Observational Study

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Clinical significance of the EMD/mesorectum ratio of T3 mid-low rectal cancer

A retrospective observational study

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Abstract

Previous studies suggested that the extramural distance (EMD) should be considered in therapeutic decision-making of rectal cancer because it can be used as an indicator of the T3 subclassification; however, reports of impact of EMD/mesorectum ratio on prognosis are rare.

The objectives of this study were to evaluate the feasibility of the extramural distance EMD/mesorectum ratio as a maker of the T3 subclassification for T3 mid-low rectal cancer and find the potential radiological marker on MRI for neoadjuvant chemoradiotherapy (nCRT).

From December 2012 to December 2016, 287 consecutive patients with MRI-staged T3 mid-low rectal cancer were enrolled. The EMD was defined as the distance from the outer edge of the muscularis propria to the outer edge of tumor, and the mesorectum was measured as the distance from outer edge of muscularis propria to mesorectal fascia (MRF) in the same layer. The association of the EMD/mesorectum ratio and other MRI or clinicopathological factors with survival was analyzed. The independent prognostic factors were estimated by Cox regression analysis.

The mean EMD/mesorectum ratio was 0.43. Based on ROC analysis, we chose a EMD/mesorectum ratio of 0.3 for further analyses. Of 287 patients, 163 (56.8%) had a EMD/mesorectum ratio $\geq$ 0.3. Patients with an EMD/mesorectum ratio $\geq$ 0.3 had a decreased recurrence free survival (RFS) and overall survival (OS) ($P < .001$; $P = .034$, respectively). Of the 163 patients, patients with nCRT had a higher RFS than patients without nCRT ($P = .001$). Multivariate analysis showed that the EMD/mesorectum ratio was the only independent prognostic factors for RFS.

Our study provided evidence that the EMD/mesorectum ratio could be used for T3 subclassification, the optimal cut-off value of EMD/mesorectum ratio was 0.3 when the ratio was applied to classify T3 mid-low rectal cancer patients, and nCRT should be performed for these patients when the EMD/mesorectum ratio is $\geq$ 0.3.

Abbreviations: APR = abdominal perineal resection, BMI = body mass index, EMD = extramural distance, EMVI = extramural vascular invasion, LAR = low anterior resection, LARC = locally advanced rectal cancer, MRF = mesorectal fascia, MRI = magnetic resonance imaging, MR-LN = lymph node on MRI, nCRT = neoadjuvant chemoradiotherapy, OS = overall survival, RFS = recurrence free survival, ROC = receiver operating characteristic, T2W = T2 weighted, TME = total mesorectal excision.

Keywords: extramural distance/mesorectum ratio, magnetic resonance imaging, mid-low rectal cancer, neoadjuvant chemoradiotherapy, prognosis, T3 subclassification

1. Introduction

The T3-stage accounts for over 60% of all rectal cancers, and has the most heterogeneity in prognosis due to the variation of extramural distance (EMD).[1] Many studies had reported the prognostic influence of the EMD in pathology,[2–4] and suggested that this parameter should be considered in therapeutic decision making.

Neoadjuvant chemoradiotherapy has become a standard treatment scheme for patients with locally advanced rectal cancer (LARC) for many years,[5–7] and the treatment now is becoming more and more individualized. Since the pathlogical T3 subclassification based on the EMD can only be acquired after operation and affected by nCRT, There is an increasing need to obtain a precise value of the preoperative radiological EMD to identify high-risk patients to receive neoadjuvant therapy, and low risk patients may not need or need to reduce the intensity of treatment to achieve better quality of life.

The MR imaging (MRI) is feasible and reproducible in a multicenter setting and yields data equivalent to histopathologic results regarding the preoperative prediction of tumor spread has

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been demonstrated by the MERCURY study.[8] Moreover, the EMD detected by MRI had been shown to be an independent prognostic factor.[9–11]

According to EMD, the European Society for Medical Oncology (ESMO) guidelines classified T3 disease into T3a (< 1 mm), T3b (1–5 mm), T3c (5–15 mm) and T3d (> 15 mm).[12] Although the subclassification has not been confirmed by any randomized trials and incorporated into any of TNM staging systems, it may offer a reference for the patient-tailored treatment. However, the thickness of the mesorectum may vary with the body mass index (BMI), tumor location and direction. For Chinese patients, the thickness of mesorectal fat is <15 mm in majority of patients and in most positions,[13] as a consequence, use of the subclassification in Chinese patients may be limited. In clinical practice, T3a with depth of invasion <1 mm is difficult to measure on MRI. Therefore, the EMD/mesorectum ratio would be a good supplement for T3 subclassification.

The aims of this study were to evaluate the feasibility of the EMD/mesorectum ratio as a marker of the T3 subclassification in the T3-stage mid-low rectal cancer, explore the optimal cut-off value of EMD/mesorectum ratio, and find the potential radiological marker on MRI for neoadjuvant chemoradiotherapy (nCRT).

2. Patients and methods

2.1. Patients

Between December 2012 and December 2016, 287 consecutive patients with MRI-staged locally advanced (cT3N0-2M0) mid-low rectal cancer who were treated with curative surgery at our medical center were studied. The middle rectal cancer included the tumors whose lower border was more than 5 cm from the anus and ≤10 cm. The tumors whose lower border was 0 to 5 cm from anus would be defined as low rectal cancer. All of the patients were evaluated by high-resolution MRI before any treatment and the clinicopathological data were retrospectively reviewed. Postoperative chemotherapy regimens, including XELOX, FOLFOX, or 5-FU, with or without radiotherapy was performed according to the postoperative pathological staging and high risk factors of each patient. The surveillance schedule after the surgery included the measurement of serum tumor marker, physical examination, abdominal imaging examination (alternate use of CT and ultrasound) every 3 months and chest CT every 6 months for the first 3 years and then every 6 months for the next 2 years.

This study was approved by the Ethics Committee of our hospital and the Ethics Committee had agreed with our request for waiver of informed consent.

2.2. MR imaging and interpretation

A 3.0 T MRI (GE Discovery MR750W) using a phased-array body coil was imaged for each patient. The standard imaging protocol includes a sagittal T2 weighted (T2W) fast spin echo and an oblique axial thin-section T2W (TR: 4000 TE: 100; SLICE: 3 mm; MATRIX: 256 × 256; FOV: 16; Plane resolution: 0.5–0.8 mm). Patients need to empty the rectum with Suppositories Glycerol and inject antispasmodic medication to inhibit bowel peristalsis in 30 minutes before the MR examinations. Two gastrointestinal radiologists (with more than 10 years of experience in MRI) who were blind to clinicopathological findings and prognosis reviewed the imaging features. Any discrepancy was solved by discussion. The EMD was measured as the outer edge of the low-signal intensity longitudinal muscularis propria to the deepest site of the tumor spread (in millimeters) in oblique axial thin-section T2W (Fig. 1A), and the mesorectum was defined as the distance form outer edge of the muscularis propria of the rectum to the mesorectal fascia (MRF) in the same layer (Fig. 1B). The tumor staging was according to the ESMO criteria based on the EMD (T3a: <1 mm, T3b: 1–5 mm, T3c: 5–15 mm, T3d: >15 mm). A lymph node on MRI (MR-LN) would be defined as positive if the short-axis diameter > 5 mm[14] or irregular border, T2 and enhancement heterogeneity.[15,16] We also evaluated the association between tumor and MRF. If the closest distance from the tumor to the MRF was 1 mm or less, then the MRF would be considered as positive. Extramural vascular invasion (EMVI) on MRI would be defined as positive, if

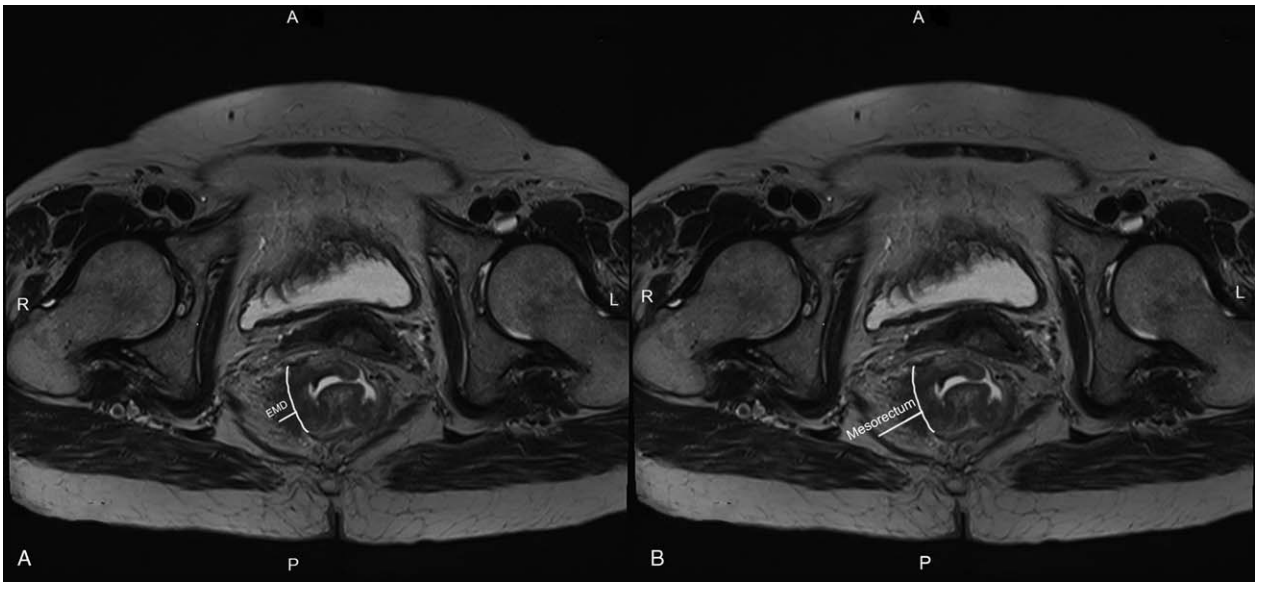

Figure 1. (A) The white line indicates the extramural distance (EMD). (B) The white line indicates the distance of mesorectum. EMD = extramural distance.

any of the following characteristics was present on 3 mm slices[2,3]: intermediate signal intensity apparent within vessels, although the contour and calibre of these vessels is only slightly expanded; obvious irregular vessel contour or nodular expansion of vessel by definite tumor signal.

2.3. Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20 software program (IBM Inc., Armonk, NY). A 2-sided $P < .05$ was considered to be statistically significant and the confidence interval (CI) was determined at the 95% level.

Continuous variables were expressed as mean and standard deviation, and categorical variables were expressed as frequency and percentage. A receiver operating characteristic (ROC) curve and relative area under the curve statistics were used to find an expected cutoff value of EMD/mesorectum ratio. The continuous variable of EMD/mesorectum ratio was applied to ROC analysis with the end point of tumor recurrence. We also used univariate logistic regression analysis for recurrence and Cox regression analysis for RFS to confirm the optimal cutoff point of EMD/mesorectum ratio. The association between the EMD/mesorectum ratio and other MRI or clinicopathological factors was analysed by the χ^2 test. Survival analysis was performed by using the Kaplan–Meier method, groups were compared using the log-rank test. The Cox regression analysis was also used to identify the preoperative independent prognostic factors for RFS.

3. Results

3.1. Patient baseline characteristics

A total of 287 MRI-staged T3 mid-low rectal cancer patients were analyzed in this study. The patients consisted of 189 (65.9%) males and 98 (34.1%) females, with a mean age of 60.3 years (range, 29–87). 160 patients (55.7%) were low rectal cancer and 127 patients (44.3%) were middle. The mean BMI was $20.3 \pm 8.4\,kg/m^2$. The mean EMD was 6.7 ± 5.2 mm (range, 0.5–33.0) (Fig. 2A), and the mean mesorectum was 17.3 ± 8.6 mm (range, 2.5–44.6) (Fig. 2B). The number of patients with MR-LN positive and negative was 129 (44.9%) and 158 (55.1%), respectively. Of these patients, 63 (30.0%) patients had an involved MRF, and 224 (70.0%) patients were negative. For EMVI, 91 patients (31.7%) were positive and 196 patients (68.3%) were negative. The median follow-up was 37 months (range 20–65 months) and no patient was lost to follow-up. 8 (2.8%) patients developed local recurrence, 50 (17.4%) patients developed distant metastasis and 26 (9.1%) patients had died by the time of last follow-up. The 5-year RFS and OS were 78.1% and 86.5%, respectively.

3.2. Statistical analysis of cutoff points

The mean EMD/mesorectum ratio is 0.43 ± 0.28 (range, 0.03–0.99). The ROC curve showed 0.27 as the cutoff value of EMD/mesorectum ratio expecting postoperative recurrence at a high true positive rate (sensitivity: 0.843), low false positive rate (1 − specificity: 0.564), high accuracy rate (0.509), high positive likelihood ratio (1.495), high positive predictive value (0.244), high OR (3.751), and low chi-square P value (<.001) among other cutoff points (Fig. 3). A value of 0.3 was then considered as an appropriate cutoff point because of feasibility in the clinical practice. Univariate logistic regression analysis showed that the value of 0.3 was a good cutoff point that had significant influence on postoperative recurrence ($\chi^2 = 12.627$, OR: 3.341, 95% CI: 1.635–6.826, $P = .001$) (Table 1A). Multivariate Cox regression analysis confirmed that the value of 0.3 was an optimal cutoff point that had the greatest impact on 5-year RFS, among all other cutoff points (highest $\chi^2 = 12.046$, higher hazard ratio [HR]: 3.073, 95% CI: 1.576–5.990, and lowest $P = .001$) (Table 1B). The accuracy of predicting postoperative recurrence was 0.533 when choosing EMD/mesorectum ratio 0.3 as the cutoff point. When the absolute value 5 mm of EMD was selected as cutoff point (equivalent to T3a+T3b vs T3c+T3d), the accuracy of

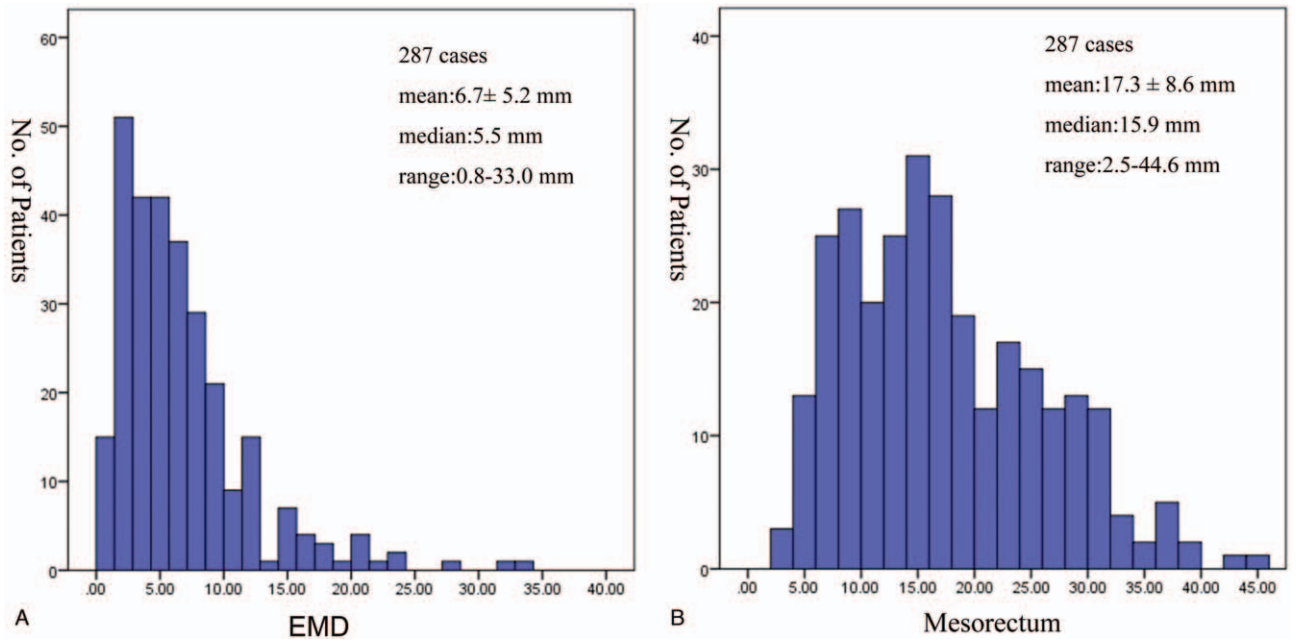

Figure 2. EMD (A) and mesorectum (B) measured on MRI. (A) The mean EMD is 6.7 ± 5.2 mm, and the median EMD is 5.5 mm (range, 0.8–33.0). (B) The mean mesorectum is 17.3 ± 8.6 mm, and the median mesorectum is 15.9 mm (range, 2.5–44.6). EMD = extramural distance.

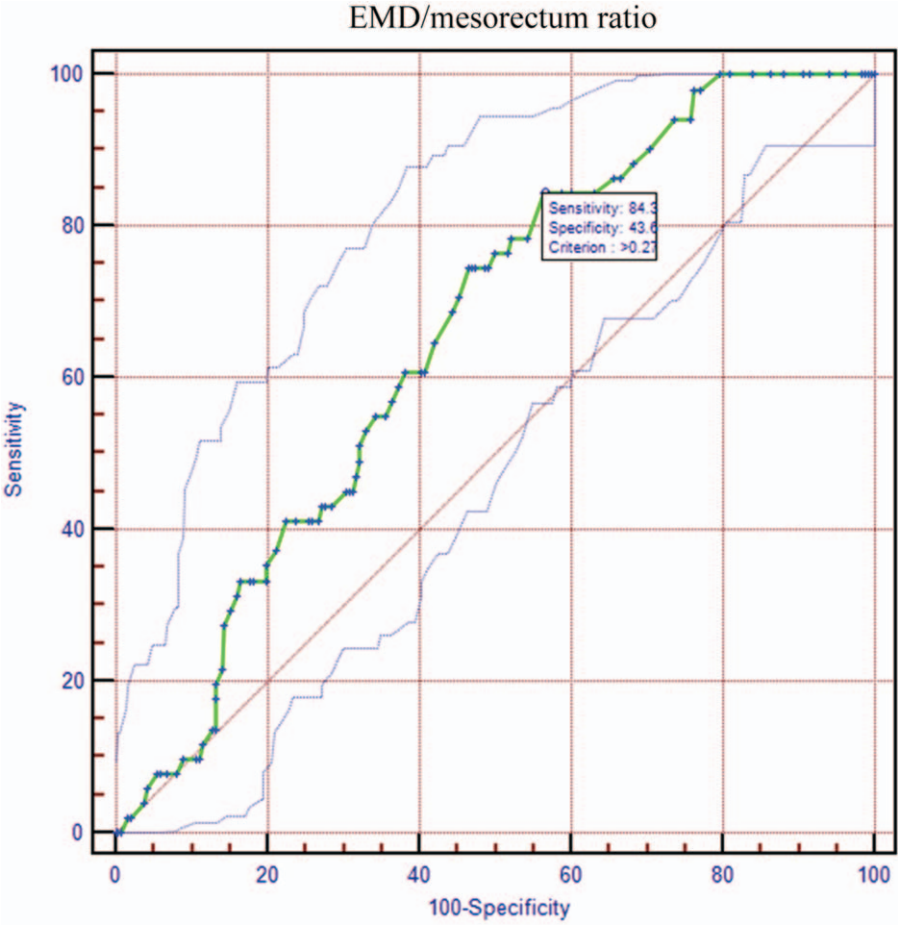

Figure 3. Cutoff point of EMD/mesorectum ratio using ROC curve analysis. The ROC curve analysis showed high sensitivity (0.843), specificity (0.436), positive likelihood ratio (1.495), positive predictive value (0.244), accuracy (0.509), OR (3.751), and smaller chi-square P (<.001) at the cutoff point of 0.27. EMD = extramural distance, ROC = receiver operating characteristic.

Table 1

Statistical Analysis of Cutoff Points for Postoperative 5-year DFS Survival.

A. Univariate Logistic Regression Analysis

EMD/mesorectum ratio	No. of patients	Rate of recurrence (%)	χ^2	OR	95% CI	*P*
≥ 0.1 vs < 0.1	267 vs 20	0.0 vs 19.1	8.144	—	—	.004
≥ 0.2 vs < 0.2	222 vs 65	21.6 vs 4.6	12.452	5.701	1.714–18.964	.005
≥ 0.3 vs < 0.3	163 vs 124	24.5 vs 8.9	12.627	3.341	1.635–6.826	.001
≥ 0.4 vs < 0.4	132 vs 155	25.0 vs 11.6	8.778	2.537	1.351–4.763	.004
≥ 0.5 vs < 0.5	102 vs 185	25.5 vs 13.5	6.234	2.189	1.186–4.042	.012
≥ 0.6 vs < 0.6	89 vs 198	24.7 vs 14.6	4.081	1.914	1.027–3.565	.041
≥ 0.7 vs < 0.7	65 vs 222	27.7 vs 14.9	5.226	2.193	1.137–4.232	.019
≥ 0.8 vs < 0.8	44 vs 243	25.0 vs 16.5	1.727	1.692	0.790–3.624	.176
≥ 0.9 vs < 0.9	20 vs 267	20.0 vs 17.6	0.071	1.170	0.374–3.659	.787

B. Multivariate Cox regression analysis

EMD/mesorectum ratio	No. of patients	5-year RFS survival (%)	χ^2	OR	95% CI	*P*
≥ 0.1 vs < 0.1	267 vs 20	76.4 vs 100.0	4.416	22.840	0.260–2003.171	.171
≥ 0.2 vs < 0.2	222 vs 65	73.5 vs 94.9	8.996	4.986	1.553–16.009	.003
≥ 0.3 vs < 0.3	163 vs 124	70.4 vs 88.0	12.046	3.073	1.576–5.990	.001
≥ 0.4 vs < 0.4	132 vs 155	71.4 vs 83.9	8.716	2.318	1.305–4.117	.003
≥ 0.5 vs < 0.5	102 vs 185	70.9 vs 82.2	6.424	2.006	1.158–3.474	.011
≥ 0.6 vs < 0.6	89 vs 198	71.2 vs 81.3	4.025	1.751	1.006–3.048	.045
≥ 0.7 vs < 0.7	65 vs 222	68.3 vs 81.2	4.841	1.886	1.062–3.349	.028
≥ 0.8 vs < 0.8	44 vs 243	71.2 vs 79.4	1.915	1.595	0.818–3.110	.166
≥ 0.9 vs < 0.9	20 vs 267	79.3 vs 78.1	0.092	1.171	0.422–3.250	.762

CI = confidence interval, EMD = extramural distance, OR = odds ratio, RFS = recurrence free survival.

predicting postoperative recurrence was 0.544, which was very close to the accuracy of using the EMD/mesorectum ratio 0.3. Therefore, the patients were subdivided into 2 groups: EMD/mesorectum ratio < 0.3 and EMD/mesorectum ratio ≥ 0.3.

3.3. Correlation between the EMD/mesorectum ratio and patient characteristics

Of the 287 patients, 124 (43.2%) had a EMD/mesorectum ratio < 0.3. The correlation between the EM/mesorectum ratio and patient characteristics was shown in Table 2. A EMD/mesorectum ratio ≥ 0.3 occurred more often in patients with BMI < 25. Patients with serum CEA level ≥ 5 ng/mL, tumor size on MRI ≥ 5 cm, tumor on anterior rectal wall, MR-LN positive and positive MRF, patients with positive EMVI also had higher proportion of EMD/mesorectum ratio ≥ 0.3. Patients with EMD/mesorectum ratio ≥ 0.3 also had higher combined resection rate and lower rate of anus-conserving surgery. For the postoperative pathological findings, patients with pathological lymph node invasion had a higher proportion of EMD mesorectum ratio ≥ 0.3.

3.4. Independent prognostic factors for survival

The results of univariate and multivariate analysis are shown in Table 3. In the univariate analysis of RFS, tumor size on MRI, EMD/mesorectum ratio, MR-LN status, EMVI, surgical approach, TNM stage after operation, venous invasion and neural invasion were associated with DFS. For OS, both patients undergone abdominoperineal resection (APR) and hartmann surgery and patients with Tumor size ≥ 5 cm, MR-LN positive, EMVI positive and venous invasion all had decreased OS (Table 3A). A Cox multivariate analysis was performed for variables with $P < .05$ in the univariate analysis. The multivariate analysis showed that EMD/mesorectum ratio ≥ 0.3 (HR 2.038; 95% CI: 1.230–4.123; $P = .032$) was the only preoperative independent adverse prognostic factor for RFS. For OS, the independent prognostic risk factors were MR-LN positive (HR 2.551; 95% CI 1.079–6.030; $P = .033$) and surgical approach (HR 3.025; 95% CI 1.346–6.797; $P = .007$) (Table 3B).

3.5. Survival analysis

The 5-year RFS and OS rate of patients with EMD/mesorectum ratio ≥ 0.3 were 70.4% and 82.1%, respectively, which were significantly worse than those of EMD/mesorectum ratio < 0.3 (88.0% and 92.2%) (HR: 3.068, 95% CI: 1.540–4.634, $P < .001$; HR: 2.591, 95% CI: 1.068–5.031, $P = .034$) (Fig. 4A and B). Furthermore, we analyzed the association between RFS rate of patients with EMD/mesorectum ratio ≥ 0.3 and nCRT. Of the 163 patients with EMD/mesorectum ratio ≥ 0.3, 61 patients had undergone nCRT with different intensity, and the baseline characteristics of the 2 groups are comparable (Table 4). Patients who undergone nCRT had higher 5-year RFS compared with patients without nCRT [86.9% vs 63.2%, HR 2.652; 95% CI: 1.229–4.357; $P = .001$ (Fig. 5)].

4. Discussion

An accurate staging system to classify patients into relatively homogeneous groups according to their prognosis is crucial, because these classifications enable clinicians to provide personalized treatment strategy or adequate surveillance to

Table 2

Correlation between EMD/mesorectum ratio and patient characteristics.

Patient characteristics	EMD/mesorectum ratio < 0.3, n (%)	EMD/mesorectum ratio ≥ 0.3, n (%)	*P* value
Gender			
Male	84 (44.4)	105 (55.6)	.556
Female	40 (40.8)	58 (59.2)	
Age			
< 65	81 (40.9)	117 (59.1)	.241
≥ 65	43 (48.3)	46 (51.7)	
BMI			
< 25	71 (37.6)	118 (62.4)	**.003**[*]
≥ 25	36 (59.0)	25 (41.0)	
Serum CEA level at initial diagnosis, ng/mL			
< 5	95 (51.4)	90 (48.6)	**<.001**
≥ 5	29 (28.4)	73 (71.6)	
Serum CA19-9 level at initial diagnosis, U/mL			
< 37	116 (44.3)	146 (55.7)	.236
≥ 37	8 (32.0)	17 (68.0)	
Tumor location			
Low	56 (35.0)	104 (65.0)	**.002**
Middle	68 (53.5)	59 (46.5)	
Tumor direction			
Anterior	24 (24.7)	73 (75.3)	
Lateral	68 (58.6)	48 (41.4)	**<.001**
Posterior	32 (43.2)	42 (56.8)	
MR T stage			
T3a	5 (100.0)	0 (0.0)	
T3b	88 (71.5)	35 (28.5)	**<.001**[†]
T3c	31 (22.5)	107 (77.5)	
T3d	0 (0.0)	21 (100.0)	
MR-LN			
Positive	43 (33.3)	86 (66.7)	**.002**
Negative	81 (51.3)	77 (48.7)	
MRF			
Positive	7 (11.1)	56 (88.9)	**<.001**
Negative	117 (52.2)	107 (47.8)	
EMVI			
Positive	26 (28.6)	65 (71.4)	**.001**
Negative	98 (50.0)	98 (50.0)	
Tumor size on MRI, cm			
< 5	104 (48.1)	112 (51.9)	**.003**
≥ 5	20 (28.2)	51 (71.8)	
Surgery			
LAR	111 (49.3)	114 (50.7)	**<.001**
APR + Hartmann	13 (21.0)	49 (79.0)	
Combined resection			
Yes	1 (5.9)	16 (94.1)	**.001**
No	123 (45.6)	147 (54.4)	
Pathological T stage			
pT0-2	24 (52.2)	22 (47.8)	.180
pT3 + pT4	94 + 6 (41.5)	122 + 19 (58.5)	
Pathological lymph node invasion			
Yes	40 (34.2)	77 (65.8)	**.011**
No	84 (49.4)	86 (50.6)	
Pathological venous invasion			
Yes	7 (28.0)	18 (72.0)	.108
No	117 (44.7)	145 (55.3)	
Pathological neural invasion			
Yes	19 (34.5)	36 (65.5)	.149
No	105 (45.3)	127 (54.7)	

APR = abdominal perineal resection, EMD = extramural distance, EMVI = extramural vascular invasion, LAR = Low anterior resection, mr T stage = magnetic resonance T stage, MRF = mesorectal fascia, MR-LN = lymph node on MRI.

[*] Data missing of BMI in 37 patients.

[†] Fisher's exact test.

Table 3

Correlation between clinicopathologic factors and RFS, OS in clinical T3 mid-low rectal cancer.

A. Univariate analysis

		RFS			OS		
		Univariate			Univariate		
Characteristic	**N**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Gender							
Female	98	1			1		
Male	189	0.854	0.477–1.529	.595	0.774	0.290–2.066	.609
Age, years							
< 65	198	1			1		
≥ 65	89	0.946	0.521–1.720	.856	2.082	0.754–5.751	.157
CEA level at initial diagnosis, ng/mL							
< 5	185	1			1		
≥ 5	102	0.945	0.529–1.686	.848	0.896	0.342–2.348	.823
CA19–9 level at initial diagnosis, U/mL							
< 37	262	1			1		
≥ 37	25	2.288	0.820–6.386	.114	2.607	0.514–13.22	.247
Neoadjuvant therapy							
No	191	1					
Yes	96	0.658	0.369–1.173	.156	0.556	0.211–1.461	.234
Tumor location							
Low (≤ 5cm)	160	1			1		
Middle (5< and ≤ 10cm)	127	0.706	0.405–1.232	.220	0.540	0.212–1.375	.196
Tumor direction							
Anterior	97	1			1		
Lateral + Posterior	190	0.936	0.526–1.666	.824	0.546	0.260–1.298	.186
Tumor size on MRI (cm)							
< 5	216	1			1		
≥ 5	71	**2.395**	**1.234–4.647**	**.010**	1.555	0.623–3.877	.344
EMD/mesorectum ratio							
< 0.3	124	1			1		
≥ 0.3	163	**3.068**	**1.540–4.634**	**.001**	**2.591**	**1.068–5.031**	**.034**
MRF							
Negative	224	1			1		
Positive	63	1.792	0.901–3.563	0.096	2.129	0.963–6.602	.060
MR-LN							
Negative	158	1			1		
Positive	129	**2.138**	**1.218–3.755**	**.008**	**3.028**	**1.371–6.685**	**.006**
EMVI							
Negative	196	1			1		
Positive	91	**2.325**	**1.338–4.042**	**.002**	1.544	0.687–3.748	.276
Surgery							
LAR	225	**1**			**1**		
APR + Hartmann	62	**1.915**	**1.103–4.274**	**.030**	**3.230**	**1.783–11.780**	**.002**
pTNM stage							
0-I	40	**1**			1		
II-III	247	**7.993**	**1.233–6.060**	**.015**	1.564	0.439–4.870	.538
Venous invasion							
No	262	**1**			**1**		
Yes	25	**2.764**	**1.623–15.520**	**.009**	**3.948**	**2.477–68.460**	**.003**
Neural invasion							
No	232	**1**			1		
Yes	55	**1.899**	**1.054–4.595**	**.036**	1.693	0.647–5.556	.248

B. Multivariate analysis

		RFS			OS		
Characteristic	**N**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Tumor size on MRI, cm							
< 5	216	1					
≥ 5	71	1.570	0.854–2.886	.146			
EMD/mesorectum ratio							
< 0.3	124	1			1		
≥ 0.3	163	**2.038**	**1.230–4.123**	**.032**	1.511	0.569–4.014	.408
MR-LN							
Negative	158	1			1		
Positive	129	1.281	0.668–2.457	.456	**2.551**	**1.079–6.030**	**.033**
EMVI							
Negative	196	1					
Positive	91	1.298	0.679–2.483	.431			
Surgery							
LAR	225	1			**1**		
APR + Hartmann	62	1.544	0.843–2.828	.160	**3.025**	**1.346–6.797**	**.007**
p/ypTNM stage							
0-I	40						
II-III	247	5.224	0.713–38.305	1.104			
Venous invasion							
No	262	1			1		
Yes	25	1.765	0.791–3.936	.165	2.523	0.894–7.123	.081
Neural invasion							
No	232	1					
Yes	55	1.554	0.819–2.952	.178			

APR = abdominal perineal resection, CI = confidence interval, EMD = extramural distance, EMVI = extramural vascular invasion, HR = hazard ratio, LAR = low anterior resection, MRF = mesorectal fascia, MR-LN = lymph node on MRI, OS = overall survival, RFS = recurrence free survival.

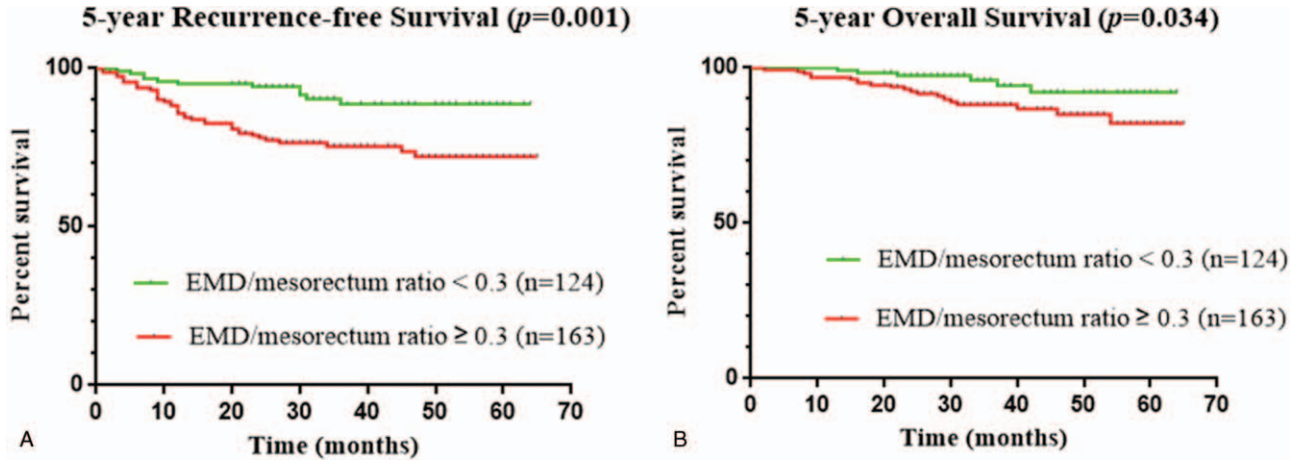

Figure 4. (A) Recurrence-free survival (RFS). The 5-year RFS rate of EMD/mesorectum ratio < 0.3 is significantly better than that of EMD/mesorectum ratio ≥ 0.3 (88.0% vs 70.4%, HR: 3.068, 95% CI: 1.540–4.634, $P < .001$). (B) Overall survival (OS). The 5-year OS rate of EMD/mesorectum ratio < 0.3 is significantly better than that of EMD/mesorectum ratio ≥ 0.3 (92.2% vs 82.1%, HR: 2.591, 95% CI: 1.068–5.031, $P = .034$). EMD = extramural distance, OS = overall survival, RFS = recurrence-free survival

patients. The depth of infiltration of primary tumor (T classification), nodal status (N classification), lymphovascular invasion, perineural invasion, and preoperative carcinoembryonic antigen level were found to have prognostic impact in multiple trials. An important aim of the present work was to evaluate the value of the EMD/mesorectum ratio as a maker of T3 subclassification in the T3 mid-low rectal cancer. To the best of our knowledge, this is the first report with such a large sample, describing the impact of EMD/mesorectum ratio, clinicopathologic, and radiologic factors on the prognosis.

The prognostic significance of the pathlogical EMD in rectal cancer was showed in many reports,[1,3,4,18–22] and the cutoff value of the EMD using to predict survival was range from 2 to 15 mm. Moreover, previous studies[9–11] had demonstrated the EMD detected by MRI was an independent prognostic factor. Cho et al[10] confirmed that the EMD detected by MRI was an independent prognostic factor in patients with T3 rectal cancer (HR: 2.186 95%CI: 1.336–3.577, $P = .002$), and the T3a (< 5 mm) patients had a higher 3-year DFS than T3b (5– 10 mm) and T3c (>10 mm) patients ($P = .016$, $P = .0001$, respectively). However, there were only 14 patients with T3c cancer in their study cohort of 146 patients, most tumors were T3a, and none of the patients had undergone nCRT which was unusual in currently clinical sets. Sueda et al[11] described the impact of EMD and CRM on prognosis, and selected a value of 4 mm as the cutoff point. In their study with 58 patients, EMD had been demonstrated to be an important preoperative prognostic factors for RFS in patients with clinical T3 lower rectal cancer (HR: 2.62 95%CI: 1.06–6.65, $P = .04$). However, the study had limited validation efficiency because of the small sample, only in the lower rectal cancer, and being from a single institute, and insufficient statistical analyses. In addition, all of these studies used the absolute value of EMD, differences of mesorectum between patients with different BMI and different directions of tumor were not considered. However, the mesorectal fat layer is rather thin in Chinese patients, and the mesorectum has been reported to be < 15 mm in the majority of patients in most positions and at most levels.[13] Moreover, the thickness of the mesorectum can vary with the BMI, tumor location, and direction. Besides, the T3a (preoperative staging of ESMO guideline) with depth of invasion <1 mm was difficult to measure on MRI and the distinction of prognosis between T2 stage and T3 stage was not remarkable when the T3 tumor has <1 mm spread. Therefore, the EMD/mesorectum ratio would be a good supplement for the absolute value of EMD. Based on our statistical analyses, the association between EMD/mesorectum ratio ≥ 0.3 and postoperative recurrence and 5-year RFS was remarkable. According to univariate and multivariate analysis, the EMD/mesorectum ratio was the only independent prognostic factor for 5-year RFS. For OS, both MR-LN and resection type were independent prognostic factors. However, regarding resection type (LAR vs APR and Hartmann), we caution against the firm conclusion because of the possibility of selection bias, surgeons would select patients with more-advanced T3 cancer or elder patients to perform APR and Hartmann surgery. Multivariate analysis showed that EMD/mesorectum ratio was not an independent prognostic factor for OS. This could be the result of short follow-up (median 37 months), effective adjuvant chemoradiotherapy and salvage surgery after recurrence. Even so, it's still obvious that EMD/mesorectum ratio ≥ 0.3 is one of the risk factors for postoperative recurrence. So, the optimal cutoff point was theoretically set to a value of 0.3. Then, the EMD/mesorectum ratio was divided into 2 groups: EMD/mesorectum ratio ≥ 0.3 and EMD/mesorectum ratio < 0.3.

Because of the special cone anatomy of the rectum, the mesorectum has different values in different locations and directions. In our study, the mean ratio in the low rectum is 0.48 ±0.28 and 0.38 ±0.2 in the middle rectum. The proportion of ratio ≥ 0.3 in the low rectum is 65.0% and significantly higher than the middle rectum (46.5%, $P = .002$). Besides, tumors located in anterior wall had a higher percentage (75.3%) of having an EMD/mesorectum ratio ≥ 0.3 compared with tumors in the lateral (41.1%) or posterior (56.8%) ($P < .001$). Moreover, patients with a EMD/mesorectum ratio ≥ 0.3 had a significantly higher proportion of positive MRF compared with patients with an EMD mesorectum ratio < 0.3 (34.4% vs 5.6%, $P < .001$). Therefore, more attention should be paid to patients with tumor located in anterior wall and lower rectum, further studies could be performed to explore the optimal cut off values in different locations and directions.

Neoadjuvant chemoradiotherapy followed by total mesorectal excision (TME) is currently considered the standard combined

Table 4

Baseline characteristics of patients with EMD/mesorectum ratio ≥ 0.3.

Patient characteristics	Patients without nCRT, n (%)	Patients with nCRT, n (%)	*P* value
Gender			
Male	64 (62.7)	41 (67.2)	.564
Female	38 (37.3)	20 (32.8)	
Age			
< 65	70 (69.3)	47 (77.0)	.286
≥ 65	31 (30.7)	14 (23.0)	
BMI			
< 25	71 (82.6)	47 (82.5)	.987*
≥ 25	15 (17.4)	10 (17.5)	
Serum CEA level at initial diagnosis, ng/mL			
< 5	58 (56.9)	32 (52.5)	.584
≥ 5	44 (43.1)	29 (47.5)	
serum CA19-9 level at initial diagnosis, U/mL			
< 37	91 (89.2)	55 (90.2)	.848
≥ 37	11 (10.7)	6 (9.8)	
Tumor location			
Low	63 (61.8)	41 (67.2)	.484
Middle	39 (38.2)	20 (32.8)	
Tumor direction			
Anterior	44 (43.1)	29 (47.5)	
Lateral	28 (27.5)	20 (32.8)	.379
Posterior	30 (29.4)	12 (19.7)	
EMD (mean ± SD, range)	8.66 ± 5.64 (1.30–33.00)	9.71 ± 5.66 (2.30–28.00)	.252
MR-LN			
Positive	53 (52.0)	33 (54.1)	.791
Negative	49 (48.0)	28 (45.9)	
MRF			
Positive	28 (27.5)	28 (45.9)	**.016**
vNegative	74 (72.5)	33 (54.1)	
EMVI			
Positive	40 (39.2)	25 (41.0)	.823
Negative	62 (60.8)	36 (59.0)	
Tumor size on MRI, cm			
< 5	73 (71.6)	39 (63.9)	.309
≥ 5	29 (28.4)	22 (36.1)	
Surgery			
LAR	72 (70.6)	42 (41.2)	.815
APR + Hartmann	30 (29.4)	19 (58.8)	
Combined resection			
Yes	7 (6.9)	9 (14.8)	.101
No	95 (93.1)	52 (85.2)	
Pathological T stage			
p/ypT2 + TRG0	10 (9.8)	12 (19.7)	.074
p/ypT3 + P/ypT4	92 (90.2)	49 (80.3)	
Pathological lymph node invasion			
Yes	53 (52.0)	24 (39.3)	.118
No	49 (48.0)	37 (60.7)	
Pathological venous invasion			
Yes	13 (12.7)	5 (8.2)	.370
No	89 (87.3)	56 (91.8)	
Pathological neural invasion			
Yes	25 (24.5)	11 (18.0)	.335
No	77 (75.5)	50 (82.0)	
Adjuvant chemoradiotherapy			
Yes	39 (38.2)	31 (50.8)	.116
No	63 (61.8)	30 (49.2)	

APR = abdominal perineal resection, BMI = body mass index, EMD = extramural distance, EMVI = extramural vascular invasion, LAR = low anterior resection, MRF = mesorectal fascia, MR-LN = lymph node on MRI.

* Data missing of BMI in 20 patients.

modality treatment for patients with LARC.[5–7] Currently, basing on risk stratification, clinicoradiologic prognostic factors are used to identify patients with rectal cancer who would benefit from nCRT. Preoperative MRI assessed MRF involvement is a strong independent predictor of poor outcome in patients with LARC.[23,24] EMVI[17,25,26] and EMD[9–11] detected on MRI are also risk factors for rectal cancer patients. However, studies evaluating the association between EMD detected by MRI and

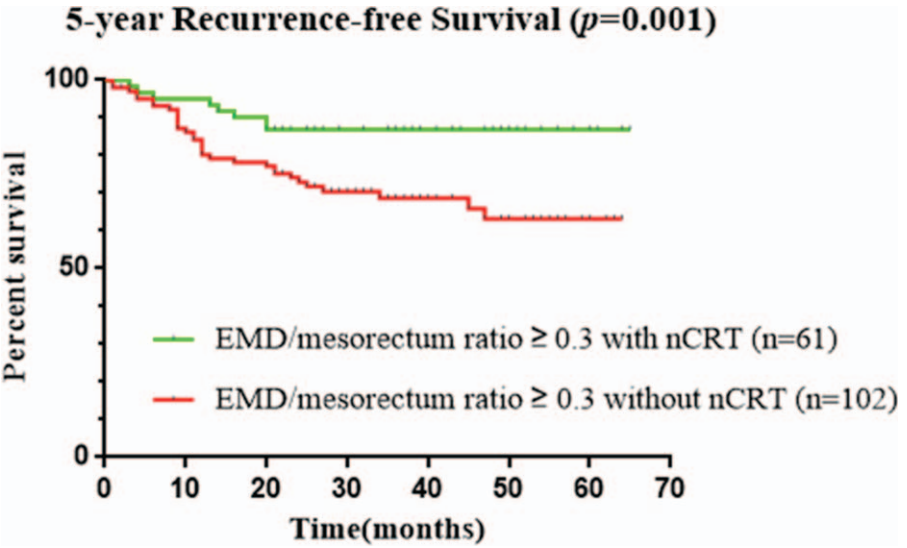

Figure 5. Recurrence-free survival for patients with EMD/mesorectum ratio ≥ 0.3. Of the 163 patients with EMD/mesorectum ratio ≥ 0.3, patients with nCRT had higher 5-year RFS than patients without nCRT (86.9% vs 63.2%, HR 2.652; 95% CI: 1.229–4.357; $P = .001$). nCRT = neoadjuvant chemoradiotherapy, EMD = extramural distance, nCRT = neoadjuvant chemoradiotherapy.

prognosis in patients with rectal cancer are scarce. In our study, patients with EMD/mesorectum ratio ≥ 0.3 had decreased 5-year RFS and OS. Besides, of the 161 patients with EMD/mesorectum ratio ≥ 0.3, the 5-year RFS of patients with nCRT was significantly higher compared with patients without nCRT [86.9% vs 63.2% HR 2.652; 95% CI (1.229–4.357); $P = .001$]. Therefore, EMD/mesorectum ratio is a reliable imaging marker for T3 subclassification in mid-low rectal cancer and can be used to select high risk patients for nCRT.

There are several limitations in the present study. First, this is a retrospective study with a relatively short follow-up. Second, the study is not a large scale randomized controlled trials and the data from only one center. However, the present data show a strong correlation between the EMD/mesorectum ratio and RFS. Third, the regimens and dose of neoadjuvant therapy were different among the patients with EMD/mesorectum ratio ≥ 0.3, including short course radiotherapy, long course chemoradiotherapy and chemotherapy with different cycles only. Even so, the significant differences of 5-year RFS had demonstrated that patients with EMD/mesorectum ratio ≥ 0.3 could benefit from neoadjuvant therapy.

5. Conclusion

The EMD/mesorectum ratio was an independent prognostic factor for 5-year RFS of T3 mid-low rectal cancer patients, and the optimal cut off value of EMD/mesorectum ratio was 0.3 when the ratio was applied to classify T3 mid-low rectal cancer patients. nCRT should be performed for these patients when the EMD/mesorectum ratio is ≥ 0.3. However, further prospective study is necessary to prove reproducibility and validity of the cutoff point and the feasibility as an imaging marker of nCRT.

Author contributions

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