapy; cT: Clinical Tumor stage; MRI: Magnetic resonance imaging.

Table 2: Pathological factors related to anterior mesorectum morphology.

Clinical factors	Linear type ($n = 90$)	Triangular type ($n = 86$)	*P* value
pT stage			0.582
pT0	19 (21.1)	21 (24.4)	
pT1	8 (8.9)	6 (7.0)	
pT2	28 (31.1)	32 (37.2)	
pT3	29 (32.2)	25 (29.1)	
pT4	6 (6.7)	2 (2.3)	
pN stage			0.041
pN0	65 (72.2)	75 (87.2)	
pN1	18 (20.0)	9 (10.5)	
pN2	7 (7.8)	2 (2.3)	
Tumor differentiation			0.924
Well moderately differentiated	82 (91.1)	78 (90.7)	
Poorly differentiated	8 (8.9)	8 (9.3)	
Histopathology			0.265
Adenocarcinoma	82 (91.1)	82 (95.3)	
Mucinous or signet ring adenocarcinoma	8 (8.9)	4 (4.7)	
Pathologic circumferential margin involvement	1 (1.1)	1 (1.2)	1.000
Tumor regression grade			0.340
0–1	48 (53.3)	52 (60.5)	
2–3	42 (46.7)	34 (39.5)	

Data are presented as *n* (%). pN: Pathologic Node stage; pT: Pathologic Tumor stage.

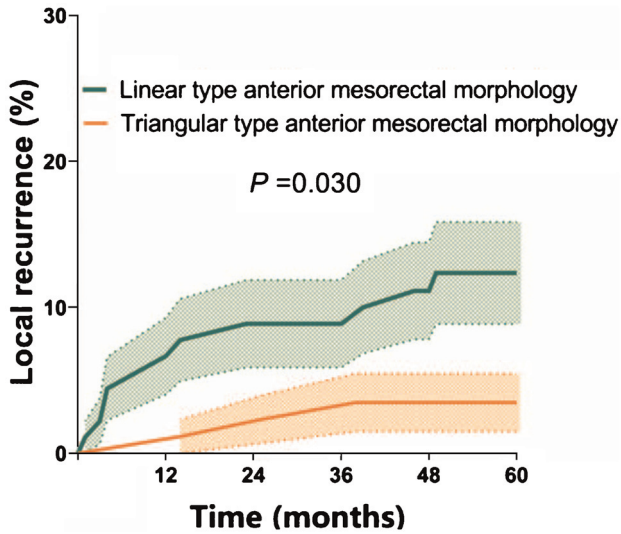

Figure 2: LR according to the morphology of the anterior mesorectum. The 5-year LR rate was statistically significantly higher in patients with linear type anterior mesorectal morphology than in patients with triangular type anterior mesorectal morphology (12.2% *vs.* 3.5%, $P = 0.030$). The 95% CI range is represented by the dotted line. CI: Confidence interval; LR: Local recurrence.

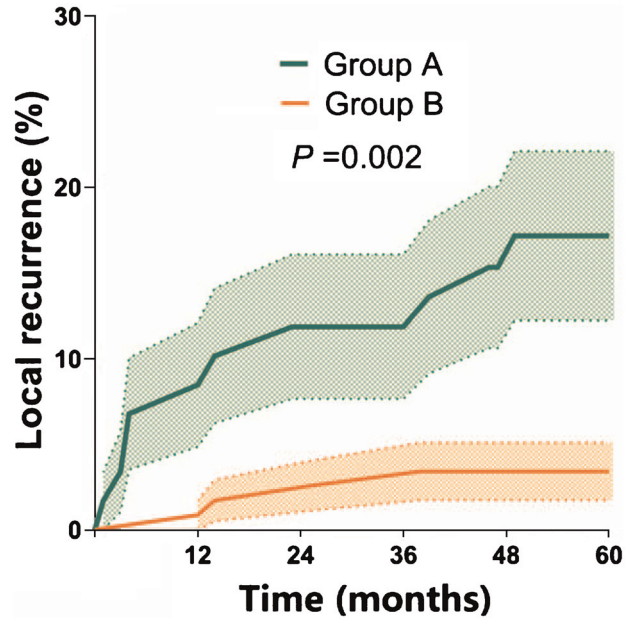

Figure 3: LR according to groups. Group A: patients with both anterior cancer and linear type anterior mesorectal morphology; Group B: patients without either anterior cancer or linear type anterior mesorectal morphology. The 5-year LR rate statistically significantly increased in patients in Group A compared with patients in Group B (16.9% *vs.* 3.4%, $P = 0.002$). The 95% CI range is represented by the dotted line. CI: Confidence interval; LR: Local recurrence.

with linear type, only one patient had non-anterior cancer, whereas the remaining ten patients had anterior cancers.

One in three LR patients with triangular type had anterior tumors. The 5-year LR rate was significantly higher in patients with linear type anterior mesorectal morphology than in patients with triangular type anterior mesorectal morphology (12.2% *vs.* 3.5%, $P = 0.030$) [Figure 2]. To evaluate the prognostic value of the combined effect of anterior tumors and linear type anterior mesorectal morphology on LR, LR was then compared between patients with both anterior cancer and linear type anterior mesorectal morphology (Group A) and others (Group B). The results showed that the 5-year LR rate statistically significantly increased in patients in Group A compared with patients in Group B (16.9% *vs.* 3.4%, $P = 0.002$) [Figure 3].

Univariate analysis was performed for the clinicopathological variables possibly affecting LR [Table 3]. The cohort was grouped as pT3–4 *vs.* pT0–2 and pN1–2 *vs.* pN0 according to the definition of locally advanced rectal cancer of either T3 or node positivity.[24] The results showed that age, anterior mesenteric morphology, a combination of linear type anterior mesorectal morphology and anterior tumors, post-CRT serum Carcinoembryonic antigen (CEA) levels, clinical T stage prior to CRT, pT stage, pN stage, and tumor regression grade were associated with LR. Since there was no collinearity between anterior mesenteric morphology and the combination of linear type anterior mesorectal morphology and anterior tumors (VIF = 1.000), these two variables were then fitted into Cox proportional hazards models simultaneously [Table 4]. The independent risk factors for LR were the combination (odd ratio [OR] = 4.283, $P = 0.014$) and a more advanced pN stage (OR = 9.291, $P < 0.001$).

Discussion

An anatomical study based on *en bloc* cadaveric specimens showed that the risk of entering the anterolateral mesorectum is great and may result in an incomplete specimen.[25] Chan *et al*[15] clinically evaluated the oncological influence of the anterior tumors by reporting that the 5-year LR rate was 15.9% in patients with rectal cancer who had an anterior component compared with 5.8% in patients with rectal cancer without an anterior component. Prior to the commencement of the present study, there were rare studies available in the literature regarding anterior mesorectal morphology in the context of rectal cancer treatment. In this study, a novel approach for image classification regarding the morphology of the anterior mesorectal morphology was proposed based on sagittal MRI. In linear type cases, the anterior mesorectum is thin and linear, while triangular type anterior mesorectum is relatively thick and has a unique triangular shape that is easy to distinguish. Triangular type anterior mesorectal morphology has a larger amount of mesorectal fat, which reflects the extra fat accumulation around rectal cancers. A larger mesorectal volume has been reported to increase the probability of negative surgical resection margins after TME.[26] In line with this concept, the present study found that linear type anterior mesorectal morphology was associated with a higher risk of CRM involvement measured by MRI than triangular type anterior mesorectal morphology. Interestingly, our results suggested that females had a higher rate of linear type anterior mesorectal morphology than males. This result is in accordance with a previous study reported by Boyle *et al*[14] on mesorectal morphology, which showed that the anterior mesorectal fat buffer was statistically significantly thinner in females than in males (2.9 *vs.* 7.8 mm).

Table 3: Univariate analysis for the predictors of local recurrence.

Factors	Regression coefficient	SE	OR	95% CI	*P* value
Gender (female *vs*. male)	0.566	0.535	1.761	0.618–5.022	0.290
Age (years)	−0.068	0.025	0.934	0.890–0.980	0.005
Anterior mesenteric morphology (triangular type *vs*. linear type)	−1.315	0.651	0.269	0.075–0.963	0.044
Circumferential location of tumor (non-anterior *vs*. anterior)	−0.421	0.651	0.656	0.183–2.353	0.518
Linear type anterior morphology and anterior tumor (yes *vs*. no)	1.681	0.592	5.371	1.684–17.130	0.004
Tumor distance to anal verge (cm)	0.087	0.161	1.091	0.795–1.498	0.588
Diabetes (yes *vs*. no)	0.160	0.764	1.173	0.263–5.242	0.834
Hypertension (yes *vs*. no)	−0.142	0.651	0.868	0.242–3.112	0.828
Pre-CRT serum CEA (ng/mL)	−0.002	0.016	0.998	0.968–1.030	0.921
Pre-CRT serum CA199 (U/mL)	0.002	0.002	1.002	0.999–36.675	0.209
Post-CRT serum CEA (ng/mL)	0.046	0.024	1.047	0.999–1.098	0.054
Post-CRT serum CA199 (U/mL)	0.006	0.005	1.006	0.997–1.016	0.200
Surgical access (Open *vs*. laparoscopy)	0.486	0.592	1.626	0.510–5.184	0.411
Surgical procedure (APR *vs*. AR)	−0.233	1.038	0.792	0.104–6.058	0.823
Histopathology (mucinous or signet ring adenocarcinoma *vs*. adenocarcinoma)	0.091	1.038	1.095	0.143–8.373	0.930
Tumor differentiation (poorly differentiated *vs*. well moderately differentiated)	−3.151	4.019	0.043	0–112.789	0.433
Clinical T stage prior to CRT (cT4 *vs*. cT2–3)	0.979	0.558	2.663	0.892–7.946	0.079
Clinical N stage prior to CRT (cN+ *vs*. cN−)	−0.091	1.054	0.913	0.116–7.209	0.931
Circumferential margin measured by MRI (positive *vs*. negative)	0.445	0.558	1.560	0.523–4.655	0.425
pT stage (pT3–4 *vs*. pT0–2)	0.944	0.540	2.570	0.892–7.409	0.081
pN stage (pN1–2 *vs*. pN0)	2.387	0.592	10.880	3.410–34.721	< 0.001
Pathologic circumferential margin (positive *vs*. negative)	−3.018	11.039	0.049	0.000– $1.2E^{+08}$	0.785
Tumor regression grade (per grade)	0.767	0.354	2.153	1.075–4.312	0.030

CA199: Carbohydrate antigen 199; CEA: Carcino-embryonic antigen; CI: Confidence interval; CRT: Neoadjuvant chemoradiotherapy; cN: Clinical Node stage; cT: Clinical Tumor stage; MRI: Magnetic resonance imaging; OR: Odds ratio; pN: Pathologic Node stage; pT: Pathologic Tumor stage; SE: Standard error.

Table 4: Multivariate analysis for the predictors of local recurrence.

Factors	Regression coefficient	SE	OR	95% CI	*P* value
Age (years)	−0.026	0.028	0.975	0.922–1.030	0.364
Anterior mesenteric morphology (triangular type *vs*. linear type)	1.009	1.243	2.744	0.240–31.387	0.417
Clinical T stage prior to CRT (cT4 *vs*. cT2–3)	0.494	0.686	1.639	0.428–6.283	0.471
Post-CRT serum CEA (ng/mL)	0.038	0.027	1.038	0.984–1.096	0.170
pT stage (pT3–4 *vs*. pT0–2)	−0.714	0.673	0.490	0.131–1.833	0.289
pN stage (pN1–2 *vs*. pN0)	2.229	0.595	9.291	2.895–29.815	<0.001
Tumor regression grade (per grade)	0.632	0.457	1.881	0.768–4.610	0.167
Linear type anterior mesenteric morphology and anterior tumor (yes *vs*. no)	1.455	0.595	4.283	1.335–13.736	0.014

CI: Confidence interval; CRT: Neoadjuvant chemoradiotherapy; cT: Clinical Tumor stage; OR: Odds ratio; pT: Pathologic Tumor stage; pN: Pathologic Node stage; SE: Standard error.

Dulk *et al*[27] found that an anterior location, specifically in women, more often required downstaging and/or more extended resection to obtain free margins.

It is known that recurrence is mostly due to inadequate radical dissection of the mesorectum.[28] Previous research revealed that 85.7% of recurrent tumors had evidence of residual mesorectal fat.[17] Thus, identifying novel LR predictors that can be evaluated by MRI preoperatively would be valuable for decisions regarding surgical strategies. In the present study, the 5-year LR rate was significantly higher in patients with linear type than in patients with triangular type anterior mesorectal morphology (12.2% *vs*. 3.5%). The present study only included patients with LR in the tumor bed, since the tumor bed is most often the origin of recurrence.[28] A larger mesorectal fat area might result in a greater capacity for tumor cells within the proper fascia, reducing the chance of CRM involvement. However, the quantitative assessment of mesorectal fat or volume, including mesorectal fat area and visceral fat area, in a previous study was complex and needed special software to measure, which is not convenient for routine clinical use by surgeons.[29] Although mesorectal fat area and visceral fat area were measured using axial images in the previous study at the level of the umbilicus (for the visceral fat area) and ischial spine (for the mesorectal fat

area), the peritoneal reflection, which was located before evaluation of anterior meso-rectum morphology in the present study, was not a fixed landmark and rather variable in axial images. Thus, the axial MRI images were not employed in our analysis, and the quantitative measurement of anterior mesorectal thickness was therefore not performed. The Kappa values obtained indicated that the evaluation was reproducible.

Thus, the classification established in this study was a simple way to describe morphological characteristics of the anterior mesorectum.

The patterns of lymph node spread were related to the circumferential situation of the tumor in the rectal wall.[30] Radical surgical excision should completely remove the whole mesorectum, especially to avoid any damage to the mesorectum on the tumor side.[30] This is particularly difficult when dissecting the anterior mesorectum for anteriorly located tumors, since the contour of the proper fascia is subject to impression by other nearby visceral organs. Although anterior mesenteric morphology alone was not confirmed to be an independent prognostic factor for LR in our present study, the patients with both linear type anterior mesorectal morphology and anterior tumors had a high risk of LR of 16.9%. Moreover, the combination of linear type anterior mesorectal morphology and anterior tumors was confirmed as an independent risk factor for LR (OR = 4.283) in the present study. One explanation is that mesorectal fat in triangular type mesentum can act as a buffer against anterior local tumor spreading [Figure 1D]. On the other hand, the breach of a small-volume mesorectal fat envelope during dissection of the anterior space may predispose patients to CRM involvement, even in early anterior cancers, and this may be of particular relevance in linear type morphology due to the relatively thin mesorectum. In addition, for patients with potential CRM involvement, tumor micrometastasis may go beyond the scope of a single TME procedure.[9] A procedure beyond TME surgery or adjuvant therapy for local control should be considered for this subgroup of patients. Thus, this combination may act as a tool to assist with risk stratification and treatment selection.

It is worth noting that the pathological CRM positive rate was only 1.1%, which was lower than that measured by MRI of 26.1% in the present study. One explanation is that the MRI measurement of CRM involvement was performed prior to CRT. It is well known that chemoradiation therapy was associated with a significantly decreased risk of CRM involvement.[31] Another explanation is that pathological CRM status was not only an indicator of tumor invasion but also an indicator of the quality of surgery. A more extended resection might achieve a negative pathological CRM for rectal cancer breaching the mesorectal plane (CRM involvement measured by MRI). A previous study by Birbeck *et al*[9] observed a variation between surgeons and over time regarding pathological CRM positive rates. Survival analysis in relation to gastrointestinal surgeons in that study showed survival improvements that paralleled a reduction in the rates of pathological CRM involvement during the study period.

Several limitations of our study need to be mentioned. First, although we used a prospectively maintained database, some missing data regarding clinical N staging could not be reconciled. Second, some MRI images were not available for download, which may have introduced selection bias. However, the effects of important variables were controlled via multivariate analysis. Third, the clinical significance for the morphology of the anterior mesorectum on sagittal MRI in rectal cancer without CRT was not evaluated, due to rectal cancer patients without CRT not being included. For mesorectum thickness, Kang *et al*[32] performed an analysis that included 50 patients with rectal cancer who underwent TME without CRT and found that mean mesorectum thickness was only 4.3 mm in the anterior quadrant and 12.5 mm in the posterior quadrant, and a tumor-positive CRM was observed more frequently in anterior tumors than in non-anterior tumors (41.1% *vs*. 10.3%). However, for morphology, no studies have evaluated the clinical significance of the anterior mesorectum morphology without CRT, which warrants further study. Fourth, the results need to be expanded with a larger population due to the small sample size in the current cohort.

In conclusion, this study proposed a novel approach for image classification regarding the morphology of the anterior mesorectum based on sagittal MRI. Compared to triangular type anterior mesorectal morphology, linear type anterior mesorectal morphology was more common in females and was associated with a higher risk of CRM involvement measured by MRI and a higher LR rate, especially for anterior tumors. In addition, the combination of linear type anterior mesorectal morphology and anterior tumors was confirmed as an independent risk factor for LR. This combination may act as a tool to assist with LR risk stratification and treatment selection.

Funding

This study was supported by grants from the National Clinical Key Specialty Construction Project (General Surgery) of China (No. 2012-649), National Natural Science Foundation of China (No. 81902378), Joint Funds for the innovation of Science and Technology, Fujian province (No. 2020Y9071), Medical Science Research Foundation of Beijing Medical and Health Foundation (No. B20062DS), Bethune Charitable Foundation (No. X-J2018-004), Fujian provincial health technology project (Nos. 2020CXA025, 2021GGA013), and Natural Science Foundation of Fujian Province (No. 2020J011030).

Conflicts of interest

None.

References

1. Lu B, Li N, Luo CY, Cai J, Lu M, Zhang YH, *et al*. Colorectal cancer incidence and mortality: the current status, temporal trends and their attributable risk factors in 60 countries in 2000-2019. Chin Med J 2021;134:1941–1951. doi: 10.1097/CM9.0000000000001619.
2. Yang Y, Wang HY, Chen YK, Chen JJ, Song C, Gu J. Current status of surgical treatment of rectal cancer in China. Chin Med J 2020;133:2703–2711. doi: 10.1097/CM9.0000000000001076.
3. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, *et al*. The TME trial after a median follow-up of 6 years:

Increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007;246:693–701. doi: 10.1097/01.sla.0000257358.56863.ce.
4. Twomey P, Burchell M, Strawn D, Guernsey J. Local control in rectal cancer. Aclinicalreviewandmeta-analysis. Arch Surg 1989;124:1174–1178. doi: 10.1001/archsurg.1989.01410100076013.
5. Bülow S, Christensen IJ, Harling H, Kronborg O, Fenger C, Nielsen HJ. Recurrence and survival after mesorectal excision for rectal cancer. Br J Surg 2003;90:974–980. doi: 10.1002/bjs.4137.
6. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, *et al*. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638–646. doi: 10.1056/NEJMoa010580.
7. Banwell VC, Phillips HA, Duff MJ, Speake D, McLean C, Williams LJ, *et al*. Five-year oncological outcomes after selective neoadjuvant radiotherapy for resectable rectal cancer. Acta Oncol 2019;58:1267–1272. doi: 10.1080/0284186X.2019.1631473.
8. Dassanayake BK, Samita S, Deen RY, Wickramasinghe NS, Hewavi-senthi J, Deen KI. Local recurrence of rectal cancer in patients not receiving neoadjuvant therapy - the importance of resection margins. Ceylon Med J 2011;56:159–161. doi: 10.4038/cmj.v56i4.3896.
9. Birbeck KF, Macklin CP, Tiffin NJ, Parsons W, Dixon MF, Mapstone NP, *et al*. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. Ann Surg 2002;235:449–457. doi: 10.1097/00000658-200204000-00001.
10. Martling A, Holm T, Bremmer S, Lindholm J, Cedermark B, Blomqvist L. Prognostic value of preoperative magnetic resonance imaging of the pelvis in rectal cancer. Br J Surg 2003;90:1422–1428. doi: 10.1002/bjs.4276.
11. Liu Q, Luo D, Cai S, Li Q, Li X. Circumferential resection margin as a prognostic factor after rectal cancer surgery: a large population-based retrospective study. Cancer Med 2018;7:3673–3681. doi: 10.1002/cam4.1662.
12. Taylor FG, Quirke P, Heald RJ, Moran BJ, Blomqvist L, Swift IR, *et al*. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol 2014;32:34–43. doi: 10.1200/JCO.2012.45.3258.
13. Jiang Y, You K, Qiu X, Bi Z, Mo H, Li L, *et al*. Tumor volume predicts local recurrence in early rectal cancer treated with radical resection: a retrospective observational study of 270 patients. Int J Surg 2018;49:68–73. doi: 10.1016/j.ijsu.2017.11.052.
14. Boyle KM, Chalmers AG, Finan PJ, Sagar PM, Burke D. Morphology of the mesorectum in patients with primary rectal cancer. Dis Colon Rectum 2009;52:1122–1129. doi: 10.1007/DCR.0b013e31819ef62f.
15. Chan CL, Bokey EL, Chapuis PH, Renwick AA, Dent OF. Local recurrence after curative resection for rectal cancer is associated with anterior position of the tumour. Br J Surg 2006;93:105–112. doi: 10.1002/bjs.5212.
16. Roncucci L. Local recurrences of rectal cancer. Minerva Chir 2005;60:167–178.
17. Syk E, Torkzad MR, Blomqvist L, Ljungqvist O, Glimelius B. Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer. Br J Surg 2006;93:113–119. doi: 10.1002/bjs.5233.
18. Malakorn S, Yang Y, Bednarski BK, Kaur H, You YN, Holliday EB, *et al*. Who should get lateral pelvic lymph node dissection after neoadjuvant chemoradiation? Dis Colon Rectum 2019;62:1158–1166. doi: 10.1097/DCR.0000000000001465.
19. Wang X, Chen G, Zhang Y, Ghareeb WM, Yu Q, Zhu H, *et al*. The impact of circumferential tumour location on the clinical outcome of rectal cancer patients managed with neoadjuvant chemo-radiotherapy followed by total mesorectal excision. Eur J Surg Oncol 2020;46:1118–1123. doi: 10.1016/j.ejso.2020.02.034.
20. Wang X, Zheng Z, Zhu H, Yu Q, Huang S, Lu X, *et al*. Timing to achieve the best recurrence-free survival after neoadjuvant chemo-radiotherapy in locally advanced rectal cancer: experience in a large-volume center in China. Int J Colorectal Dis 2021;36:1007–1016. doi: 10.1007/s00384-020-03829-y.
21. Bujko K, Kolodziejczyk M, Nasierowska-Guttmejer A, Michalski W, Kepka L, Chmielik E, *et al*. Tumour regression grading in patients with residual rectal cancer after preoperative chemo-radiation. Radiother Oncol 2010;95:298–302. doi: 10.1016/j.radonc.2010.04.005.
22. Ye D, Zhu Z, Chen F, Lie C, Li W, Lin Y, *et al*. Correlation between endorectal ultrasound and magnetic resonance imaging for predicting the circumferential resection margin in patients with mid-low rectal cancer without preoperative chemoradiotherapy. J Ultrasound Med 2020;39:569–577. doi: 10.1002/jum.15135.
23. Torkzad MR, Blomqvist L. The mesorectum: morphometric assessment with magnetic resonance imaging. Eur Radiol 2005;15:1184–1191. doi: 10.1007/s00330-005-2657-5.
24. Hong TS, Ryan DP. Adjuvant chemotherapy for locally advanced rectal cancer: is it a given? J Clin Oncol 2015;33:1878–1880. doi: 10.1200/JCO.2015.60.8554.
25. Kraima AC, West NP, Treanor D, Magee DR, Bleys RL, Rutten HJ, *et al*. Understanding the surgical pitfalls in total mesorectal excision: investigating the histology of the perirectal fascia and the pelvic autonomic nerves. Eur J Surg Oncol 2015;41:1621–1629. doi: 10.1016/j.ejso.2015.08.166.
26. Allen SD, Gada V, Blunt DM. Variation of mesorectal volume with abdominal fat volume in patients with rectal carcinoma: assessment with MRI. Br J Radiol 2007;80:242–247. doi: 10.1259/bjr/66311683.
27. den Dulk M, Marijnen CA, Putter H, Rutten HJ, Beets GL, Wiggers T, *et al*. Risk factors for adverse outcome in patients with rectal cancer treated with an abdominoperineal resection in the total mesorectal excision trial. Ann Surg 2007;246:83–90. doi: 10.1097/01.sla.0000259432.29056.9d.
28. Wiig JN, Wolff PA, Tveit KM, Giercksky KE. Location of pelvic recurrence after 'curative' low anterior resection for rectal cancer. Eur J Surg Oncol 1999;25:590–594. doi: 10.1053/ejso.1999.0712.
29. Yoon J, Chung YE, Lim JS, Kim MJ. Quantitative assessment of mesorectal fat: new prognostic biomarker in patients with mid-to-lower rectal cancer. Eur Radiol 2019;29:1240–1247. doi: 10.1007/s00330-018-5723-5.
30. Zheng YC, Zhou ZG, Li L, Lei WZ, Deng YL, Chen DY, *et al*. Distribution and patterns of lymph nodes metastases and micro-metastases in the mesorectum of rectal cancer. J Surg Oncol 2007;96:213–219. doi: 10.1002/jso.20826.
31. Homan J, Bökkerink GM, Aarts MJ, Lemmens VE, van Lijnschoten G, Rutten HJ, *et al*. Variation in circumferential resection margin: reporting and involvement in the South-Netherlands. Eur J Surg Oncol 2015;41:1485–1492. doi: 10.1016/j.ejso.2015.07.015.
32. Kang BM, Park YK, Park SJ, Lee KY, Kim CW, Lee SH. Does circumferential tumor location affect the circumferential resection margin status in mid and low rectal cancer? Asian J Surg 2018;41:257–263. doi: 10.1016/j.asjsur.2016.12.001.

How to cite this article: Wang X, Zheng Z, Chen M, Lin J, Lu X, Huang Y, Huang S, Chi P. Morphology of the anterior mesorectum: a new predictor for local recurrence in patients with rectal cancer. Chin Med J 2022;135:2453–2460. doi: 10.1097/CM9.0000000000002024