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Prognostic significance of MRI-detected extramural venous invasion according to grade and response to neo-adjuvant treatment in locally advanced rectal cancer A national cohort study after radiologic training and reassessment

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A B S T R A C T

Background: Detection of grade 3–4 extra mural venous invasion (mrEMVI) on magnetic resonance imaging (MRI) is associated with an increased distant metastases (DM)-rate. This study aimed to determine the impact of different grades of mrEMVI and their disappearance after neoadjuvant therapy.

Methods: A Dutch national retrospective cross-sectional study was conducted, including patients who underwent resection for rectal cancer in 2016 from 60/69 hospitals performing rectal surgery. Patients with a cT3-4 tumour ≤8 cm from the anorectal junction were selected and their MRI-scans were reassessed by trained abdominal radiologists. Positive mrEMVI grades (3 and 4) were analyzed in regard to 4-year local recurrence (LR), DM, disease-free survival (DFS) and overall survival (OS).

Results: The 1213 included patients had a median follow-up of 48 months (IQR 30–54). Positive mrEMVI was present in 324 patients (27%); 161 had grade 3 and 163 had grade 4. A higher mrEMVI stage (grade 4 vs grade 3 vs no mrEMVI) increased LR-risk (21% vs 18% vs 7%, <0.001) and DM-risk (49% vs 30% vs 21%, $p < 0.001$) and decreased DFS (42% vs 55% vs 69%, $p < 0.001$) and OS (62% vs 76% vs 81%, $p < 0.001$), which remained independently associated in multivariable analysis. When mrEMVI had disappeared on restaging MRI, DM-rate was comparable to initial absence of mrEMVI (both 26%), whereas LR-rate remained high (22% vs 9%, $p = 0.006$).

Conclusion: The negative oncological impact of mrEMVI on recurrence and survival rates was dependent on grading. Disappearance of mrEMVI on restaging MRI decreased the risk of DM, but not of LR.

1. Introduction

In the treatment of rectal cancer, neoadjuvant (chemo)radiotherapy ((C)RT) and surgical strategies have evolved over the last decades with an important role for magnetic resonance imaging (MRI) characteristics on clinical decision making [1,2]. Despite these treatment advances, distant metastases (DM)-rates remain high; up to 37% for locally advanced cases [3]. In recent years, extra mural venous invasion (EMVI) has gained renewed interest due to its association with DM-rate [4]. EMVI as a pathological finding has been recognized since the late 1930s,

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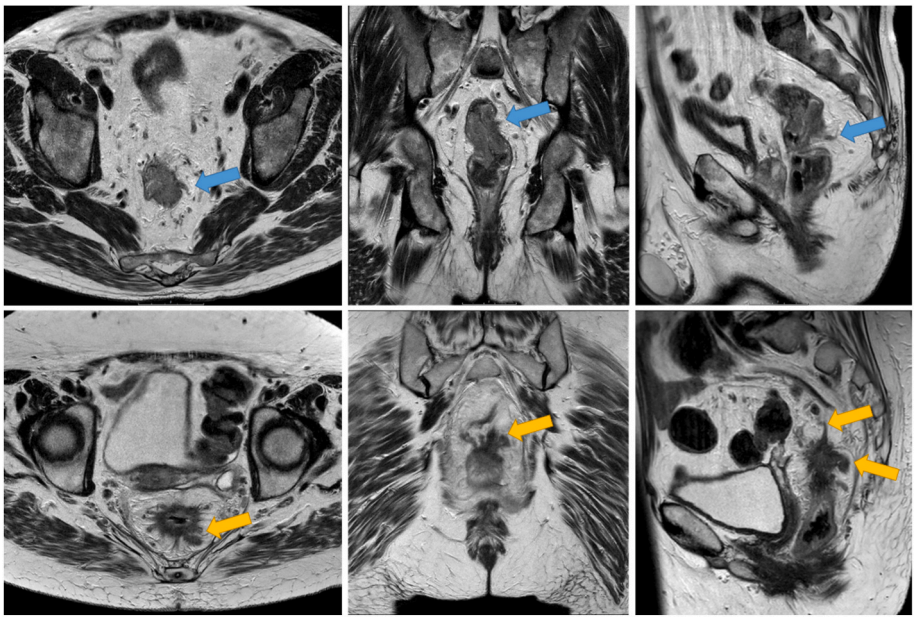

Fig. 1. MrEMVI grade 3 and mrEMVI grade 4 on primary MRI
Top: transversal, coronal and sagittal planes of grade 3 EMVI (blue arrow); tumour growth into a vascular structure without (nodular) expansion. Bottom: transversal, coronal and sagittal planes of grade 4 EMVI (yellow arrow); nodular growth into vascular structure with nodular expansion.

but has not been widely used because of inconsistencies in reporting [5]. More recently, MRI-detected EMVI (mrEMVI) revealed to be a prognostic MRI-characteristic with good inter-observer agreement and associated with increased DM-rate [6]. As a result, the updated ESGAR guideline recommends standard reporting of mrEMVI on primary and restaging MRI [7]. Nevertheless, consensus on tailoring treatment strategies based on mrEMVI is lacking and guidelines recommendations are inconsistent [8,9].

MrEMVI is defined as tumour involvement of vessels beyond the muscularis propria, and can be graded from 0 to 4 [10]. Grade 0 to 2 mrEMVI are negative predictors of histological presence of EMVI and associated with better oncological outcomes compared to grade 3 and 4 mrEMVI. In grade 0–2 there is no definitive vascular invasion, whereas grade 3 and 4 do show vascular invasion and are 'positive' predictors for histological presence of EMVI [10]. Grade 3 is described as tumour signalling within the vessel, and in grade 4 this invasion should be nodular or irregular (Fig. 1) [10]. Presence of mrEMVI has been associated with other poor predictive factors, such as a higher TNM-stage and a threatened or invaded mesorectal fascia (MRF) [11,12]. Although, mrEMVI remains independently associated with oncological outcomes, only a few small cohort studies have taken other MRI-based prognosticators such as tumour deposits (mrTDs) and enlarged lateral lymph nodes (mrLLNs, $\geq$7.0 mm short axis) into account [11–14]. Moreover, no study has evaluated the difference in oncological outcomes for mrEMVI grade 3 and 4.

Regression of mrEMVI after neoadjuvant treatment seems to be beneficial for prognosis [15–17]. In a meta-analysis disease free survival (DFS) ranged between 70 and 87% in cases where mrEMVI disappeared, and between 43 and 71% when mrEMVI remained present (HR 2.2; 95% CI 1.6–3.2) [18]. Eun Sun Lee et al. confirmed this finding in univariate analysis, but this was no longer significant in the multivariable model [19]. Unfortunately, most studies assessing mrEMVI regression are limited by sample size, and consequently lack statistical power.

This cross-sectional population-based study aimed to evaluate the prognostic impact of mrEMVI after reassessment of MRI-scans by trained radiologists, and to correlate different mrEMVI grades and regression after neoadjuvant therapy to 4-year oncological outcomes.

2. Methods

A retrospective cross-sectional cohort study (Snapshot design) was conducted in the Netherlands and included 3057 patients from 67 hospitals out of the 69 providing rectal cancer care, who underwent surgical resection for primary rectal cancer in 2016. The Dutch ColoRectal Audit (DCRA) was used to identify eligible patients, and was subsequently enriched with an extensive number of variables on detailed disease and treatment characteristics, as well as long-term outcomes. Between 2020 and 2022 data collection was performed for local patients by a collaborative team (surgeons, residents and abdominal radiologists). The Medical Ethics Committee of the Amsterdam UMC approved the study and determined it to be exempt from the Dutch Medical Research Involving Human Subjects Act. More detailed information of the methods is described in previous publications [14,30].

2.1. MRI reassessment

MRI reassessment was done in 60 of the 67 hospitals by 75 abdominal radiologists in their own respective hospitals. Radiologists attended a 2-h interactive training with ten example MRI-scans, regarding mrEMVI, mrTDs and mrLLNs, as previously described [20]. This training led to an improvement in short-axis size measurement of mrLLNs [21]. The radiologists then reassessed the available primary, restaging and follow-up MRI-scans of patients with a cT3/4-stage tumour located $\leq$8 cm of the anorectal junction. Quality of MRI scans was sufficient for classifications of mrEMVI grade of all participants. Re-evaluation was only performed by one radiologists per MRI scan, and therefore, inter-observer agreement could not be evaluated in this study. Throughout the re-evaluation process, radiologists had access to electronic patient files, containing treatment and outcomes information and all performed MRI scans.

2.2. Patient selection and definitions

Patients who were treated for a regrowth or according to a watch and wait protocol were excluded due to incomplete registration in the DCRA database. Moreover, thirteen patients whose surgical resection solely included a local excision were excluded to create a homogeneous

Table 1
Baseline characteristics

	Whole cohort (n = 1214)	mrEMVI gr (0–2) (n = 890, 73.3%)	mrEMVI gr (3–4) (n = 324, 26.7%)	p-value	mrEMVI gr 3 (n = 161, 13.3%)	mrEMVI gr 4 (n = 163, 13.4%)	p-value
Variable	n (%)	n (%)	n (%)		n (%)	n (%)	
Gender: male	804 (66.2)	573 (64.4)	231(71.3)	**0.024**	117 (72.7)	114 (69.9)	0.587
Mean age in years (SD)	66.5 (10.9)	66.6 (10.7)	66.0 (11.3)	0.347	65.8 (11.3)	66.1 (11.3)	0.757
ASA[a]				0.052			0.308
I/II	996 (82.0)	741 (83.3)	130 (79.4)		130 (81.8)	125 (77.2)	
III/IV	205 (16.9)	139 (15.6)	29 (20.6)		29 (18.2)	37 (22.8)	
Distance to the ARJ on MRI (cm, mean, SD)	3.5 (2.5)	3.4 (2.5)	3.8 (2.5)	**0.003**	3.8 (2.5)	3.9 (2.4)	0.312
Tumour location according to the LOREC criteria:				**0.002**			0.267
On/below attachment of the levator ani muscle	691 (56.9)	530 (59.6)	85 (49.7)		85 (52.8)	76 (46.6)	
Clinical T-stage				**<0.001**			**0.002**
T3, MRF not threatened	661 (54.4)	529 (59.4)	132 (40.7)		77 (47.8)	55 (33.7)	
T3, MRF threatened	366 (30.1)	267 (30.0)	99 (30.6)		52 (32.3)	47 (28.8)	
T4	187 (15.4)	94 (10.6)	93 (28.7)		32 (19.9)	61 (37.4)	
Clinical N-stage (mesorectal)				**<0.001**			0.148
N0	358 (29.5)	312 (35.1)	46 (14.2)		28 (17.4)	18 (11.0)	
N1	480 (39.5)	372 (41.8)	108 (33.3)		56 (34.8)	52 (31.9)	
N2	376 (31.0)	206 (23.1)	170 (52.5)		77 (47.8)	93 (57.1)	
Synchronous metastases[b]	117 (9.6)	62 (7.0)	55 (17.0)	**<0.001**	21 (13.0)	34 (20.9)	0.061
Tumour deposits present on primary MRI	179 (14.7)	63 (7.1)	116 (35.8)	**<0.001**	37 (23.0)	79 (48.5)	**<0.001**
mrLLNs present				**0.016**			**0.002**
No mrLLN	847 (69.8)	634 (71.2)	213 (65.7)		118 (73.3)	95 (58.3)	
Only mrLLN(s) without malignant features or <5.0 mm	153 (10.8)	116 (13.0)	37 (11.4)		16 (9.9)	17 (10.4)	
At least one mrLLN present ≥5.0 mm with malignant feature(s) or ≥7.0 mm	214 (19.4)	140 (15.7)	74 (22.8)		27 (16.8)	51 (31.3)	
Neoadjuvant treatment				**<0.001**			0.082
None	223 (18.4)	197 (22.1)	26 (8.0)		13 (8.1)	13 (8.0)	
5 × 5 Gy short interval radiotherapy	200 (16.5)	176 (19.8)	24 (7.4)		18 (11.2)	6 (3.7)	
5 × 5 Gy long interval radiotherapy	186 (15.3)	120 (13.5)	66 (20.4)		31 (19.3)	35 (21.5)	
CRT	605 (49.8)	397 (44.6)	208 (64.2)		99 (61.5)	109 (66.9)	
Surgery				0.114			0.509
Hartmann procedure (HP)	198 (16.3)	131 (14.7)	67 (20.7)		76 (47.2)	71 (43.6)	
Lower anterior resection (LAR)	576 (47.4)	429 (48.2)	147 (45.4)		53 (32.9)	54 (33.1)	
Abdominal perineal resection (APR)	433 (35.7)	326 (36.6)	107 (33.0)		32 (19.9)	35 (21.5)	
Proctocolectomy/total exenteration	7 (0.6)	4 (0.4)	3 (0.9)		0 (0.0)	3 (1.2)	
Resection Margin: R1[c]	99 (8.2)	61 (6.9)	37 (11.7)	**0.006**	14 (8.7)	24 (14.7)	0.092
CRM positive (≤1.0 mm)[d]	75 (76.5)	47 (78.3)	28 (73.7)	0.614	11 (78.6)	17 (10.4)	0.733
DRM positive (≤1.0 mm)[d]	19 (19.4)	10 (16.7)	9 (23.7)		3 (21.4)	6 (25.0)	
CRM and DRM positive (≤1.0 mm)[d]	4 (4.1)	3 (5.0)	1 (2.6)		0 (0.0)	1 (4.2)	
Adjuvant chemotherapy	24 (2.0)	17 (1.9)	7 (2.2)	0.816	2 (1.2)	5 (3.1)	0.259

[a] 13 missing values.
[b] metastases <3months of surgery.
[c] 1 missing value.
[d] 1 missing value, as percentage of R1.

representative group (Fig. S1).

For mrEMVI measurement, the largest size mrEMVI in any plane was used, measured from the outside of the rectal wall. MrTDs were described as irregular deposits, often related to or located within a vessel, while mrLLNs had a regular cortex and were not related to vessels. MrLLNs in the internal iliac or obturator compartment were categorized into absent and present with or without malignant potential. Malignant potential was defined as short-axis size ≥7.0 mm, or 5.0–6.9 mm with malignant feature(s) (round shape, heterogeneity, loss of fatty hilum, irregular border) [14,23]. R0 resection was defined as a negative CRM and DRM (both >1.0 mm).

2.3. Guideline recommendations

In 2016 the Dutch guideline recommended no neoadjuvant therapy for cT1-T3abN0 rectal cancer, neoadjuvant short-course RT (5 × 5Gy) for intermediate risk tumours (cT3cdN0 or cT1-3N1(MRF-)) and CRT (28 × 1.8Gy or 25 × 2Gy in combination with Capecitabine) for high risk tumours (cT4, MRF+, cN2, mrLLNs or mrEMVI) [22]. After short-course radiotherapy for intermediate tumours, there was a choice for a short-interval before surgery, or a long-interval in combination with restaging MRI before surgery. As a result, more advanced tumours were more likely to undergo a restaging MRI. Total neoadjuvant treatment (TNT) was not regularly applied in 2016 in the Netherlands. The guideline did not recommend of adjuvant chemotherapy for rectal cancer patients.

2.4. Outcome measures

Patients were categorized in three groups based on mrEMVI grading according to Smith et al.: negative (grade 0–2), grade 3 and grade 4 [10]. Characteristics of all patients were analyzed and compared based on the mrEMVI-subgroups. Four year actuarial recurrence rates (local recurrence (LR) and DM), DFS and overall survival (OS) were analyzed in patients without synchronous metastases (<3 months from surgery). In multivariable models, pre-operative variables (cT/N-stage, mrLLNs and mrTDs) were tested for their prognostic impact besides mrEMVI after correction for treatment variables (type of neoadjuvant therapy and surgery) and post-operative outcomes (R0 resection). In patients for whom a restaging MRI was performed after neoadjuvant therapy, disappearance of mrEMVI was analyzed with regard to type of neoadjuvant therapy, presence of mrTDs and mrEMVI-size.

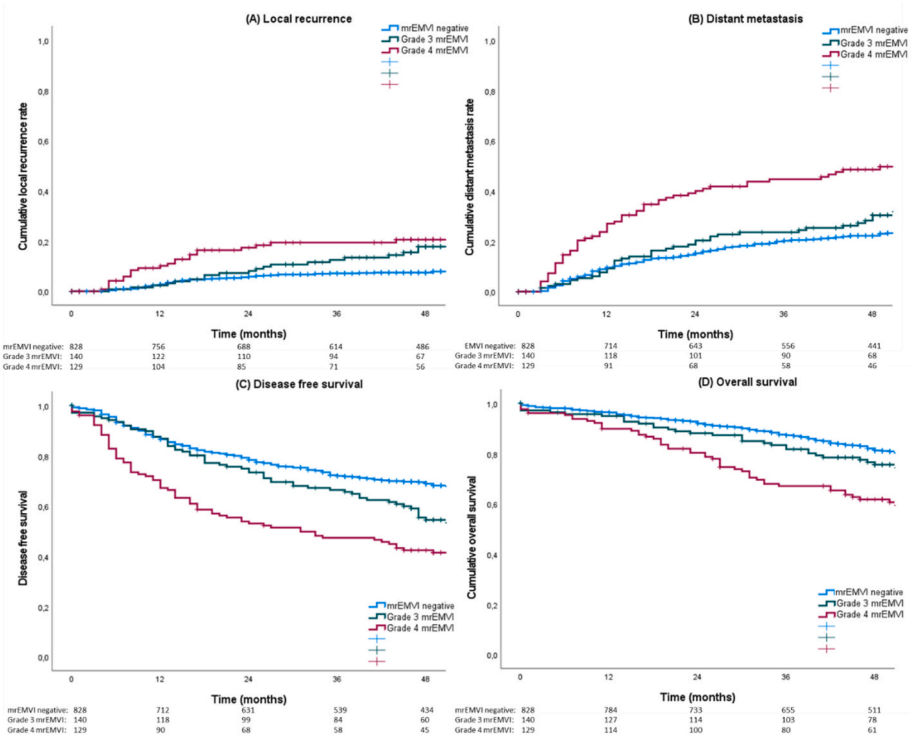

Fig. 2. The influence of mrEMVI on primary MRI on oncological outcomes and survival
(A) 4-year local recurrence rate for mrEMVI negative patients (7.4%), grade 3 mrEMVI (17.8%) and grade 4 mrEMVI (20.6%, $p < 0.001$). (B) 4-year distant metastases rate for mrEMVI negative patients (21.2%), grade 3 mrEMVI (30.4%) and grade 4 mrEMVI (48.5%, $p < 0.001$). (C) 4-year disease free survival mrEMVI negative patients (68.9%), grade 3 mrEMVI (54.5%) and grade 4 mrEMVI (42.4%, $p < 0.001$). (D) 4-year overall survival for mrEMVI negative patients (81.2%), grade 3 mrEMVI (75.6%) and grade 4 mrEMVI (61.8%, $p < 0.001$).

MrEMVI-grading on restaging MRI was categorized into four groups; mrEMVI negative on primary and restaging MRI, disappearance of mrEMVI (grade 3–4 on primary MRI and grade 0–2 on restaging MRI), grade 3 and grade 4 mrEMVI, and correlated with 4-year LR, DM, DFS and OS.

2.5. Statistics

Analyses were conducted using version 28 IBM SPSS statistics (Chicago, IL). For categorical data, numbers and percentages were presented. For continuous data, means with standard deviation or medians with interquartile range were presented based on their distribution. The X^2-test or an independent *t*-test was used for comparison of mrEMVI-subgroups and mrEMVI-disappearance. Oncological outcomes (LR, DM, OS, DFS) were determined with Kaplan-Meier survival analyses and compared using the log-rank test. To correct for covariates, a multivariable analysis was conducted using Cox proportional hazard; including variables with a p-value <0.10 in univariable analysis. Significance was set at a two-sided p-value of <0.05.

3. Results

The median follow-up of the 1214 included patients was 48 months (IQR 30–54). On primary MRI, 26.7% of the patients had grade 3 or 4 mrEMVI, of which 49.7% had grade 3 (n = 161) and 50.3% had grade 4 (n = 163). The mean mrEMVI size was 11.5 mm (SD 9.3), and grade 4 mrEMVI was significantly larger than grade 3 mrEMVI (15.6 mm vs 7.4 mm, $p < 0.001$).

In patients with mrEMVI, tumours were located further from the anorectal junction ($p = 0.003$), cT-stage ($p < 0.001$) and cN-stage ($p < 0.001$) were higher, and both mrTDs and mrLLNs with malignant potential were present more often (both $p < 0.001$, Table 1). Patients with mrEMVI received neoadjuvant therapy more often ($p < 0.001$), resection margins were more often involved ($p = 0.003$) and synchronous metastases occurred more frequently ($p < 0.001$). When comparing grade 3 to grade 4 mrEMVI, grade 4 mrEMVI had a higher cT-stage and more often mrTDs on primary MRI compared to grade 3 mrEMVI, while other characteristics did not differ at baseline.

3.1. Oncological implications of different mrEMVI grades on primary MRI

In patients without synchronous metastases (n = 1097), absence of mrEMVI was associated with a 7.4% 4-year LR-rate and a 21.2% 4-year DM-rate (Fig. 2A and B). Presence of grade 3 increased these rates to 17.8% LR ($p = 0.003$) and 30.4% DM ($p = 0.051$). Presence of grade 4 mrEMVI compared to grade 3 further increased the risk of LR (20.6%, $p = 0.277$) and DM (48.5%, $p = 0.001$). The presence of grade 3 and 4 mrEMVI remained independently associated with an increased LR-risk (grade 3 HR 1.810; grade 4 HR 1.675, $p = 0.047$), as well as DM-risk (grade 3 HR 1.273; grade 4 HR 1.822, $p = 0.002$) after uni- and multivariable analyses (Table S1 and Table 2a).

The 4-year DFS was 68.9% in the absence of mrEMVI, being significantly worse for grade 3 (54.5%, $p = 0.005$), and the lowest for grade 4 (42.4%, $p = 0.006$ compared to grade 3 mrEMVI, Fig. 2C and D). Four-year OS was 81.2% without mrEMVI, 75.6% in the presence of grade 3 mrEMVI ($p = 0.187$), and 61.8% in grade 4 mrEMVI ($p = 0.005$, compared to grade 3 mrEMVI). Grade 3 and 4 mrEMVI on primary MRI were independently associated with decreased DFS (grade 3 HR 1.344; grade 4 HR 1.692, $p = 0.002$) and OS (grade 3 HR 1.231; grade 4 HR 1.792, $p = 0.007$) after uni- and multivariable analyses (Table S1 and Table 2b).

3.2. MrEMVI, mrTDs and mrLLNs

In total, 442 patients had primary rectal cancer with either mrEMVI, mrTDs and/or mrLLNs on primary MRI. Of these patients, 289 patients

Table 2a
Multivariate analysis of mrEMVI on primary MRI on oncological outcomes

(A) Oncological outcomes		*Local Recurrence*			*Distant metastases*		
Variable	No	HR	95% CI	P	HR	95% CI	P
Tumour location according to the LOREC criteria:				0.067			0.555
Above	461	1.000			1.000		
On/below	636	1.571	0.969–2.547		1.085	0.825–1.432	
Clinical T stage				0.161			**0.049**
T3, MRF threatened	610	1.000			1.000		
T3, MRF not threatened	328	1.299	0.772–2.185		1.263	0.924–1.726	
T4	159	1.759	0.985–3.142		1.581	1.096–2.280	
Mesorectal clinical N stage				0.110			0.630
N0	344	1.000			1.000		
N1	440	0.670	0.377–1.191		1.134	0.817–1.575	
N2	313	1.158	0.646–2.077		1.194	0.825–1.728	
EMVI[a]				**0.047**			**0.003**
Negative (gr 0–2)	828	1.000			1.000		
Present gr 3	140	1.810	1.071–3.059		1.273	0.894–1.813	
Present gr 4	129	1.675	0.947–2.962		1.822	1.282–2.590	
Tumour deposits[a]				**0.029**			**0.005**
Not present	962	1.000			1.000		
Present	147	1.814	1.062–3.098		1.591	1.147–2.207	
LLNs present[a]				**0.035**			0.787
No LLN	769	1.000			1.000		
Only LLN(s) without malignant features or <5.0 mm	138	1.271	0.674–2.395		1.029	0.704–1.504	
At least one LLN present >5.0 mm with malignant features or ≥7.0 mm	190	1.843	1.159–2.930		1.112	0.824–1.500	
Neoadjuvant radiotherapy				**0.010**			**0.010**
None	211	1.000			1.000		
5 × 5 Gy short interval	192	0.156	0.045–0.535		0.746	0.461–1.206	
5 × 5 Gy long interval	145	0.790	0.392–1.596		1.285	0.820–2.015	
CRT	549	0.522	0.272–1.003		0.760	0.499–1.158	
Type of surgery[b]				0.081			**0.005**
LAR	532	1.000			1.000		
APR	389	1.306	0.761–2.242		1.657	1.218–2.254	
HP	176	1.882	1.081–3.277		1.360	0.954–1.940	
Margin status				**<0.001**			**<0.001**
R0	1019	1.000			1.000		
R1	78	3.722	2.279–6.077		2.078	1.455–2.968	

[a] Present on primary MRI.
[b] 3 cases of proctocolectomy and one case of total pelvic exenteration were included in the APR group, if a local excision + completion TME was performed, the patient is classified in the corresponding TME group.

(65.4%) were treated in accordance with the current Dutch guideline and received neoadjuvant CRT, while 31 (7.0%) did not receive neoadjuvant therapy, 33 (7.5%) received 5 × 5Gy RT with a short interval to surgery and 89 patients (20.1%) received 5 × 5Gy RT with a long interval to surgery.

In multivariable analysis (Table 2), mrTDs were associated with increased risk of LR (p = 0.029) and DM (p = 0.005). The presence of mrLLNs with malignant potential was associated with increased risk of LR (p = 0.035), but not with DM. In addition to presence of mrEMVI, cT-stage (p = 0.006) and mrTDs (p = 0.022) were associated with worse DFS, whereas cT-stage (p = 0.010) and mrEMVI were associated with worse OS.

3.3. Changes of mrEMVI on restaging MRI

A restaging MRI was performed in 633 of the 791 irradiated patients (80.0%). On restaging MRI, mrEMVI was visible in 18.6% (118/633), of which in four cases mrEMVI was not present on primary MRI (Fig. S2). Of grade 3 mrEMVI 74.5% disappeared, compared to 20.9% of grade 4 (p < 0.001). Regarding type of neoadjuvant therapy, 46.6% (n = 81) of mrEMVI disappeared after CRT, compared to 45.6% (n = 21) after short course radiotherapy (p = 0.913). The initial mean size of mrEMVI in patients in whom mrEMVI disappeared was similar compared to remaining mrEMVI in grade 3 (7.8 mm vs 7.0 mm, p = 0.403), but significantly lower in grade 4 (10.7 mm vs 18.5 mm, p = 0.005). Moreover, mrTDs on primary MRI were more often present when mrEMVI remained present as compared to mrEMVI disappearance (45.8% vs 29.4%, p = 0.013).

3.4. Oncological implications of mrEMVI disappearance

Four-year LR-rates remained high despite of mrEMVI disappearance (21.7%) compared to mrEMVI negative patients on primary MRI (9.3%, p = 0.006, Fig. 3). LR-rates in patients with remaining grade 3 or 4 mrEMVI were 14.7% and 26.9%, respectively (p = 0.161). DM-rates in patients where mrEMVI disappeared were comparable to patients who were mrEMVI negative at primary MRI (25.8% vs 26.3%, p = 0.835), and significantly lower compared to those with remaining mrEMVI (48.6% for grade 3 and 56.0% for grade 4; p = 0.001). OS and DFS were similar for mrEMVI disappearance compared to those who were mrEMVI negative at primary MRI (DFS 58.0% vs 62.8%, p = 0.481; OS 75.8% vs 77.9%, p = 0.813), and both higher compared to grade 3 and 4 mrEMVI (Fig. 3). This was confirmed in multivariable analysis (Tables S2 and S3).

4. Discussion

This study describes different mrEMVI grades in relation to recurrence and survival outcomes from a large national multicentre cohort of 1214 distal cT3/4 rectal cancer patients. MRI-scans were reassessed after dedicated training, thereby identifying 324 cases of mrEMVI (27%). MrEMVI was more frequently present in those with other poor prognostic values (cT4-stage, MRF involvement, cN+, mrTDs and mrLLNs). However, irrespective of these factors, mrEMVI was independently associated with a higher LR and DM-risk and worse DFS and OS. As compared to grade 3, grade 4 mrEMVI increased DM-rate (49% vs 30%) and worsened DFS and OS even further (DFS; 42% vs 55%, OS; 62% vs 76%), whereas LR-rate was similar for both grades (21% vs

Table 2b
Multivariate analysis of mrEMVI on primary MRI on survival.

(B) Survival	*Disease free survival*				*Overall survival*		
Variable	No.	HR	95% CI	P	HR	95% CI	P
Age				0.113			**<0.001**
≤65	487	1.000			1.000		
>65	610	1.169	0.961–1.466		1.749	1.322–2.313	
Tumour location according to the LOREC criteria:				0.070			0.079
Above	461	1.000			1.000		
On/below	636	1.239	0.982–1.562		1.297	0.971–1.733	
Clinical T stage				**0.006**			**0.010**
T3, MRF threatened	610	1.000			1.000		
T3, MRF not threatened	328	1.355	1.047–1.752		1.411	1.020–1.954	
T4	159	1.633	1.199–2.224		1.777	1.218–2.592	
Mesorectal clinical N stage				0.805			
N0	344	1.000					
N1	440	1.037	0.793–1.355				
N2	313	1.105	0.814–1.500				
EMVI[a]				**0.002**			**0.007**
Negative (gr 0–2)	828	1.000			1.000		
Present gr 3	140	1.344	1.006–1.795		1.231	0.838–1.808	
Present gr 4	129	1.692	1.246–2.297		1.792	1.243–2.583	
Tumour deposits[a]				**0.022**			0.272
Not present	962	1.000			1.000		
Present	147	1.401	1.049–1.871		1.218	0.857–1.733	
LLNs present[a]				0.570			
No LLN	769	1.000					
Only LLN(s) without malignant features or <5.0 mm	138	1.146	0.844–1.556				
At least one LLN present >5.0 mm with malignant features or ≥7.0 mm	190	1.102	0.853–1.425				
Neoadjuvant radiotherapy				**<0.001**			**<0.001**
None	211	1.000			1.000		
5 × 5 Gy short interval	192	0.710	0.474–1.062		0.662	0.400–1.094	
5 × 5 Gy long interval	145	1.462	1.010–2.117		1.579	1.032–2.415	
CRT	549	0.804	0.568–1.139		0.797	0.536–1.185	
Type of surgery[b]				**0.003**			0.015
LAR	532	1.000			1.000		
APR	389	1.513	1.171–1.955		1.477	1.066–2.046	
HP	176	1.460	1.091–1.954		1.608	1.119–2.310	
Margin status				**<0.001**			**<0.001**
R0	1019	1.000			1.000		
R1	78	2.105	1.551–2.858		2.212	1.544–3.168	

[a] Present on primary MRI.
[b] 3 cases of proctocolectomy and one case of total pelvic exenteration were included in the APR group, if a local excision + completion TME was performed, the patient is classified in the corresponding TME group.

18%).

This study is the first to show a difference between grade 3 and 4 mrEMVI based on primary MRI staging regarding the prognostic impact on distant recurrence and survival after correction for other poor prognostic factors in uni- and multivariate analyses. Also, it is one of the first studies in which mrEMVI assessments are conducted by multiple abdominal radiologists, in a near clinical setting. Unfortunately, correlation between mrEMVI presence on primary MRI with pathological presence cannot be made, due to the high percentage (92%) of patients who received neoadjuvant therapy and because the pathological parameter has not been collected in any patient. Moreover, radiologists were able to access all performed MRI scans and outcomes because of the study set-up, and each MRI-scan was only re-evaluated by one radiologists, making it impossible to measure inter-observer variability. Despite these limitations, these findings indicate that discrimination between grade 3 and 4 mrEMVI are important for risk stratification, which might add during multidisciplinary team discussions on neoadjuvant treatment planning.

Current guidelines, including the American Society for Radiation Oncology and Dutch national guideline, include mrEMVI as a criterion for neoadjuvant (C)RT but do not include mrEMVI grade [9,24]. The European Society for Medical Oncology recommends a PET-CT scan for those with extensive mrEMVI on primary MRI, but a definition of 'extensive' is lacking [8]. Based on this study, 'extensive' might be restricted to grade 4 mrEMVI, as 21% of these patients developed metastases within 3 months of surgery, compared to 7% in absence of mrEMVI. Moreover, the number of synchronous metastases in this study is likely to be an underrepresentation of rectal cancer patients in general, since synchronously metastasized patients are often not eligible for a surgical resection and thus not registered in the DCRA and consequently not included in this study. Contrary to the American and Dutch guidelines, the National Institute for Health and Care Excellence has recently removed mrEMVI presence from their 2020 guideline and recommends treatment planning solely based on TNM-staging, conform the Australian and Japanese guidelines [25–27]. This suggests that despite the inevitable role of mrEMVI, there is still no consensus. This study shows that the accurate identification and assessment of mrEMVI is of importance for accurate staging and consequent multidisciplinary team decisions. The level of consensus among radiologists regarding the definition and criteria for identifying EMVI may significantly impact its incorporation into guidelines. Further exploration and collaboration with radiological experts is warranted to investigate inter-observer variability between grade 3 and 4 mrEMVI, to establish a widely accepted and standardized definition of mrEMVI.

The question is whether current neoadjuvant treatment regimens are appropriate for patients with mrEMVI. While the majority of the patients with mrEMVI (66%) received neoadjuvant CRT, there might still be a role to further downsize mrEMVI by treating all patients according to the current guidelines with CRT. When mrEMVI disappeared after neoadjuvant treatment, the DM-rate decreased to 26% (mrEMVI negative group also 26%), while the LR-rate remained high. This indicates other factors, such as the high cT4-stage and positive resection margin, might

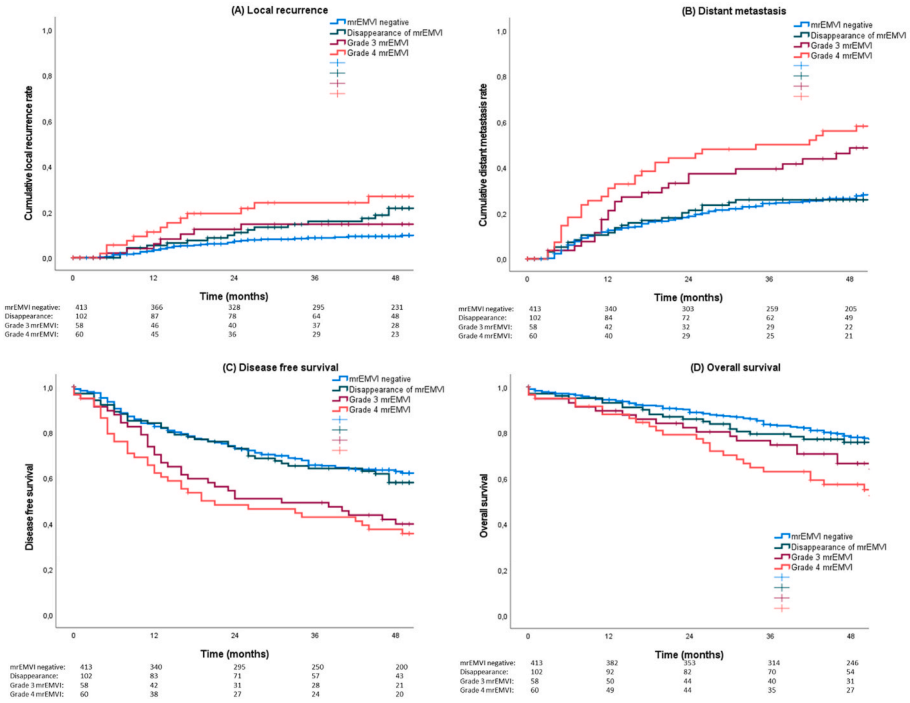

Fig. 3. The influence of mrEMVI on restaging MRI on oncological outcomes and survival
(A) 4-year local recurrence rate for mrEMVI negative patients on both primary and restaging MRI (9.3%), disappearance of mrEMVI on restaging MRI (21.7%), grade 3 mrEMVI on restaging (14.7%) and grade 4 mrEMVI (26.9%, $p < 0.001$). (B) 4-year distant metastases rate for mrEMVI negative patients on both primary and restaging MRI (26.3%), disappearance of mrEMVI on restaging MRI (25.8%), grade 3 mrEMVI on restaging (48.6%) and grade 4 mrEMVI (56.0%, $p < 0.001$). (C) 4-year disease free survival for mrEMVI negative patients on both primary and restaging MRI (62.8%), disappearance of mrEMVI on restaging MRI (58.0%), grade 3 mrEMVI on restaging (39.8%) and grade 4 mrEMVI (37.5%, $p < 0.001$). (D) 4-year overall survival for mrEMVI negative patients on both primary and restaging MRI (77.9%), disappearance of mrEMVI on restaging MRI (75.8%), grade 3 mrEMVI on restaging (66.5%) and grade 4 mrEMVI (57.3%, $p < 0.001$).

be contributing to this poor oncological outcome. While this study is limited by its retrospective character, and the 'low' DM-rate for those with mrEMVI regression after neoadjuvant therapy is only a correlation, neoadjuvant therapy might play a role in lowering the high DM-rates. On the other hand, for those with persistent mrEMVI, and thus a higher risk of DM, there might be a role for additional systemic therapy in addition to neoadjuvant (C)RT, in the form of TNT or by adding adjuvant chemotherapy. TNT is used as an organ sparing alternative for (C)RT and has shown promising results in tumour regression, but has not yet been investigated in light of mrEMVI and might give useful insights [28]. The role of adjuvant chemotherapy in patients with persistent mrEMVI after CRT has been retrospectively evaluated by Chand et al., who found an improved 3-year DFS from 54% to 75% when comparing observation only to adjuvant chemotherapy in 663 mrEMVI positive patients (HR 0.46, CI 0.27–0.78) [29]. However, such retrospective analyses have a high risk of allocation and selection bias due to the selection of fit patients for additional adjuvant chemotherapy, while those suffering for complications and inherently have a worsen prognosis will not be able to start adjuvant therapy.

The findings of this study suggest that the regression of mrEMVI is a positive predictive factor for the development of metastases and disease-free survival. However, further research is required to fully understand the underlying mechanisms and factors that contribute to this effect; is this due to tumour biology or is there a role for more aggressive treatment? MrEMVI disappearance is associated with mrEMVI grade, as well as with the presence of mrTDs and mrEMVI size. However, these three factors are also strongly associated with each other; grade 4 mrEMVI is often larger and has mrTDs more often. While mrEMVI grade 3 is associated with a higher chance of disappearance (74% vs 20% in grade 4), and the DM-rate was comparable for remaining grade 3 and grade 4 mrEMVI, while the LR-rate significantly increased only for grade 4 (HR 2.26, 95%CI 1.1–4.65) on restaging MRI. A higher mrEMVI-grade is associated with other poor biological prognostic factors, and together these contribute to the poor prognostic outcomes, especially DM-rate.

Some previous studies argued that mrEMVI should be used in treatment planning instead of TNM-stage and MRF involvement. In our study however, we show prognostic value of mrEMVI alongside these factors, as well as a role for mrTDs and mrLLNs. MrTDs are strongly associated with mrEMVI, and seem to follow a similar pattern as mrEMVI. The presence of mrTDs on primary MRI increases the chance of LR as well as DM, while after neoadjuvant therapy, the presence of mrTDs on restaging MRI is only associated with DM in multivariable analysis. On the other side, mrLLNs with a short axis ≥7 mm or 5.0–6.9 mm with malignant features were associated with an increased LR-rate on primary MRI, but not with an increased DM-rate in a multivariable analysis. This confirms available literature in which presence of intermediate or enlarged mrLLNs are considered as local disease, while mrTDs and mrEMVI are more strongly associated with systemic disease [14, 23]. This makes it important to adequately report the presence of mrEMVI, mrTDs and mrLLNs in radiology reports, and discuss them during the multidisciplinary meeting. Only then it will be possible to make a patient-tailored treatment plan consisting of neoadjuvant treatment, TME or beyond-TME approach, lateral lymph node dissection and/or adjuvant treatment to potentially lower LR-rate as well as DM-rate and improve DFS and OS.

5. Conclusion

Presence of grade 3 mrEMVI on primary MRI increases LR and DM rates and worsens DFS and OS, while grade 4 worsens these rates even further. Therefore, both grade 3 and 4 mrEMVI should be an indication for neoadjuvant treatment. MrEMVI regression on restaging MRI results in lower DM-rates, but not LR-rates, while persistent mrEMVI on restaging MRI is associated with high DM-rates. Future research is

needed to find factors which contribute to mrEMVI regression and to investigate treatment strategies in those with persisting mrEMVI after neoadjuvant treatment.

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Trial registration

ClinicalTrials.gov, identifier: NCT05539417 https://www.clinicaltrials.gov/ct2/show/NCT05539417.

CRediT authorship contribution statement

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Declaration of competing interest

The authors have declared no conflicts of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2024.108307.

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