Predictive value of MRI-detected extramural vascular invasion in stage T3 rectal cancer patients before neoadjuvant chemoradiation

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PURPOSE
We set out to explore the probability of MRI-detected extramural vascular invasion (mr-EMVI) before chemoradiation to predict responses to chemoradiation and survival in stage T3 rectal cancer patients.

METHODS
A total of 100 patients with T3 rectal cancer who underwent MRI examination and received neoadjuvant chemoradiation and surgery were enrolled. The correlation between mr-EMVI and other clinical factors were analyzed by chi-square. Logistic regression model was performed to select the potential factors influencing tumor responses to neoadjuvant chemoradiation. A Cox proportional hazards regression model was performed to explore potential predictors of survival.

RESULTS
The positive mr-EMVI result was more likely to be present in patients with a higher T3 subgroup (T3a+b = 7.1% vs. T3c+d = 90.1%, $P < 0.001$) and more likely in patients with mesorectal fascia involvement than in those without MRF (65% vs. 38.8%, $P = 0.034$). Compared with mr-EMVI (+) patients, more mr-EMVI (-) patients showed a good response (staged ≤ ypT2N0) (odds ratio [OR], 3.020; 95% confidence interval [CI], 1.071–8.517; $P = 0.037$). In univariate analysis, mr-EMVI (+) (hazard ratio [HR], 5.374; 95% CI, 1.210–23.872; $P = 0.027$) and lower rectal cancers (HR, 3.326; 95% CI, 1.135–9.743; $P = 0.028$) were significantly associated with decreased disease-free survival. A positive mr-EMVI status (HR, 5.727; 95% CI, 1.286–25.594; $P = 0.022$) and lower rectal cancers (HR, 3.137; 95% CI, 1.127–8.729; $P = 0.029$) also served as prognostic factors related to decreased disease-free survival in multivariate analysis.

CONCLUSION
The mr-EMVI status before chemoradiation is a significant prognostic factor and could be used for identifying T3 rectal cancer patients who might benefit from neoadjuvant chemoradiation.

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The definition of histopathologic extramural vascular invasion (EMVI) is tumor cells invading the veins beyond the muscularis propria, which indicates a poor prognosis in rectal cancer patients and has drawn great attention in the pathologic reporting of colorectal cancer (1, 2). Magnetic resonance imaging (MRI) has come to play an increasingly significant role in evaluating rectal cancer before therapy, because of its multidimensional imaging and excellent soft-tissue contrast. MRI detection of EMVI (mr-EMVI) has also been shown to be accurate and correlate with the pathology of patients who have undergone primary surgery (3, 4). Several retrospective studies have confirmed that mr-EMVI may be regarded as one of the risk factors for metastasis in rectal cancer (5–7). The newest version of the Society for Medical Oncology (ESMO) guidelines also regards mr-EMVI as a significant risk factor (8).

The majority of rectal cancers are identified at the T3 stage (9), and the prognosis for T3 rectal cancer is highly variable on whether treated with or without neoadjuvant chemoradiation (10). The popular and controversial topic is whether all T3 rectal cancer patients need neoadjuvant chemotherapy (11). It has been reported that the subdivided pT3 could identify stage II rectal cancer patients (pT3N0) who might not benefit from adjuvant treatment
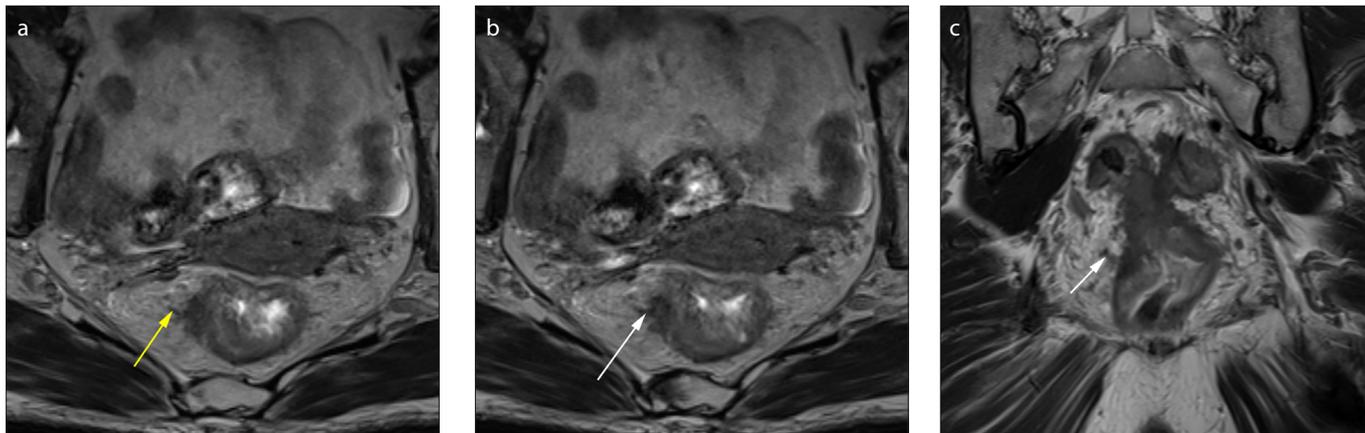
Figure 1. a–c. The performance of mr-EMVI (+) on axial T2-weighted thin-section images **(a, b)** and coronal T2-weighted image **(c)**. The *yellow arrow* points to an extramural vasculature of neighboring image **(a)**. The *white arrow* points to an invaded extramural vessel **(b, c)**.

(12). While the survival benefit of neoadjuvant chemoradiation is yet to be quantified in this context, our research may provide evidence of the benefits of neoadjuvant chemoradiation in T3 stage rectal cancer patients, particularly when mr-EMVI is detected before chemoradiation.

This study aimed to evaluate the probability of mr-EMVI, detected prior to neoadjuvant chemoradiation, as a factor to predict response to chemoradiation and survival of patients with T3 rectal cancer.

Methods

Patients and treatment

We obtained ethics committee approval from the local Institutional Review Board and informed consent from patients. Between April 2012 and November 2013, 100 patients with MRI-staged T3 rectal cancer (N0 or N (+)), who were treated with neoadjuvant chemoradiation followed by surgery at our hospital were collected in this retrospective study. Patient information and medical records were collected from our oncology database. Two radiologists, who were blinded to the clinical and patho-

Main points

- mr-EMVI status should be considered as a significant prognostic factor to identify stage T3 rectal cancer patients who could benefit from neoadjuvant chemoradiation.

- mr-EMVI status may reflect T3 rectal cancer aggressiveness.

- mr-EMVI status determinations are likely to prove indispensable for individualizing treatment and follow-up protocols in T3 rectal cancer patients.

logic information, independently reviewed rectal magnetic resonance images. All patients had histologically confirmed rectal adenocarcinomas, and the TNM stage was assessed depending on the 7th American Joint Committee on Cancer (AJCC) classification (13). The exclusion criteria were: 1) incomplete neoadjuvant chemoradiation treatment, 2) patients who did not undergo surgery within 6–10 weeks after complete neoadjuvant chemoradiation, and 3) metastatic disease later found, before or at the time of surgery.

The neoadjuvant chemoradiation regimen was conventional radiation combined with concurrent 5-fluorouracil (5-FU)-based chemotherapy. The whole pelvis received a total dose of 45–55 Gray (Gy) in 1.8–2.0 Gy daily fractions. Surgery was planned to take place 6–10 weeks after the completion of chemoradiation. The patient received adjuvant chemotherapy regimens, including capecitabine or 5-FU.

MRI examination

MRI examination was performed before treatment on a 3.0 T MRI magnet (Signa Horizon, GE Medical Systems) with a phased-array body coil. A bowel preparation was not needed before MRI examinations. The main MRI protocol included sagittal T2-weighted imaging scan (repetition time [TR], 2760 ms; echo time [TE], 105 ms; field of view [FOV], 260 mm×260 mm; matrix, 320×224; section thickness, 3.0 mm; bandwidth, 41.67 kHz/pixel); axial T2 fast spin-echo (TR, 3960 ms; TE, 105 ms; FOV, 370 mm×370 mm; matrix, 224×224; section thickness, 5.0 mm; bandwidth, 62.50 kHz/pixel), T2-weighted thin-section axial images (TR, 3960 ms; TE, 105 ms; FOV, 160 mm×160 mm; ma-

trix, 384×224; section thickness, 3.0 mm; bandwidth, 62.50 kHz/pixel) and coronal T2-weighted imaging scan (TR, 2675 ms; TE, 85 ms; FOV, 240 mm×240 mm; matrix, 416×224; section thickness, 4.0 mm; bandwidth, 31.25 kHz/pixel).

Radiologic evaluation

All images were independently reviewed by two radiologists (T.T. is specialized in rectal imaging with 9 years of experience and Y.Q.S. has 4 years of experience), who were blinded to clinical and pathologic information. Two radiologists, in consensus, used a workstation to review the rectal magnetic resonance images and the T3 sub-classification was established depending on radiologic measurement of maximal extramural depth beyond the outer margin of the muscularis propria on axial thin-section T2-weighted images. The definitions used to sub-classify T3a–T3d tumors were taken from the ESMO Guidelines (T3a, tumor depth <1 mm beyond the outer border of muscularis propria; T3b, 1–5 mm; T3c, 5–15 mm; T3d, >15 mm) (8). If the lymph node was of mixed signal intensity and had irregular, sharp, or obscure borders or the short axis was greater than 5 mm, it was diagnosed as mr-N positive (+). Rectal cancers could be divided into lower and mid-high rectal cancers according to a cutoff value of a 5 cm distance from the anorectal angle to the distal margin of the lower tumor border. The length of tumor was measured on the sagittal plane along the tumor's longitudinal axis. The mr-EMVI status was regarded as (+) if typical imaging morphologic appearances could be identified, which included a consecutive spread of tumor signal within the vascular network, i.e., vessel appeared

as a tube containing a flow signal void on T2-weighted image (Fig. 1), resulting in vessel expansion and irregular vessel borders on T2-weighted image (Fig. 1b, 1c) (14, 15). They also evaluated the tumor's relationship with the mesorectal fascial (MRF) envelope. A measured distance within 1 mm between the outermost margin of the tumor and MRF on T2-weighted thin-section axial images was indicative of MRF involvement. When there was disagreement between the two radiologists, a third radiologist would reanalyze the imaging data, and the majority opinion was accepted.

Histopathology evaluation

All TNM statuses were determined according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system (13). A pathologist with 8 years of experience evaluated all histopathology cases. To evaluate tumor response, we classified the down-staging of rectal cancer, which was lower T and/or N stage in postoperative definite staging compared with pretreatment clinical staging. Tumor down-staging was defined as ypT0–2N0 (the "yp" prefix indicates pathologic staging after preoperative chemoradiation [y] and postoperative pathologic resection specimen [p]) (16). In our research, we consider tumor down-staging as good tumor response.

Follow-up

Laboratory tests mainly including full blood count, liver function, and plasma carcinoembryonic antigen level were obtained at 3 monthly intervals during the first 2 years, and 6 monthly thereafter, as well as chest X-ray or computed tomography (CT), abdomen MRI or CT scans and the pelvis MRI scan at 3 monthly intervals. Colonoscopy was performed 1 year postoperatively, and then once at 2 yearly intervals.

Patient outcome endpoints included disease-free survival (DFS) and overall survival (OS). Any disease recurrence within the pelvis was classified as local failure; a distant metastasis was defined as any failure outside the pelvis. Recurrence and distant metastasis was pathologically diagnosed by surgical resection, biopsy or cytology, and/or radiologic new findings lesions, which grew over time. DFS and OS were considered as the time interval between neoadjuvant chemoradiation initiation and the last follow-up, or the date of disease recurrence of any type of death from any cause, respectively.

Table 1. Correlation between mr-EMVI and clinical factors

		n	mr-EMVI (-)	mr-EMVI (+)	χ²	P
mr-T3	a+b	56	52	4	70.168	<0.001
	c+d	44	4	40		
mr-N	(-)	6	4	2	-	0.692*
	(+)	94	52	42		
MRF	(-)	80	49	31	4.474	0.034
	(+)	20	7	13		
mr-Tumor length	<5 cm	44	28	16	1.860	0.173
	≥5 cm	56	28	28		
Tumor location	Mid-High	68	37	31	0.218	0.641
	Low	32	19	13		
Age	<50 years	28	16	12	0.021	0.886
	≥50 years	72	40	32		
Gender	Male	72	44	28	2.726	0.099
	Female	28	12	16		

mr-, MRI detected; EMVI, extramural vascular invasion; MRF, mesorectal fascia.
*Fisher's Exact Test.

Statistical analysis

The chi-square test was applied to compare frequencies between two groups based on mr-EMVI status. The variables with $P < 0.05$ (showing evidence of association) in univariate analysis could be retested in multivariate analyses using a logistic regression model to select the potential factors influencing tumor responses to neoadjuvant chemoradiation, and odd ratios (OR) with 95% confidence intervals (CIs) were calculated. Survival curve was described by Kaplan-Meier method, and outcome differences based on groups were compared by log-rank test. The variables with $P < 0.05$ in univariate analysis could be retested in multivariate analyses using a Cox proportional hazards regression model to select the potential predictors of survival, and hazard ratio (HR) with 95% CI were calculated. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (SPSS 19.0; SPSS Inc.)

Results

The study population was predominantly male (72%). Twenty-eight patients were younger than 50 years old, and 72 patients were older than 50 years old. In terms of tumor staging, 6 patients were mr-T3a, 50 were mr-T3b, 39 were mr-T3c, and only 5 patients were mr-T3d. The mr-N (+) signature was present in 94 patients. Twenty patients had involvement of the MRF, while the rest of patients did not, and 56 patients were diagnosed as mr-EMVI (-), while 44 were mr-EMVI (+). The tumor length was less than 5 cm in 44 patients, while the tumors in the remaining 56 patients were equal to or greater than 5 cm. Thirty-two patients had lower cancer and 68 patients had mid-high cancer. There were 37 patients that showed a good response (ypT0-2N0) and 63 patients that showed a poor response (ypT3-4 or N1-2).

Table 1 displays the differences of mr-EMVI presentation between the different subgroups. The number of patients with mr-EMVI differed significantly between the T3 sub-classification groups (T3c+d, 90.1% vs. T3a+b, 7.1%, $P < 0.001$) and the MRF (+) and MRF (-) groups (65% vs. 38.8%, respectively, $P = 0.034$). However, there were no significant differences in the likelihood of a mr-EMVI (+) diagnosis between mr-N (-) vs. mr-N (+), tumor mr-length <5 cm vs. ≥5 cm, lower rectal cancer versus mid-high rectal cancer, <50 years old vs. ≥50 years old, or male vs. female. These findings suggest that mr-EMVI (+) (Fig. 2a–2d) was more likely to be present in patients with higher T3 sub-classifications and MRF (+) than mr-EMVI (-) (Fig. 2e, 2f).

Univariate analysis showed that mr-EMVI was related to treatment response, and
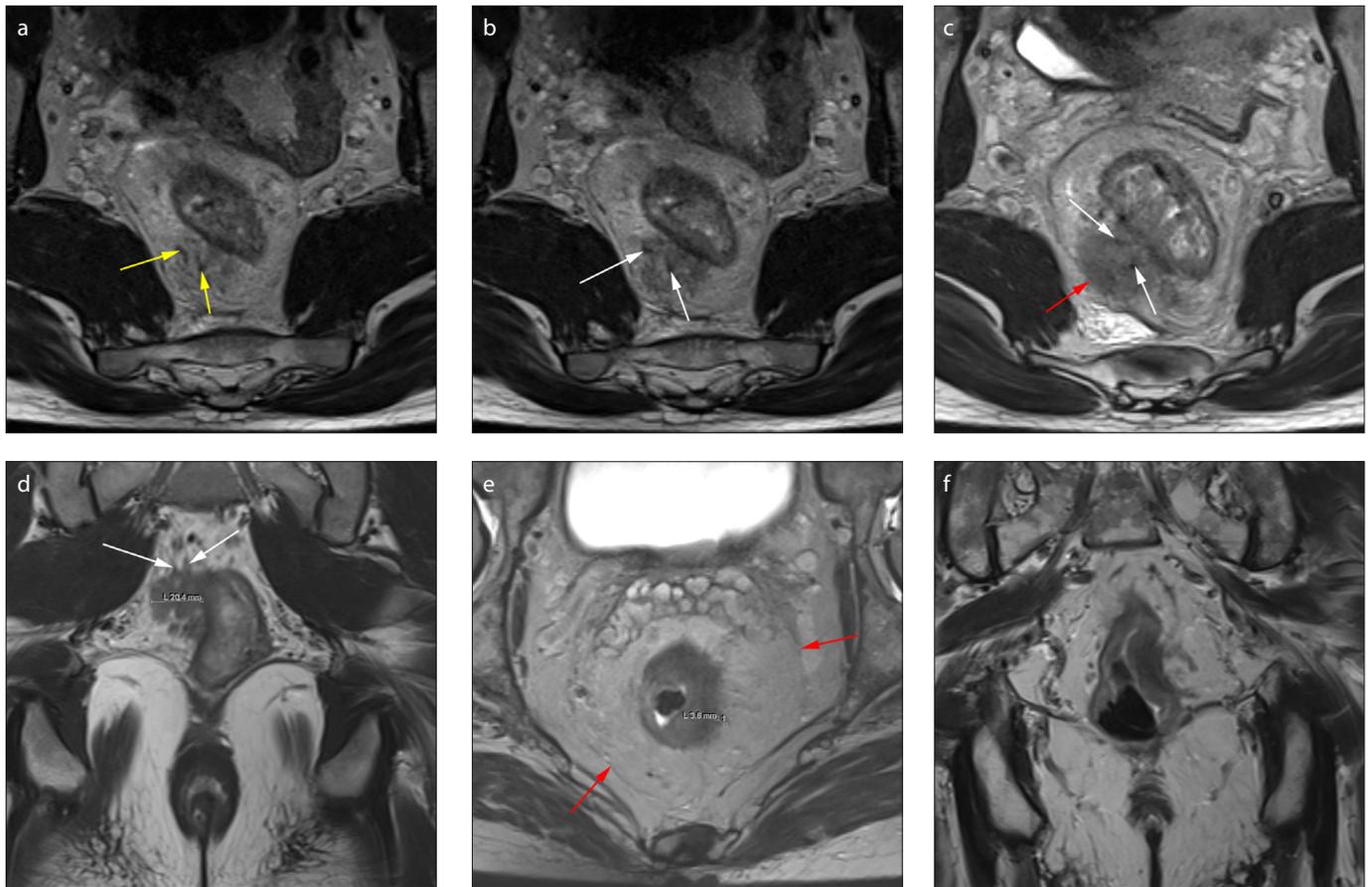
Figure 2. a–f. Panels **(a–d)** show a more invasive lesion in a 29-year-old man with rectal cancer that staged mr-T3d and MRF (+), with positive mr-EMVI. The value of maximal extramural depth (EMD) was 20.4 mm and the MRF was invaded *(red arrow,* **c)**. The *yellow arrow* points to an extramural vasculature of neighboring image **(a)**. The *white arrow* points to an invaded extramural vessel **(b–d)**. Panels **(e, f)** show a less invasive lesion in a 69-year-old man with rectal cancer that staged mr-T3b and MRF (-), with negative mr-EMVI. The value of EMD was 3.6 mm and the MRF was negative *(red arrows,* **e)**. The mr-EMVI (+) was more likely present in patients with higher T3 sub-classifications and MRF (+) than mr-EMVI (-).
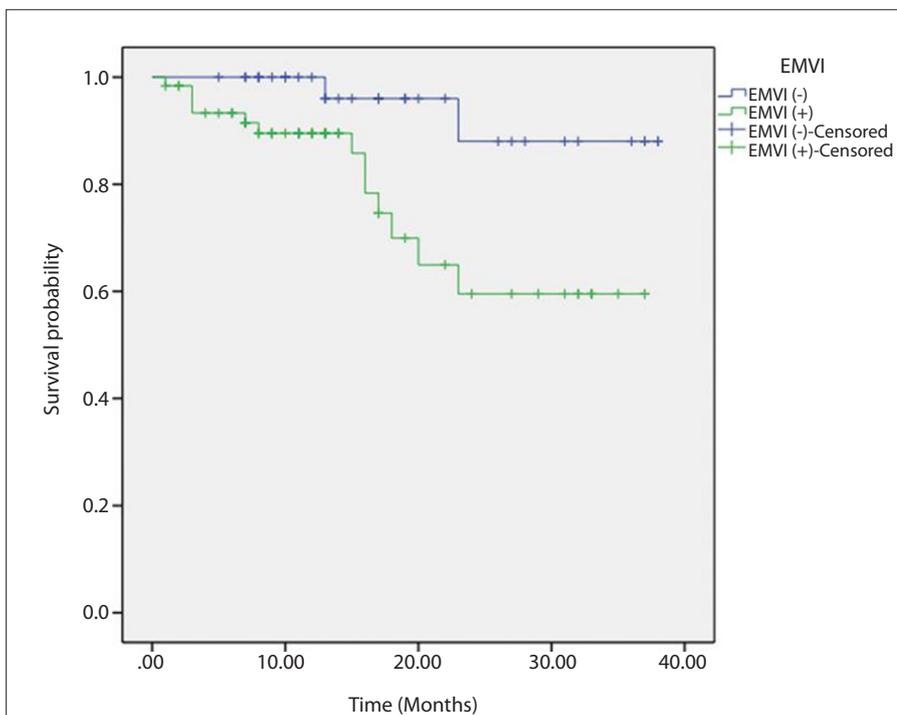
Figure 3. Disease-free survival stratified by mr-EMVI in mr-T3 rectal cancer patients.

further multivariate analysis showed that the only factor in our study significantly influencing the response to neoadjuvant chemoradiation was mr-EMVI (+) (OR, 3.020; 95% CI, 1.071–8.517; *P* = 0.037). Fifty-six patients were mr-EMVI (-); roughly 50% of these (27/56) responded well to neoadjuvant chemoradiation, while roughly 20% of mr-EMVI (+) (10/44) responded well to neoadjuvant chemoradiation (Table 2). The treatment response to neoadjuvant chemoradiation did not appear to be affected by other imaging factors.

The follow-up time ranged from 1 to 38 months. During follow-up, 15 recurrences or metastasis incidences were identified in the overall population, including 5 death events. No patients were lost to clinical follow-up after treatment. As shown in Fig. 3, the DFS was significantly lower in mr-EMVI (+) patients than in mr-EMVI (-) patients (*P* = 0.013). However, the OS was not significantly lower in patients with mr-EMVI (+) compared with patients with mr-EMVI (-) (*P* = 0.420).

Table 2. Univariate and multivariate analysis of influence factors of neoadjuvant treatment of mr-T3 rectal cancer using logistic regression model

Factors	Subgroup	n	Treatment response Good	Treatment response Poor	Univariate analysis P	Multivariate analysis OR	Multivariate analysis 95% CI	Multivariate analysis P
mr-T3	a+b	56	22	34				
	c+d	44	15	29	0.539	1.776	0.749–4.210	0.192
mr-N	(-)	6	3	3				
	(+)	94	34	60	0.667*	1.857	0.306–11.273	0.501
MRF	(-)	80	30	50				
	(+)	20	7	13	0.836	0.955	0.297–3.074	0.955
mr-EMVI	(-)	56	27	29				
	(+)	44	10	34	0.009	3.020	1.071-8.517	0.037
mr-Tumor length	<5 cm	44	13	31				
	≥5 cm	56	24	32	0.171	0.377	0.138–1.028	0.057
Tumor location	Mid-High	68	24	44				
	Low	32	13	19	0.607	1.406	0.535–3.690	0.489
Age	<50 years	28	11	17				
	≥50 years	72	26	46	0.768	1.280	0.492–3.333	0.613
Gender	Male	72	27	45				
	Female	28	10	18	0.868	0.918	0.345–2.444	0.864

OR, odds ratio; CI, confidence interval; mr-, MRI-detected; MRF, mesorectal fascia; EMVI, extramural vascular invasion.
*Fisher's Exact Test.

Table 3. Univariate and multivariate analysis of prognostic factors for disease-free survival in mr-T3 patients using Cox proportional hazards regression model

Factors	Subgroup	Univariate analysis HR	Univariate analysis (95% CI)	Univariate analysis P	Multivariate analysis HR	Multivariate analysis (95% CI)	Multivariate analysis P
mr-T3	a+b						
	c+d	1.575	0.564–4.401	0.386			
mr-N	(-)						
	(+)	1.345	0.299–6.064	0.699			
MRF	(-)						
	(+)	1.607	0.113–22.915	0.726			
mr-EMVI	(-)						
	(+)	5.374	1.210–23.872	0.027	5.727	1.286–25.594	0.022
mr-Tumor length	<5 cm						
	≥5 cm	0.561	0.203–1.551	0.265			
Tumor location	Mid-High						
	Lower	3.326	1.135–9.743	0.028	3.137	1.127–8.729	0.029
Age	<50 years						
	≥50 years	1.117	0.355–3.514	0.850			
Gender	Male						
	Female	0.628	0.142–2.789	0.541			

HR, hazard ratio; CI, confidence interval; mr-, MRI-detected; MRF, mesorectal fascia; EMVI, extramural vascular invasion.

A Cox proportional hazards model was performed to investigate the impact of the variables on DFS and OS. Both mr-EMVI (+) status (HR, 5.374; 95% CI, 1.210–23.872; P = 0.027) and lower rectal cancers (HR, 3.326; 95% CI, 1.135–9.743; P = 0.028) were associated with a decreased DFS in the univariate analysis (Table 3). Multivariate analysis revealed that mr-EMVI (+) (HR, 5.727; 95% CI, 1.286–25.594; P = 0.022) and lower rectal cancers (HR, 3.137; 9,% CI: 1.127–8.729; P = 0.029) remained the independent prognostic factors for decreased DFS (Table 3). However, there was no factor associated with decreased OS (Table 4).

Discussion

The results of our study provide additional information about mr-EMVI in patients with mr-T3 rectal cancer and its association with tumor response to neoadjuvant chemoradiation and the oncologic outcomes during follow-up. In this retrospective study, we have demonstrated that mr-EMVI (+) before treatment can predict the tumor response to neoadjuvant chemoradiation, and it is also an independent predictive factor of tumor recurrence in patients with mr-T3 rectal cancer.

The prognostic inhomogeneity of T3 rectal cancer patients is widely recognized and of significant concern (12). Many clinical and standard radiologic factors have been inves-

Table 4. Univariate analysis of prognostic factors for overall survival in mr-T3 patients using Cox proportional hazards regression model*

		Univariate analysis		
		HR	(95% CI)	*P*
mr-T3	a+b			
	c+d	2.026	0.514–7.989	0.313
mr-N	(-)			
	(+)	0.011	0.042–39.962	0.279
MRF	(-)			
	(+)	3.837	0.292–50.345	0.309
mr-EMVI	(-)			
	(+)	6.900	0.631–24.678	0.308
mr-Tumor length	<5 cm			
	≥5 cm	0.201	0.021–1.954	0.167
	Mid-High			
Tumor location	Lower	1.902	0.190–19.032	0.584
Age	<50 years			
	≥50 years	1.140	0.118–11.022	0.910
Gender	Male			
	Female	1.830	0.185–18.111	0.605

HR, hazard ratio; CI, confidence interval; MRF, mesorectal fascia; EMVI, extramural vascular invasion.
*Multivariate analysis could not be performed as none of the variables were significant in univariate analysis.

tigated to identify patients that are more likely to elicit favorable responses to neoadjuvant chemoradiation for rectal cancer, with the goal of optimizing treatment and follow-up protocols. Although it is already known that mr-EMVI, which is readily identifiable on MRI, has shown prognostic value in some studies and guidelines of rectal cancer, the predictive value of mr-EMVI before chemoradiotherapy has not been previously investigated in highly heterogeneous T3 rectal cancers. In this regard, the aim of the present work was to evaluate the feasibility of mr-EMVI status to predict tumor responses to neoadjuvant chemoradiation and survival in T3 rectal cancer patients.

The finding that mr-EMVI (+) was more likely present in patients with higher T3 sub-classifications (T3c+d, EMD ≥5 mm) and MRF (+) than mr-EMVI (-) suggested that mr-EMVI status might reflect tumor invasion. In support of our results, a study by Jhaveri et al. (14) found that there were significantly more mr-EMVI (+) tumors within 5 mm of the mesorectal fascia (40%; 6/15) compared with those that were more than 5 mm away from the mesorectal fascia (9%; 1/11) (*P* = 0.039). There were also more mr-EMVI (+) tumors with an extramural penetration depth of more than 5 mm

(45.5%; 5/11) compared with less penetrative tumors (13.3%; 2/15) (*P* = 0.034). In our study, tumors were grouped according to a tumor depth less than or greater than 1 mm from the mesorectal fascia. Given the remarkable association observed here, it is highly recommended that mr-EMVI status should be determined and considered in tumors either with a MRF (+) or those that have an extramural invasion depth greater than 5 mm.

Tumor response to neoadjuvant chemoradiation can be evaluated based on ypTN after surgery, which correlates with local recurrence and survival outcomes. Patients tend to have a lower local recurrence rate and better survival outcomes with better treatment responses. In this study, we classified ypT0-2N0 patients as "good responders" and ypT3-4 or N1-2 groups as "poor responders." Patients with mr-EMVI (+) are more likely to show a poor response; the OR for mr-EMVI (+) was 3.020 in our study by multivariate analysis. There was an increased rate and risk of a poor response in mr-EMVI (+) patients, independent of other tumor characteristics. This result may be related to tumor hypoxia. Tumor invasion in the vein affects normal flow velocity and causes diameter changes, which subse-

quently alter the tumor blood supply. Radiotherapy of hypoxic tumors can create free radicals via the application of ionizing radiation (e.g., OH-), and these free radicals can irreversibly damage tumor cells, thereby reducing the sensitivity of radiotherapy. Hypoxia can also restrict the diffusion of chemotherapeutic agents and promote the expression of multidrug resistance genes, thus rendering the tumor resistant to chemotherapy and reducing sensitivity to chemoradiotherapy. Previous studies also have shown that the greater the degree of venous invasion and the larger the diameter of the vein that is invaded, the poorer the patient prognosis becomes.

We also found that patients that were mr-EMVI (+) showed worse DFS compared with mr-EMVI (-) T3 rectal cancer patients. We found that mr-EMVI status not only influenced the treatment response to chemoradiotherapy, but was also closely associated with DFS in mr-T3 rectal cancers. Circulating tumor cells (CTCs) originate from the primary tumor and vessel surrounding the tumor, which is one of the main routes of metastasis. CTCs are not only used as a prognostic factor, but also as a predictive biomarker in colorectal cancer and there exists a directly proportional relationship with EMVI (17). In addition, correlations were found between mr-EMVI scores and vascular endothelial growth factor (VEGF) expression in T3 rectal cancers (18). VEGF is an antigenic mediator, and angiogenesis is associated with tumor growth, transmural extension, local lymphatic metastases, and the distant metastasis of colorectal tumors. Therefore, we concluded that the detection of mr-EMVI correlated with tumor survival, which has been confirmed by previous studies. In agreement with our findings, a study by Chand (19) et al. demonstrated the importance of mr-EMVI as a potential prognostic factor in rectal cancer, giving further evidence of the usefulness and importance of MRI detection of tumor characteristics, prior to making treatment decisions. Furthermore, the importance of EMVI in stage II disease has also been shown in multivariate analysis to be a prognostic factor of disease recurrence (20). In addition, we found that lower rectal cancers have a lower DFS rate in our study. The distal tapering of the mesorectal fat implies that lower rectal cancers more easily invade the MRF, neighboring organs, and pelvic wall. In this case, it will be more difficult for the surgeon to perform a tumor-free resection. Therefore, such sit-

uations have been closely associated with local recurrences and tumor metastasis.

This study has some limitations. First, we have not evaluated the mr-EMVI status on restaging MRI or changes in mr-EMVI status after neoadjuvant chemoradiation. Some patient restaging MRI analyses were not performed using the rectal MRI protocol, but rather the pelvic MRI protocol, which did not include these high-resolution thin-section axial T2-weighted images. It is difficult to evaluate the EMVI status on these images, and we have less experience in evaluating mr-EMVI after neoadjuvant chemoradiation. Second, we have not used tumor regression grading (TRG) to describe tumor response, because TRG scores are not available in some patients' histopathologic reports. Third, the distribution of patients was uneven. T3a is often mistaken for T2, which may be one of the reasons few patients are T3a. Tumor invasion greater than 15 mm (referring to T3d) is rare, because the Chinese mesorectum is generally thinner than the European and American mesorectums. Finally, if the follow-up time were longer, the results would have more clinical significance. Thus, we have continued following enrolled patients for future studies.

In conclusion, the present analysis of mr-EMVI status not only demonstrates a correlation with prognostic factors, but also shows promising results as far as its value in predicting tumor response and long-term outcomes of T3 rectal cancers that receive neoadjuvant chemoradiation. Multicenter prospective studies are needed to confirm the predictive and prognostic significance of mr-EMVI.

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