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Prognostic value of MRI in assessing extramural venous invasion in rectal cancer: multi-readers' diagnostic performance

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Abstract

Objectives This study was conducted in order to determine the prognostic value of MRI for extramural venous invasion (EMVI) in rectal cancer compared to pathology and to assess the diagnostic performance of multireaders.

Methods We retrospectively enrolled 222 patients (M:F = 148:74; mean age ± standard deviation, 61.5 ± 12 years) with histopathologically proven rectal cancers who underwent preoperative MRI between 2007 and 2016. Among them, 74 patients had positive EMVI on pathology (pEMVI) and 148 patients had negative pEMVI. Three radiologists with 7 (reviewer 1), 3 (reviewer 2), and 1 (reviewer 3) year of experience in rectal MR imaging determined the presence of EMVI on MRI (mrEMVI) using a 5-point grading system. Using histopathologic results as the reference standard, radiologists' performances were analyzed and compared with receiver operating characteristic (ROC) analysis. For assessment of interobserver variation, intraclass correlation coefficients (ICC) were used. Lastly, Kaplan–Meier estimation and Cox proportional hazard models were used for survival analysis.

Results The area under the ROC curve (AUC) was highest in reviewer 1 (0.829), followed by reviewer 2 (0.798) and reviewer 3 (0.658). Differences in AUCs between reviewer 1 or 2 and reviewer 3 were statistically significant ($p < 0.001$). ICC was substantial between reviewers 1 and 2. Overall survival (OS) was significantly different according to the positive circumferential resection margin, adjuvant treatment, and the presence of mrEMVI, but not by the presence of pEMVI.

Conclusions For experienced radiologists, the diagnostic performance of mrEMVI was good, resulting in better prediction of OS than with pEMVI, with substantial interobserver agreement.

Key Points

- *When read by experienced radiologists, MR can provide reliable diagnostic performance in assessing EMVI for patients with rectal cancer.*
- *Positive mrEMVI is an adverse prognostic factor of overall survival and may influence the clinical decision-making.*

Keywords Rectal neoplasms · Blood vessels · Magnetic resonance imaging · Chemoradiotherapy · Prognosis

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Abbreviations

CRT	Chemoradiation therapy
EMVI	Extramural venous invasion
mrEMVI	EMVI evaluated on MR
pEMVI	Pathologically detected EMVI

Introduction

Extramural venous invasion (EMVI), defined as the presence of tumor cells in the vasculature beyond the muscularis propria, has been demonstrated to be a negative prognostic indicator resulting in poor survival outcomes and frequent disease recurrence [1–3]. Therefore, identification of EMVI would be critical for accurate preoperative risk stratification and may influence the decision-making in regard to the selection of adjuvant chemotherapy or more intensive neoadjuvant treatment [1–3]. Traditionally, EMVI has been detected using histopathological analysis of surgical specimens. However, relying on pathological identification has been shown to result in substantial underestimation [4] and a wide variability in incidence (8–81%) [1, 5–9]. The most likely reasons for such underestimation and variability in its reported incidence may be the inconsistent pathological definitions used for EMVI as well as the lack of a standardized method of identifying venous invasion, such as the use of elastic tissue stains which would help distinguish lymphatic from venous invasion [4].

Recently, investigators have reported that EMVI may be better identified using MRI instead of pathological identification, both before and after neoadjuvant therapy [10–12]. Indeed, MRI may be superior to routine histopathology analysis of the resection specimens in identifying EMVI, particularly if it is not specifically sought out for or if the pathologic technique is limited to conventional hematoxylin and eosin (H&E) stain [4]. Moreover, MRI has the advantage of demonstrating the vascular anatomy in vivo and thus tumor invasion may be more readily identified. Therefore, recording the presence of EMVI on MRI (mrEMVI) has become routine in most institutions since its introduction and validation [11, 13, 14]. Yet, although a few recent studies have reported the diagnostic performance and prognostic effects of mrEMVI [11, 15, 16], the number of patients in these studies was small or had included only patients who either underwent or did not undergo neoadjuvant chemoradiation therapy (CRT), but not both.

Therefore, the objectives of our study are to determine the prognostic value of mrEMVI in patients who underwent surgery with and without neoadjuvant treatment compared to EMVI on pathology (pEMVI) and to assess the diagnostic performance of multireaders using mrEVMI.

Materials and methods

This retrospective study was approved by our institutional review board and the requirement for written informed consent was waived.

Patients

Patients with histopathologically proven rectal adenocarcinomas who had undergone preoperative MRI between January 2007 and December 2016 were identified from the pathology and imaging database of our hospital. Among them, 876 patients who met the following criteria were initially enrolled: extent of surgery was large enough to contain mesorectal tissue including veins, pathologically detected EMVI (pEVMI) of the surgical specimen was described in the pathologic report, and the time interval between preoperative MRI and surgery was within 60 days. Exclusion criteria were as follows: specimen did not contain the mesorectum, the quality of rectal MR was suboptimal, and recurred rectal cancer. The number of patients in whom the quality of rectal MR was suboptimal was two. In one patient, MR evaluation was not possible due to artifacts induced by an inserted metal stent through the tumor. In the remaining patient, tumor which was located at the upper part of the rectum was not fully covered on MRI. Of the 876 patients, 74 had positive pEMVI. Among the remaining 802 patients who had negative pEMVI, 148 patients were selected to comprise a 2:1 control group after matching their age, sex, and T and N staging. Finally, 222 patients (M:F = 148:74; mean age ± standard deviation, 61.5 ± 12 years) were included. Of these 222 patients, 75 patients underwent neoadjuvant CRT, while the remaining 147 patients underwent surgery without CRT. Detailed information on the type of surgery and adjuvant treatment is described in the Supplementary material. Figure 1 shows a flow

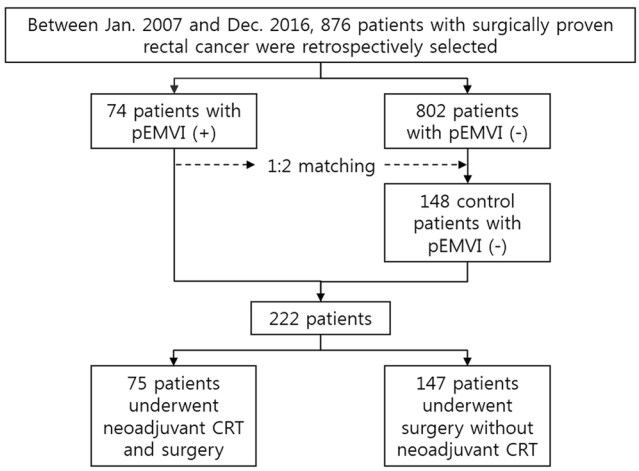

Fig. 1 Flow diagram of the patient population. pEMVI = pathologically detected extramural venous invasion, CRT = chemoradiation therapy

diagram of the patient population. Table 1 summarizes the demographics of the study population.

Neoadjuvant chemoradiation therapy

The protocol of chemoradiation therapy in our hospital has been described previously [17]. In brief, for radiation therapy, 45 Gy/25 fractions (1.8 Gy/day) was delivered to the pelvis over 5.5 to 6 weeks. A 5.4-Gy/3 fraction boost was then subsequently delivered to the primary tumor. During the first and fifth weeks of radiation therapy, the patients concurrently received an intravenous injection of two cycles of 5-fluorouracil (500 mg/m^2/day) for 3 days. Thereafter, all patients waited 4 to 6 weeks before surgery.

MR image acquisition

MRI was performed with a 1.5-T (Signa Excite HD [$n = 82$] or Signa HDxt [$n = 36$], GE Medical Systems) or 3-T scanner (Discovery 750 W [$n = 14$] or Signa Excite [$n = 1$], GE Medical Systems; Ingenia [$n = 73$] or Achieva dStream [$n = 16$], Philips Medical Systems) and an eight-channel, phased-array torso coil (USA Instruments) using the standard imaging protocol. One hour before the MRI examination, one bisacodyl suppository (Dulcolax, Boehringer Ingelheim) was administrated for bowel preparation. Thirty minutes prior to the MRI, 20 mg of scopolamine butylbromide (Buscopan, Boehringer Ingelheim) was intravenously injected to reduce colonic motility, unless otherwise contraindicated. Finally, prior to the examination, approximately 100 mL of a sonography transmission gel (Supersonic, Sungheung) was injected into the rectum for optimal rectal distension [18, 19].

MR sequences included the standard T2-weighted, fast-spin-echo imaging at three planes (sagittal, oblique axial, and coronal) using the following parameters: echo time (TE)/repetition time (TR) of 80–118/2500–11,317 ms, slice thickness of 3–5 mm, echo train length of 16–28, matrix of 320 × 320 to 580 × 365, and a field of view of 160 × 160 to 240 × 240. The oblique axial and coronal images were obtained orthogonal and parallel to the long axis of the rectum, respectively. Other MRI sequences including a pre- and postcontrast, axial, T1-weighted, three-dimensional (3D) spoiled-gradient-echo sequence and diffusion-weighted imaging were also performed.

MR image analysis

Three radiologists with 11 (senior faculty radiologist, reviewer 1), 7 (junior faculty radiologist, reviewer 2), and 4 (resident, reviewer 3) years of experience in abdominal radiology and 7, 3, and 1 year of experience in rectal MR interpretation, respectively, were asked to independently evaluate the presence of

Table 1 Clinical and histopathological characteristics of the 222 study patients

		Negative pEMVI ($n = 148$)	Positive pEMVI ($n = 74$)	p value
M:F		97:51	51:23	0.857
Age (years, mean ± SD) (range)		61.7 ± 12.0 (29–85)	61.1 ± 12.1 (32–87)	0.706
Time interval* (days, mean ± SD) (range)		8.4 ± 8.8 (1–55)	7.8 ± 6.6 (1–24)	0.620
Preoperative serum level of CEA (ng/mL, mean ± SD) (range)		142.6 ± 1179.6 (0.5–16,000)	44.0 ± 210.1 (0.9–1530)	0.483
Positive circumferential resection margin		12	17	0.002
Number of patients with neoadjuvant CRT		51	24	0.880
Type of surgery	AR or LAR	103	50	0.967
	ULAR	22	12	
	APR	15	7	
	Others	8	5	
Number of patients with adjuvant treatment		130	68	0.492
Pathologic T stage	T1 or T2	20	3	0.568
	T3 or T4	128	71	
Pathologic N stage	N0	25	7	0.188
	N1	83	40	
	N2	40	27	

pEMVI pathologically detected extramural venous invasion, *CEA* carcinoembryonic antigen, *SD* standard deviation, *CRT* chemoradiation therapy, *AR* anterior resection, *LAR* lower anterior resection, *ULAR* ultra-low anterior resection, *APR* abdominoperineal resection

*Time interval between MR and surgery

mrEMVI on a 5-point scoring system (0, definitely absent; 1, probably absent; 2, indeterminate; 3, probably present; 4, definitely present) [11]. Scores of 3 or 4 were designated as being positive for EMVI. T and N stages were also evaluated. Reviewers 1 and 2 were board-certified radiologists. The radiologists were blinded to the clinical information and pathologic reports of the patients. If a patient had more than one MR examination, mrEMVI was determined on the last MR taken prior to surgery. After independent review, all discrepancies were resolved through a consensus meeting among the three radiologists. Thereafter, the causes of false-positives (FPs) and false-negatives (FNs) for mrEMVI were determined based on histopathologic results.

Clinical and histopathologic analysis

Clinical information including serum level of carcinoembryonic antigen (CEA), type of surgery, status of circumferential resection margin (CRM), adjuvant treatment, patients' status (recurred or not recurred and dead or alive), and recurrence-free survival (RFS) or overall survival (OS) days after surgery for rectal cancer were also collected. RFS was defined as the time interval between surgery and the first date of local and/or distant recurrence or the last follow-up date without recurrence. Follow-up data for OS assessment was completed by reviewing the electronic medical record of our hospital as well as by contacting the Resident Service Division of the Ministry of Public Administration and Security. The endpoints of this study were either patient's death or March 31, 2018.

Two pathologists (14 and 4 years of experience in the interpretation of rectal cancer specimens) retrospectively reviewed all H&E-stained slides of the 222 surgical specimens for the presence of pEMVI, in consensus. The pathologists could refer to the clinical information and the results of rectal MR examinations. pEMVI was diagnosed when a tumor was detected within the endothelial-lined space beyond the muscularis propria.

Statistical analysis

Univariate analysis was performed using the independent *t* test or Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. A p value < 0.05 was considered to indicate a statistically significant difference. Diagnostic performances of each reviewer were evaluated using receiver operating characteristic (ROC) curve analysis for all patients and separately for patients with or without neoadjuvant CRT. Areas under the curve (AUC), sensitivity, and specificity were calculated based on binary analysis. Multireader ROC analysis was also performed to compare the competence of the reviewers. Agreement among the reviewers was assessed using the interclass correlation coefficient (ICC). The following convention was used to interpret the values of ICC: less than 0.20 indicated poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement [20].

Univariate and multivariate analyses were conducted to determine factors related to RFS and OS of the patients. Survival curves were calculated using the Kaplan–Meier method and their difference was analyzed using the log-rank test. A univariate Cox proportional hazards model was used for each variable, and variables showing p values < 0.05 were included for multivariate analysis. Thereafter, a Cox proportional hazards regression model was used to identify independent predictive factors of RFS and OS. All statistical analyses were performed using Medcalc version 14.8.1.0 (MedCalc) or SPSS version 23.0 software (IBM Corp.).

Results

Radiologists' diagnostic performances for mrEMVI

Table 2 summarizes the AUC, sensitivity, and specificity of each radiologist for the evaluation of mrEMVI based on histopathologic results. Regardless of whether the patient had undergone CRT, AUC was greatest in reviewer 1 (0.829 for all patients, 0.831 for patients without CRT, and 0.824 for patients with CRT), followed by reviewer 2 (0.798, 0.804, and 0.786, respectively), and reviewer 3 (0.658, 0.668, and 0.629, respectively). AUCs of all reviewers were not significantly different between patients without and with CRT (p = 0.912, 0.800, and 0.613, respectively). Differences in AUCs between reviewers 1 and 2 were not significant (p = 0.087), whereas differences in AUCs between the experienced radiologists (reviewer 1 or 2) and reviewer 3 were statistically significant (p < 0.001). Representative examples are presented in Figs. 2 and 3.

After the consensus meeting, the sensitivity and specificity of mrEMVI were 77.0% (57/74) and 85.8% (127/148), respectively. The number of patients in whom mrEMVI grade was changed through the consensus review among the reviewers was 1, 12, and 77 for reviewers 1, 2, and 3, respectively. From the consensus results, there were 21 FPs and 17 FNs for the evaluation of mrEMVI. The causes of FPs were as follows: tumors in lymphatics (n = 8), subserosal extension of the tumor itself without venous involvement (n = 7), marked fibrosis mimicking EMVI (n = 3), perivascular tumor infiltration without intravascular extension (n = 2), and abundant acellular mucin in the perivascular area without tumor in veins (n = 1) (Fig. 4). Among the 21 FP cases, nine patients (42.9%) underwent neoadjuvant CRT, whereas the remaining 12 patients (57.1%) did not. With regard to the 17 FN cases, the causes were microscopic pEMVI which were not discernible

Table 2 Diagnostic performance for the evaluation of mrEMVI based on histopathologic results

		Area under the curve	*p* value	Sensitivity (%)	Specificity (%)
Total patients (*n* = 222)	Reviewer 1	0.829 (0.772, 0.876)	< 0.001	77.0 (57/74)	85.8 (127/148)
	Reviewer 2	0.798 (0.739, 0.849)	< 0.001	73.0 (54/74)	85.1 (126/148)
	Reviewer 3	0.658 (0.592, 0.720)	< 0.001	78.4 (58/74)	46.6 (69/148)
Patients without CRT (*n* = 147)	Reviewer 1	0.831 (0.761, 0.888)	< 0.001	76.0 (38/50)	87.6 (85/97)
	Reviewer 2	0.804 (0.731, 0.865)	< 0.001	72.0 (36/50)	85.6 (83/97)
	Reviewer 3	0.668 (0.585, 0.743)	< 0.001	84.0 (42/50)	45.4 (44/97)
Patients with CRT (*n* = 75)	Reviewer 1	0.824 (0.718, 0.902)	< 0.001	79.2 (19/24)	82.4 (42/51)
	Reviewer 2	0.786 (0.676, 0.872)	< 0.001	75.0 (18/24)	92.2 (47/51)
	Reviewer 3	0.629 (0.509, 0.728)	0.045	66.7 (16/24)	49.0 (25/51)

Numbers in parentheses are 95% confidence intervals

mrEMVI extramural venous invasion evaluated on rectal MRI, *CRT* chemoradiation therapy

on MR (*n* = 15) and misinterpretation of pEMVI owing to the partial volume averaging artifact (*n* = 2) (Fig. 5). Of the FN cases, five patients (29.4%) underwent neoadjuvant CRT, while the other 12 patients (70.6%) did not. Regarding the number of FPs and FNs by each reviewer, there were 21, 22, and 79 FPs and 18, 20, and 16 FNs for reviewers 1, 2, and 3, respectively.

In all patients, mrEMVI showed substantial to fair interobserver agreement (Table 3). The agreement (ICC = 0.692) between more experienced radiologists (reviewers 1 and 2) was higher than that (ICC = 0.549) between less experienced radiologists (reviewers 2 and 3).

Survival

For all patients, the median follow-up period was 37.0 months (interquartile range (IQR), 19.0–63.0 months) and the mean ± SD follow-up period was 42.6 ± 29.5 months. On subgroup analysis according to the presence of pEMVI, the median and mean ± SD follow-up periods were 38.0 months (IQR 19.0–65.5 months) and 44.4 ± 30.0 months, respectively, in the pEMVI-negative group and 32.0 months (IQR, 19.0–56.0 months) and 38.9 ± 28.5 months, respectively, in the pEMVI-positive group. With regard to mrEMVI, the median and mean ± SD follow-up periods were 42.0 months (IQR, 19.0–67.5 months) and 42.0 ± 30.4 months, respectively, in the mrEMVI-negative group and 28.5 months (IQR, 19.0–56.0 months) and 36.5 ± 27.1 months, respectively, in the mrEMVI-positive group.

For all 222 patients, the estimated 1-, 3-, and 5-year survival rates were 88.0, 70.4, and 68.0% for RFS and 91.7, 80.1, and 71.1% for OS, respectively. For RFS, on subgroup analysis according to pEMVI, the estimated 1-, 3-, and 5-year survival rates were 92.2, 71.6, and 68.1% in the negative pEMVI group and 79.4, 68.1, and 68.1% in the positive pEMVI group, respectively, and the differences were not significant (*p* = 0.264). In terms of mrEMVI, the estimated 1-, 3-, and 5-year RFS rates were 91.9, 75.2, and 71.6% in the negative mrEMVI group and 80.7, 61.9, and 61.9% in the positive mrEMVI group, respectively, with a statistically significant difference (*p* = 0.029) (Fig. 6). For OS, on subgroup analysis according to pEMVI, the estimated overall 1-, 3-, and 5-year survival rates were 93.8, 83.5, and 71.9% in the negative pEMVI group and 87.7, 73.4, and 71.0% in the positive

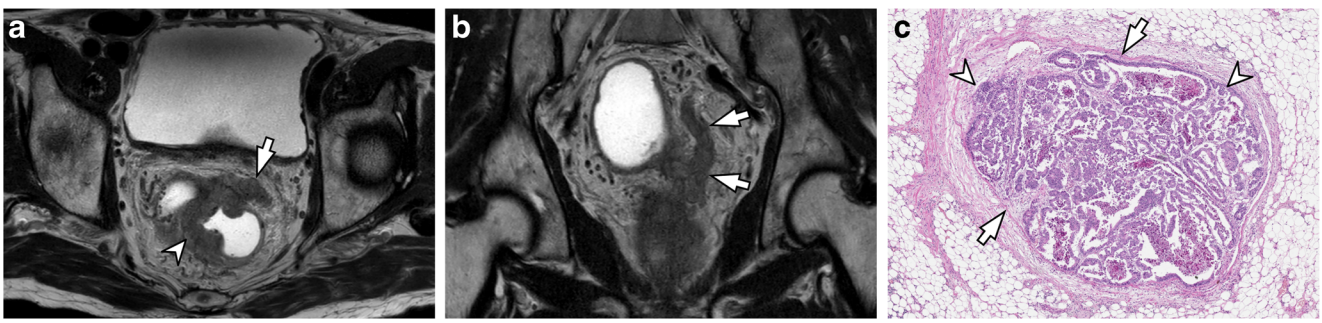

Fig. 2 An 87-year-old man with rectal cancer. **a**, **b** On axial (**a**) and coronal (**b**) T2-weighted MR images, a serpiginous extension of the tumor signal (arrows) is noted around the tumor (arrowhead). This patient was graded as 4 (definitely present) for mrEMVI by all three radiologists and subsequently underwent Hartmann's operation without neoadjuvant chemoradiation therapy. **c** On microscopy (H&E stain, original magnification × 40), a smooth-contoured tumor cluster (arrowheads) is surrounded by elastic lamina of vascular wall (arrows) in perirectal adipose tissue. Therefore, positive EMVI was confirmed on histopathology

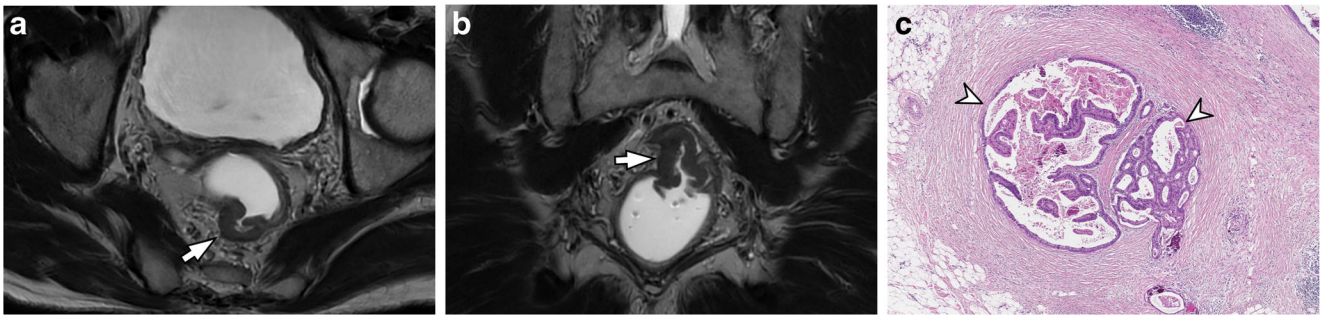

Fig. 3 A 68-year-old man with rectal cancer. **a**, **b** On axial (**a**) and coronal (**b**) T2-weighted MR images, there was no mesorectal fat stranding around the tumor (arrow) on both axial (**a**) and coronal (**b**) images. This patient was graded as 0 (definitely absent) by the senior faculty member, as 1 (probably absent) by the junior faculty member, and as 2 (indeterminate) by the resident. The patient underwent low anterior resection without concurrent chemoradiation therapy. **c** Well-circumscribed tumor nodules (arrowheads) were observed without evidence of vascular smooth muscle layer or elastic lamina around the tumor nodule. Therefore, EMVI was negative on histopathologic examination

pEMVI group, respectively, and the differences were not significant ($p = 0.146$). In terms of mrEMVI, however, the estimated overall 1-, 3-, and 5-year survival rates were 93.6, 85.9, and 75.0% in the negative mrEMVI group and 88.3, 69.0, and 63.9% in the positive mrEMVI group, respectively, with a statistically significant difference ($p = 0.011$) (Fig. 6).

The number of censored patients was 115 in patients without pEMVI and 52 in patients with pEMVI. All censored patients were alive until the last day of the follow-up period. The number of deceased patients during the study period was 33 in those without pEMVI and 22 in those with pEMVI. With regard to mrEMVI, the number of deceased patients was 29 in patients without mrEMVI and 26 in patients with mrEMVI. Among those 55 patients, 48 deaths (87.3%) were related to rectal cancer progression and the remaining seven (12.7%) to causes unrelated to rectal cancer (three with lung cancer, one with hypertensive injury, one with variceal bleeding, one with myocardial infarction, and one with an unknown extrinsic cause).

The predictive factors of RFS and OS are shown in Table 4. In terms of RFS, at univariate analysis using the Cox proportional hazard model, positive CRM and positive mrEMVI were significant factors affecting RFS. At multivariate Cox regression analysis, positive CRM was the only statistically significant predictor of RFS. Regarding OS, univariate analysis revealed that positive CRM, adjuvant treatment, pathologic N2 stage, and positive mrEMVI were shown to significantly affect OS. At multivariate analysis, positive CRM, adjuvant treatment, and mrEMVI were the statistically significant predictors of OS.

Discussion

Our study demonstrated that the assessment of EMVI on MR was able to predict RFS and OS better than pEMVI. More specifically, a significant difference was found in the RFS and OS according to mrEMVI, but not with pEMVI. Moreover, mrEMVI was shown to be one of the predictive factors of OS in patients with rectal cancer according to multivariate analysis which is concordant with the results of a recent study [16]. Indeed, although previous studies had reported that pEMVI may be an independent predictor of poor OS [21–23], several clear drawbacks have been reported

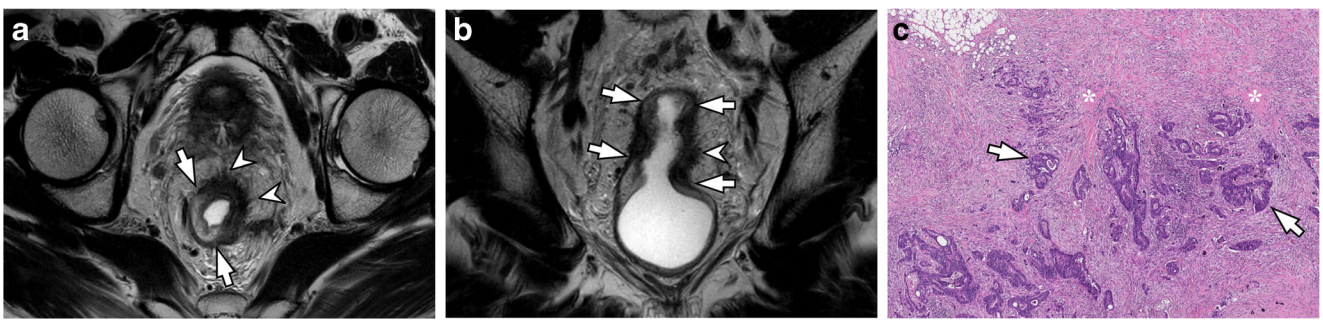

Fig. 4 False-positive case at mrEMVI in a 57-year-old man with rectal cancer who received neoadjuvant chemoradiation therapy. **a**, **b** On axial (**a**) and coronal (**b**) T2-weighted MR image, there was a hypointense tumor signal (arrows) from 11 to 6 o'clock of the rectum. Note the spiculated peritumoral low signal intensities (arrowheads) around the tumor. This patient was graded as 4 (definitely present) for mrEMVI by all three radiologists. **c** On microscopy, however, infiltrative tumor glands (arrows) were observed in fibrotic perirectal tissue (*) without intravenous tumor cells. Therefore, negative EMVI was confirmed on histopathology

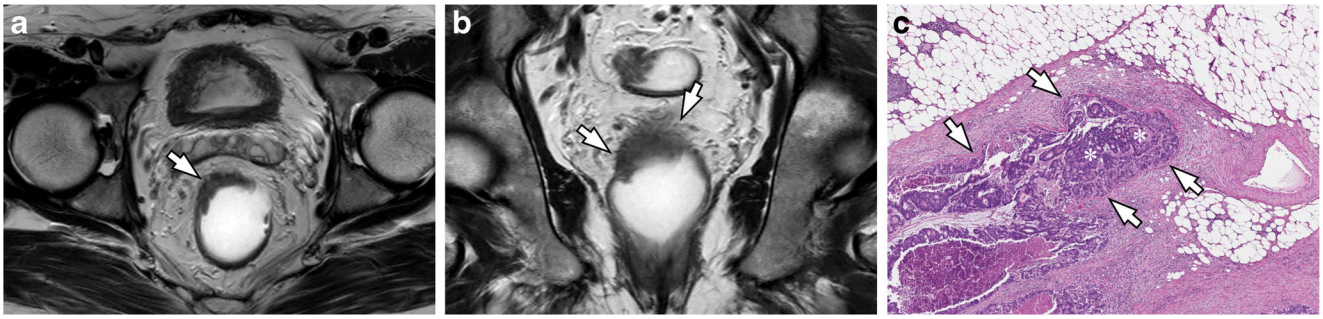

Fig. 5 False-negative case for mrEMVI in a 74-year-old man with rectal cancer. **a**, **b** On axial (**a**) and coronal (**b**) images, all three radiologists graded this patient as 0 (definitely absent) for mrEMVI although there was subtle peritumoral infiltration. **c** On microscopy, protruding tumor cluster (*) surrounded by vascular wall elastic lamina (arrows) of an extramural small venule of < 2 mm in diameter was observed in perirectal adipose tissue. Therefore, positive EMVI was confirmed on histopathology obtained after low anterior resection

[24–27]. First, even in our study, we found that longitudinal dissection had been performed for the pathologic specimen of rectal cancers although accumulating evidence suggests that sections taken perpendicular to the tumor at the area of maximal invasion are most likely to identify pEMVI [24]. Second, only H&E staining had been done for microscopic evaluation of pEMVI even though the rate of EMVI with H&E staining has been reported to be as low as 8%, and poor agreement even between specialized gastrointestinal histopathologists has been documented for pEMVI when using H&E alone [25, 26]. Thus, transverse slicing of the pathologic specimen and the routine use of special staining such as orcein and elastin van Gieson may be potential solutions for the improvement of the detection performance of pEMVI. In particular, the application of special staining has been shown to increase the detection of pEMVI from 19.6 to 58% [27]. Third, on pathology, there might be a change of wrong classification of tumor deposits as nodes when in fact these are EMVI tumor deposits which have obliterated the vessel wall. Furthermore, a single sectioning of pathologic specimens does not always allow anatomical visualization of the course of a vessel. To the contrary, with mrEMVI, we obtained the most up-to-date high-resolution MR imaging which is a prerequisite for the evaluation of mrEMVI, using a small FOV of 16 × 16 cm, and optimal field alignment perpendicular to the long axis of the rectum or vessels, providing high-quality images. These above reasons may partially be responsible for our results which showed that mrEMVI may be a better prognostic marker than pEMVI.

We also found that the diagnostic performance of the experienced radiologists on mrEMVI was better compared to previous studies [15, 28]. In detail, the AUCs of reviewers 1 and 2 who had 7 and 3 years of experience in rectal MR, respectively, were 0.824–0.831 and 0.786–0.804, respectively, regardless of neoadjuvant CRT. However, the AUCs of reviewer 3 were only 0.629–0.668 which was significantly lower than that of reviewer 1 or 2 ($p < 0.001$). Furthermore, substantial agreements (ICC value = 0.692–0.693) were achieved between the faculty members, while fair to moderate agreements (ICC value = 0.376–0.577) were observed between the faculty member (reviewer 1 or 2) and the resident. Thus, we believe that a certain degree of training may improve the performance on mrEMVI. Further studies regarding this issue, such as that using the cumulative summation method which is an evaluation tool for the learning curve of a specific procedure applied to medicine [29], should be performed in the future.

As for the effect of CRT on the diagnostic performance of radiologists at mrEMVI, all reviewers showed better diagnostic performances in patients without CRT than in patients with CRT, although there was no statistical significance. Considering the edema, inflammation, and fibrosis caused by neoadjuvant treatment, the assessment of mrEMVI after CRT may be hindered [30, 31]. Hence, the results of our study are reasonable.

Table 3 Interobserver agreement on mrEMVI

	Reviewers 1 and 2	Reviewers 1 and 3	Reviewers 2 and 3
Total patients ($n = 222$)	0.692 (0.496, 0.801)	0.377 (0.082, 0.578)	0.549 (0.330, 0.690)
Patients without CRT ($n = 147$)	0.693 (0.510, 0.801)	0.376 (0.041, 0.599)	0.542 (0.238, 0.717)
Patients with CRT ($n = 75$)	0.693 (0.419, 0.829)	0.383 (0.112, 0.587)	0.577 (0.396, 0.713)

Data are ICC values and numbers in parentheses are 95% confidence intervals. Reviewer 1 = senior faculty radiologist, reviewer 2 = junior faculty radiologist, reviewer 3 = resident

mrEMVI extramural venous invasion evaluated on rectal MRI, *CRT* chemoradiation therapy

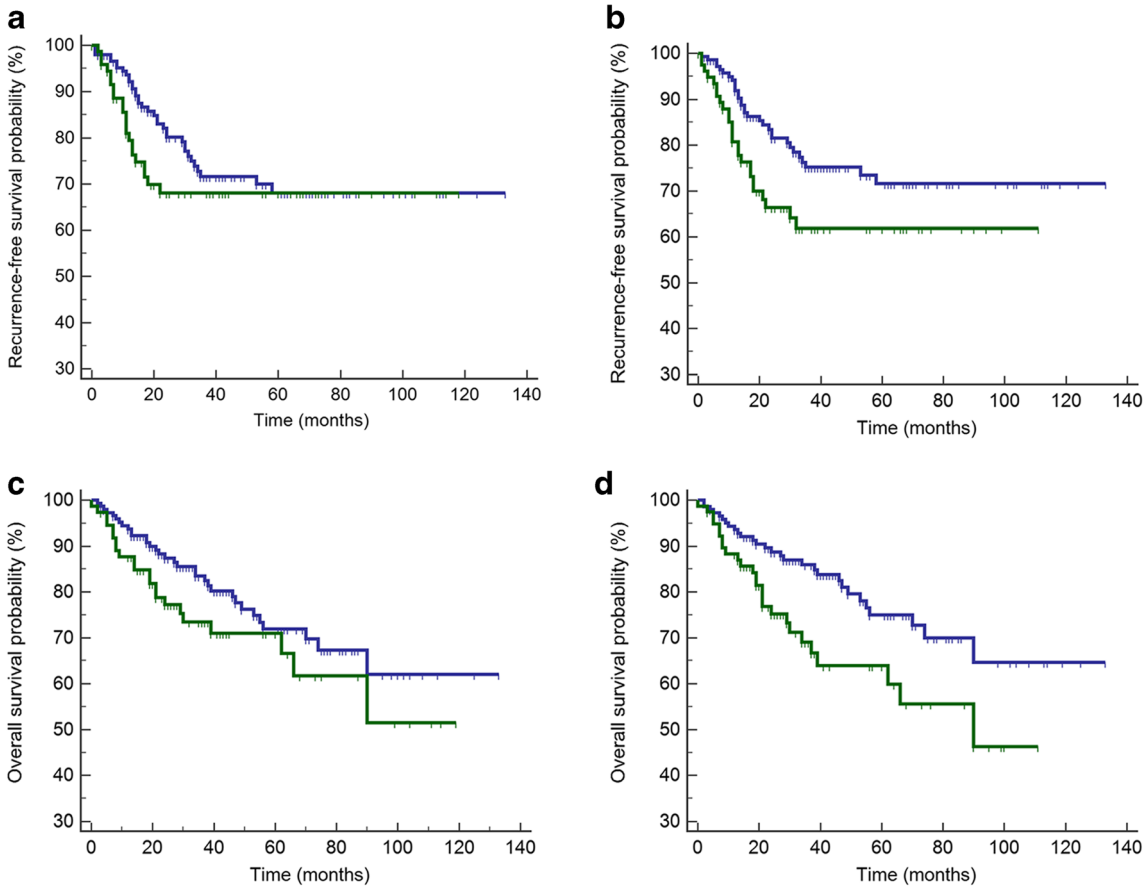

Fig. 6 Survival analysis. **a**, **b** On the Kaplan–Meier graph, the recurrence-free survival of the 148 patients with negative pEMVI was not significantly different from that of the 74 patients with positive pEMVI ($p = 0.146$) (**a**), while that of the 78 patients with positive mrEMVI was significantly worse than that of the 144 patients with negative mrEMVI ($p = 0.029$) (**b**). **c**, **d** In terms of overall survival, survival rate of the 148 patients with negative pEMVI was not significantly different from that of the 74 patients with positive pEMVI ($p = 0.146$) (**c**). However, overall survival of the 78 patients with positive mrEMVI was significantly worse than that of the 144 patients with negative mrEMVI ($p = 0.011$) (**d**). pEMVI = pathologically-detected extramural venous invasion, mrEMVI = extramural venous invasion evaluated on rectal MRI

In regard to the misinterpretation of mrEMVI, there were 21 cases of FPs and 17 cases of FNs in our study after careful review between both radiologists and pathologists. One reason for the FPs was tumors in lymphatics on histopathology which were misinterpreted as mrEMVI in eight patients. Indeed, the differentiation between tumors in lymphatics and extramural venous structures remains extremely challenging using current MR technology as they share the same MR finding of a serpiginous extension of the tumor signal at the mesorectum [30]. In addition, subserosal ($n = 7$) and perivascular ($n = 2$) tumor extension without invasion into extramural veins, peritumoral fibrosis induced by CRT ($n = 3$), and abundant acellular mucin ($n = 1$) were other causes of FPs. The limited resolution of current MR scanners may be responsible for these FPs. In terms of FNs, microscopic tumor depositions at extramural veins which exceeded the detection ability of current MR systems were shown to be the main cause of FNs ($n = 15$). According to several previous studies, compared to the group with negative pEMVI, the group with pEMVI in large vessels (≥ 3 mm) had a significantly higher risk for distant metastasis or poor survival, while pEMVI in small vessels (< 3 mm) showed no significant difference in risk [32, 33]. Therefore, FNs induced by microscopic tumor deposition at small extramural venules in our study may not have caused serious clinical consequence.

There are several limitations in our study. First, pEMVI was evaluated on routine H&E staining slides of the surgical specimen rather than using special staining for elastin fiber. Furthermore, sectioning of the surgical specimen was performed in a longitudinal direction rather than a transverse direction. Both of these limitations may affect the diagnostic performance for detection of EMVI on pathology. However, as our pathologists meticulously and retrospectively reviewed the microscopic slides for pEMVI, we believe that the possibility of underestimation for pEMVI may have been partially reduced. Nonetheless, a well-designed prospective study using standardized optimal histopathological and MR analysis would give a clear comparison of the diagnostic performances

Table 4 Univariate and multivariate analyses of the predictive factors for survival

		Recurrence-free survival				Overall survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		Hazard ratio	*p* value	Hazard ratio	*p* value	Hazard ratio	*p* value	Hazard ratio	*p* value
Sex		0.658 (0.359, 1.204)	0.174			1.046 (0.590, 1.855)	0.878		
Age		0.991 (0.970, 1.013)	0.431			1.018 (0.994, 1.043)	0.142		
Neoadjuvant CRT		1.587 (0.939, 2.685)	0.085			1.365 (0.803, 2.321)	0.253		
Positive circumferential resection margin		2.428 (1.246, 4.733)	0.009	2.235 (1.138, 4.388)	0.020	4.001 (2.124, 7.538)	< 0.001	3.544 (1.859, 6.756)	< 0.001
Adjuvant treatment		1.866 (0.583, 5.975)	0.293			0.408 (0.205, 0.815)	0.011	0.355 (0.175, 0.719)	0.004
Pathologic T stage	T1 or T2		0.140				0.088		
	T3 or T4	2.404 (0.751, 7.698)				24.214 (0.620, 946.210)			
Pathologic N stage	N0		0.261				0.073		0.171
	N1	1.704 (0.661, 4.394)	0.270			2.096 (0.735, 5.980)	0.167	1.938 (0.676, 5.556)	0.218
	N2	2.207 (0.832, 5.856)	0.112			3.156 (1.089, 9.146)	0.034	2.645 (0.906, 7.722)	0.075
Positive pEMVI		1.359 (0.791, 2.334)	0.267			1.500 (0.869, 2.549)	0.150		
Positive mrEMVI		1.782 (1.051, 3.021)	0.032	1.669 (0.979, 2.845)	0.060	1.967 (1.156, 3.347)	0.013	2.026 (1.171, 3.504)	0.012

Numbers in parentheses are 95% confidence intervals

CRT chemoradiation therapy, *pEMVI* pathologically detected extramural venous invasion, *mrEMVI* extramural venous invasion evaluated on rectal MRI

between MRI and pathology. Second, various MR machines and protocols have been used in our study owing to the retrospective nature of this study. Therefore, a prospective study using a single MR machine with a standardized protocol is warranted to overcome the heterogeneity of our study design. Lastly, we included both groups of patients who underwent CRT and who did not. This heterogeneity in the patient population may limit the clinical implication of our study results.

In conclusion, for experienced readers, the diagnostic performance of mrEMVI was good, resulting in better prediction of RFS and OS than pEMVI in patients with rectal cancers, with substantial interobserver agreement.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Joon Koo Han.

Conflict of interest The authors declare that they have no conflict of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- case–control study
- performed at one institution

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