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Original Article

Persistent extramural vascular invasion positivity on magnetic resonance imaging after neoadjuvant chemoradiotherapy predicts poor outcome in rectal cancer

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ABSTRACT

Background: In rectal cancer, extramural vascular invasion (EMVI) is the presence of tumour cells in blood vessels outside the muscular layer, which is associated with poor prognosis. Regression of EMVI on MRI following neoadjuvant chemoradiotherapy or its persistence may have prognostic implications.
Methods: This retrospective study included 52 patients with rectal cancer who underwent total mesorectal excision following long-course neoadjuvant chemoradiotherapy (CRT). EMVI assessments were done on previous pelvic MRIs obtained before neoadjuvant CRT and eight weeks after the completion of neoadjuvant chemoradiotherapy in initially EMVI positive cases.
Results: Persistently EMVI positive patients had worse overall survival and disease-free survival compared to initially EMVI negative patients and patients who returned to negative ($p < 0.001$ for both). Multivariate analysis identified persistent EMVI positivity after neoadjuvant treatment (HR, 102.9; $p = 0.003$) as significant independent predictor of worse overall survival; and persistent EMVI positivity (HR, 17.0; $p = 0.002$), mesorectal fascia involvement after neoadjuvant treatment (HR, 8.0; $p = 0.017$), and poor differentiation (HR, 10.3, $p = 0.012$) as significant independent predictors of worse disease-free survival.
Conclusion: Persistent EMVI positivity after neoadjuvant therapy appears to be an independent factor for poor overall survival; and persistent EMVI positivity as well as mesorectal fascia involvement on post neoadjuvant therapy MRI and poor differentiation appears to be important predictors of poor disease-free survival in rectal cancer patients.

1. Introduction

Colorectal cancer represents a significant cause of morbidity and mortality. It is the fourth common cancer and second leading cause of death.[1] For locally advanced rectal cancers, neoadjuvant therapy followed by surgical excision is the recommended treatment modality.[1] Magnetic resonance imaging (MRI) is among the recommended tools for initial evaluation.[1]

In rectal cancer, extramural vascular invasion (EMVI) is defined as the presence of tumour cells in blood vessels outside the muscular layer, which is associated with poor prognosis. Histopathological demonstration of EMVI is possible after surgical resection but it may be associated with under-reporting due to inconsistent definitions, techniques and changes due to preoperative treatments.[2–5] However, it is also possible to accurately detect EMVI preoperatively with MRI, both before and after neoadjuvant therapy.[6–11] Histologically- or MRI-detected EMVI positivity has been shown to be a poor prognostic factor.[9,11–25] In addition, mesorectal fascia involvement[10,26,27] and poor differentiation[28–30] have been reported as predictors of poor prognosis in rectal cancer.

Tissue changes occur following neoadjuvant chemoradiotherapy (CRT), which may alter the accuracy of MRI examinations. On the other hand, such changes may represent a good response to neoadjuvant treatment as well. Therefore, prognostic

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significance may be altered. Regression of EMVI following neoadjuvant CRT or its persistence may have additional prognostic implications; however, studies examining the potential prognostic role of post neoadjuvant MRI-detected EMVI positivity are relatively scarce.[11,13,14,26,31] Identifying the ideal time point for outcome prediction may aid in treatment planning.

This study aimed to examine the prognostic significances of pre neoadjuvant CRT and post neoadjuvant CRT MRI-determined EMVI and change in EMVI status in response to neoadjuvant treatment (i.e. regression or persistence) in patients with rectal cancer.

2. Methods

2.1. Patients

This retrospective study included 52 patients with middle or low rectal cancer who underwent total mesorectal excision in our institution between August 2007 and October 2017 following long-course neoadjuvant chemoradiotherapy and a 10–12 weeks waiting period. Patients with distant metastasis at the time of diagnosis, histopathological diagnosis other than adenocarcinoma, a tumour distance >10 cm from the anal verge, and without available follow-up data were excluded. All operations were performed by two experienced colorectal surgeons. All patients received post-operative adjuvant chemotherapy. MRI images of the patients were retrospectively reviewed by an experienced radiologist for EMVI assessment and other radiological parameters. Survival data were retrieved retrospectively from patient records, which were completed during follow-up. Follow up was based on routine outpatient visits (every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter) and involved laboratory tests (including serum CEA and CA 19-9), radiological imaging (chest CT and abdominopelvic CT) every 3–6 months or every year.

The study protocol was approved by the local ethics committee of Acibadem Mehmet Aydinlar University (date, November 21, 2019; no, ATADEK-2019-18/17) and the study was conducted in accordance with the Declaration of Helsinki, relevant guidelines and regulations. Due to the retrospective and non-experimental nature of the study, informed consent was waived by the ethics committee.

2.2. Chemoradiotherapy regime

All patients received long-course preoperative chemoradiotherapy, which was delivered using a True-Beam linear accelerator (Varian Medical Systems, California, USA) with volumetric modulated arc therapy (VMAT) technique. Primary rectal tumour and pelvic lymphatics received 25 fractions of radiotherapy at a dose of 180cGy/fraction. This was followed by 3–5 fractions of boost to the primary tumour. Thus, the total radiation dose was 5040–5400 cGy. Capecitabine at the dose of 825 mg/m2/day was administered concurrently with radiotherapy.

2.3. Postoperative adjuvant chemotherapy

Patients received FOLFOX as adjuvant chemotherapy at the beginning of each 14-day cycle for a total of 12 cycles, administered through a permanent central port catheter. FOLFOX protocol was as follows: oxaliplatin 85 mg/m2, folinic acid 400 mg/m2, and 5-FU 400mg/m2 i.v bolus, followed by 5-FU 2200 mg/m2 through infusion pump over 48 h. Dose adjustments were made in case of toxicity.

2.4. Magnetic resonance imaging

Patients underwent pelvic magnetic resonance imaging (MRI) examination before neoadjuvant chemoradiotherapy for staging and 8 weeks after the completion of neoadjuvant radiotherapy for response evaluation. Examinations were done with a 3.0 T MRI device (Siemens, Munich, Germany) by using an eight-channel phased-array body coil in the supine position. To reduce colonic motility, 20 mg of scopolamine butylbromide (Buscopan, Zentiva, Istanbul, Turkey) was administered intramuscularly 30 min before imaging procedures. Pelvic MRI protocol included the following: T2-weighted high-resolution axial, coronal, and sagittal images; T1-weighted axial images; diffusion-weighted axial images; and gadolinium-enhanced T1-weighted fat-suppressed axial, sagittal, and coronal images.

2.5. MR-based EMVI evaluation

EMVI was evaluated, scored and patients were classified as positive or negative before and after neoadjuvant chemoradiotherapy retrospectively using two different systems, as defined previously.[7,14] EMVI evaluation before neoadjuvant therapy was based on a 5-point scoring system (0–4), where a score >2 was considered the indication of pre-treatment EMVI positivity.[14] Eight weeks after the completion of neoadjuvant therapy, patients initially positive for EMVI were evaluated based on another 5-point scoring system (1–5), where a score >3 was the indication of posttherapy EMVI positivity.[14] Patients initially negative for EMVI did not undergo posttreatment scoring. Fig. 1 shows examples of MRI images showing EMVI status and mesorectal fascia invasion.

2.6. Statistical analysis

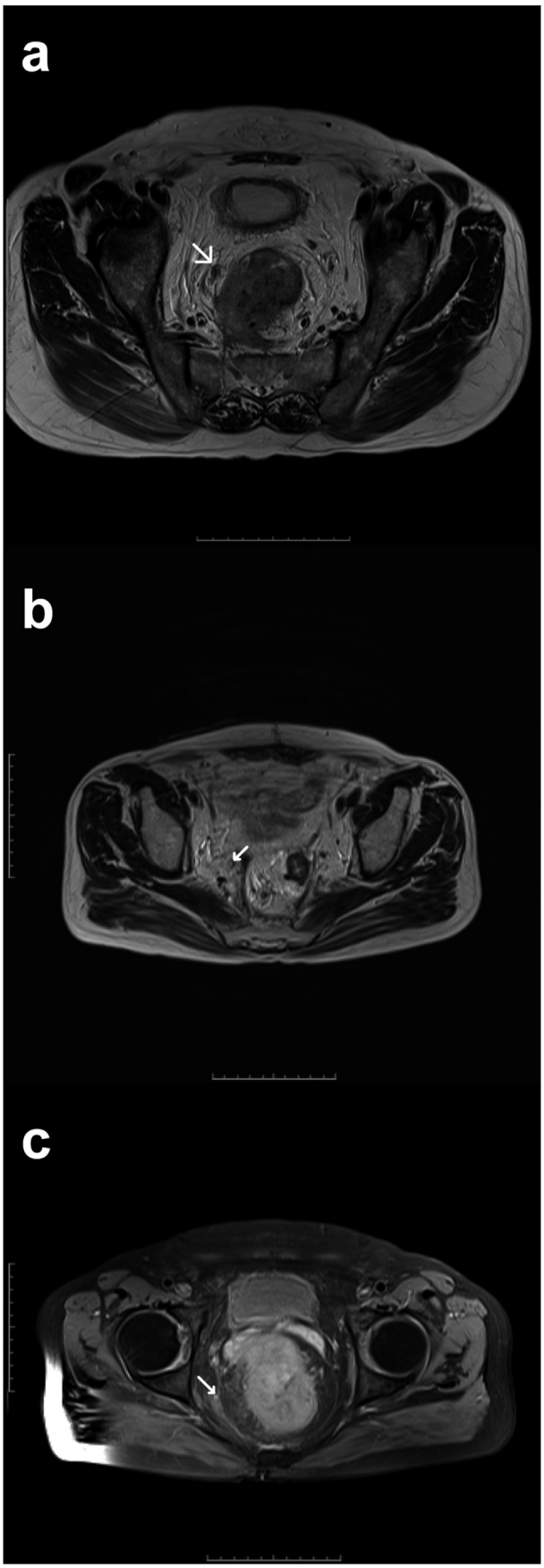
Statistical Package for Social Sciences (SPSS) version 21 for windows (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Descriptive data were presented as mean ± standard deviation or number (frequency), where appropriate. Survival data presented as mean survival ±standard error of the mean (95% confidence intervals). Mean overall survival (OS) and mean disease-free survival (DFS) was estimated using Kaplan–Meier test. OS was defined as the time between surgery and death, and patients alive at the last follow-up were censored. DFS was defined as the time between surgery and disease recurrence (local recurrence/distant metastasis) or death, and patients without these events at the last follow-up were censored. Log-rank test was used for univariate analysis. Multivariate analysis of potential factors for OS and DFS were done using Cox proportional hazard model. A two-sided p value of <0.05 was considered an indication of statistical significance.

3. Results

Table 1 shows demographical, clinical, and pathological characteristics of patients. Table 2 shows MRI findings before and after neoadjuvant chemoradiotherapy. Almost two thirds of patients were positive for EMVI before the treatment; however, majority turned to negative after neoadjuvant treatment. Only 17.3% of the patients remained persistently positive. No perioperative or post-operative complication that would alter adjuvant therapy protocol after surgery or survival was developed.

3.1. Overall survival

Mean duration of follow-up was 69.2 ± 38.3 months (median, 66.9; range, 9.0–161.0 months). Eleven patients died during follow-



up (21.2%). Mean overall survival was 130.3 ± 8.1 months (95% CI, 114.4–146.3). Median overall survival was not reached. Mean overall survival for patients initially EMVI negative, initially positive but returned to negative, and patients with persistent EMVI positivity was 153.3 ± 7.4, 123.9 ± 6.4, and 40.3 ± 10.0 months, respectively. Persistently EMVI positive patients had worse overall survival compared to initially EMVI negative patients and patients who returned to negative ($p < 0.001$ for both comparisons). However, the latter two groups did not differ regarding overall survival. Table 3 shows potential predictors of overall survival on univariate analysis, where worse overall survival was associated with a distance from anal verge ≤4 cm, EMVI positivity before neoadjuvant treatment, persistently positive EMVI positivity, mesorectal fascia involvement after neoadjuvant therapy, persistent lymph node involvement on MRI after CRT, pre-treatment T4 disease, poor differentiation, venous invasion, and circumferential resection margin positivity ($p < 0.05$ for all). Multivariate analysis identified persistent EMVI positivity after neoadjuvant treatment (HR, 102.9; $p = 0.003$) as significant independent predictor of worse overall survival. Fig. 2a shows Kaplan–Meier overall survival curves for patients with versus without persistent EMVI positivity.

3.2. Disease-free survival

Mean duration of follow-up for disease-free survival was 66.4 ± 39.4 months (median, 61.9; range, 5.3–161.0 months). Twelve patients developed distance metastasis (23.1%) and four patients had local recurrence (7.7%) during follow-up. Mean disease-free survival was 112.5 ± 9.3 months (95% CI, 94.4–130.7). Median survival was not reached. Mean disease-free survival for patients initially EMVI negative, initially positive but returned to negative, and patients with persistent EMVI positivity was 145.7 ± 10.0, 101.0 ± 9.6, and 35.9 ± 10.5 months, respectively. Persistently EMVI positive patients had worse disease-free survival compared to initially EMVI negative patients and patients who returned to negative ($p < 0.001$ for both comparisons). However, the latter two groups did not differ regarding disease-survival. Table 4 shows potential predictors of disease-free survival on univariate analysis, where worse disease-free survival was associated with a distance from anal verge ≤4 cm, EMVI positivity before neoadjuvant treatment, persistently positive EMVI positivity, mesorectal fascia involvement after neoadjuvant therapy, persistent lymph node involvement on MRI after CRT, pre-treatment T4 disease, poor differentiation, venous invasion, lymphatic invasion, and circumferential resection margin positivity ($p < 0.05$ for all). Multivariate analysis identified persistent EMVI positivity (HR, 17.0; $p = 0.002$), mesorectal fascia involvement (HR, 8.0; $p = 0.017$) after neoadjuvant treatment, and poor differentiation (HR, 10.3, $p = 0.012$) as significant independent predictors of worse disease-free survival. Fig. 2b shows Kaplan–Meier disease-free survival curves for patients with versus without persistent EMVI positivity.

4. Discussion

This study identified persistent EMVI positivity after neoadjuvant chemoradiotherapy assessed by MRI, rather than EMVI positivity on initial evaluation, as a significant indicator of poor

Fig. 1. Examples of MRI images showing EMVI status and mesorectal fascia invasion. a) MRI obtained before neoadjuvant chemoradiotherapy shows signal void loss (arrow) indicating extramural vascular invasion (EMVI+) in the mesorectum, b) MRI obtained after neoadjuvant chemoradiotherapy shows fibrosis and negative extramural vascular invasion (EMVI-) (arrow) in the same patient with Fig. 1a. This patient was EMVI + before neoadjuvant treatment and returned to EMVI- status, c) Arrow indicates mesorectal fascia involvement.

Table 1
Demographical, clinical and pathological characteristics.

Characteristics	n = 52
Age, y (mean ± SD)	55.7 ± 12.0
Male gender	34 (65.4%)
Surgery	
LAR	27 (51.9%)
APR	7 (13.5%)
Coloanal anastomosis	6 (11.5)
Turnbull-Cutait	12 (23.1%)
Distance from anal verge, cm (mean ± SD)	4.6 ± 1.7
Total number of nodes harvested (mean ± SD)	25.9 ± 11.1
Pathological findings	
Venous invasion	29 (55.8%)
Perineural invasion[a]	17 (32.7%)
Lymphatic invasion[a]	12 (23.1%)
N status	
N0	36 (69.2%)
N1	7 (13.5%)
N2	9 (17.3%)
Differentiation	
Well	9 (17.3%)
Moderate	34 (65.4%)
Poor	9 (17.3%)
Positive CRM	1 (1.9%)
T Clinical	
T3	42 (80.8%)
T4	10 (19.2%)
T downstaging[b]	31 (59.6%)
N downstaging[b]	31 (59.6%)
Pathological complete response	6 (11.5%)

N downstaging indicates return to absence of any lymph node metastasis on pathological examination from any N on MRI. Unless otherwise stated, data presented as n (%). SD, standard deviation. LAR, low anterior resection; APR, abdominoperineal resection; CRM, circumferential resection margin.

[a] One patient has missing data.

[b] Based on pre-CRT clinical evaluation and postoperative pathological examination.

Table 2
Magnetic resonance imaging findings before and after neoadjuvant chemoradiotherapy.

Characteristics	n = 52
Posttreatment mesorectal fascia involvement	20 (38.5%)
Pretreatment EMVI positivity	33 (63.5%)
Posttreatment EMVI positivity	9 (17.3%)
Posttreatment EMVI status change	
Initially negative	19 (36.5%)
Initially positive but turned negative	24 (46.2%)
Persistently positive	9 (17.3%)

Data presented as n (%). EMVI, extramural vascular invasion.

overall and disease-free survival. In addition, poor differentiation on pathological examination and mesorectal fascia involvement on post neoadjuvant MRI as well as persistent EMVI positivity emerged as predictors of disease-free survival. This study is among the few studies examining the prognostic role of EMVI change in response to neoadjuvant therapy in patients with rectal cancer.

To date, several studies has examined the prognostic role of EMVI status on MRI after completion of neoadjuvant treatment in rectal cancer with conflicting results.[11,13,14,26,31] In a recent study, Song, et al. compared the prognostic value of MRI findings before and after neoadjuvant CRT, including EMVI, in 399 rectal cancer patients.[26] They reported a tendency for post-CRT MRI findings to correlate better with prognosis than pre-CRT MRI findings. In that study, multivariate analyses were performed for pre-CRT and post-CRT MRI parameters separately; and EMVI emerged as the only significant predictor for OS and DFS among pre-CRT parameters. Among post-CRT parameters on the other hand, N status, mesorectal fascia invasion and EMVI emerged as significant predictors for OS and DFS. In addition, post-CRT mesorectal fascia involvement and EMVI was associated with worse OS, DFS and local recurrence rate. Although our findings are in line with those of Song, et al., pre-CRT EMVI did not emerge as a significant predictor for worse OS in our study. A weak association was found on univariate analysis, but the association disappeared on multivariate analysis and persistent EMVI positivity emerged as a significant predictor for worse overall survival.

Another recent study evaluated the predictive roles of pre-neoadjuvant and post-neoadjuvant MRI parameters in rectal cancer.[31] In that study, T stage, nodal involvement, circumferential resection margin (CRM) status and EMVI was assessed by MRI before and after neoadjuvant chemoradiotherapy. Pre-neoadjuvant CRM and EMVI positivity and post-neoadjuvant high T stage, N positivity, CRM positivity, and EMVI positivity were associated with increased recurrence. Pre-neoadjuvant CRM and EMVI positivity were associated with worse DFS, whereas among MRI parameters assessed after neoadjuvant therapy only EMVI positivity was associated with worse DFS outcome. However, regression of EMVI after neoadjuvant treatment had a trend for association with improved outcomes, but this did not reach statistical significance.

In the study by Lee et al., prognostic significances of pre-neoadjuvant and post-neoadjuvant EMVI as evaluated on MRI and histologically confirmed EMVI, along with other parameters were examined.[13] The study identified increased stage, EMVI positivity and CRM positivity on histopathological examination as significant independent predictors for DFS, and high grade and EMVI positivity on histopathological examination as significant independent predictors for OS. None of the MRI based parameters emerged as independent predictor, although post-adjuvant MRI EMVI positivity was associated with worse survival on univariate analysis.

In a 2014 study by Chand et al., 62 rectal cancer patients with positive EMVI on MRI before neoadjuvant treatment were included and patients underwent MRI evaluation after neoadjuvant treatment for the regression of EMVI: good responders, >50% fibrosis; poor responders, <50% fibrosis.[14] A good response was associated with improved 3-year DFS and lower recurrence risk. The same group of investigators included 188 patients with positive EMVI on MRI before neoadjuvant treatment in their 2015 study and evaluated the prognostic roles of MRI-detected EMVI and histopathology-detected EMVI after neoadjuvant treatment.[11] Both parameters were associated with worse survival and disease recurrence and the authors concluded that presence of EMVI positivity after neoadjuvant treatment is prognostic whether detected by MRI or pathological examination.

Our findings are mostly in line with previous reports regarding EMVI positivity. Inconsistent findings regarding the differences in the prognostic roles of pre-neoadjuvant and post-neoadjuvant EMVI positivity may be due to the differences in standardization of definitions and methods of analyses in different studies. Post-neoadjuvant EMVI on MRI may well be a good indicator of adequate response to neoadjuvant chemotherapy and aid in identifying subset of this patients in this regard. Subset of patients with potentially worse prognosis despite neoadjuvant chemoradiotherapy may benefit from additional therapies following neoadjuvant chemotherapy but before surgery. A recent study examined the role of adding 2, 4 or 6 cycles of consolidation mFOLFOX6 chemotherapy after chemoradiotherapy but before total mesorectal excision in patients with locally advanced rectal cancer.[32] In that study, adding neoadjuvant consolidation chemotherapy was associated with improved disease-free survival.[32] Thus, patients that do not adequately respond to neoadjuvant therapy as evidenced by persistent EMVI on MRI may be candidates for consolidation chemotherapy before surgery; however, such a

Table 3
Potential predictors of overall survival on univariate and multivariate analysis.

	Overall survival	Univariate	Multivariate	HR (95% CI)
	Months (95% CI)	*p* value*	*p value*†	
All patients (n = 52)	130.3 ± 8.1 (114.4–146.3)			
Distance from anal verge				
≤4 (median) (n = 32)	98.7 ± 9.1 (80.9–116.5)	0.026	0.165	
>4 (n = 20)	153.9 ± 6.8 (140.6–167.2)			
Pretreatment extramural vascular invasion (mrEMVI)				
Negative (n = 19)	153.3 ± 7.4 (138.9–167.8)	0.035	0.854	
Positive (n = 33)	99.1 ± 9.0 (81.5–116.6)			
Extramural vascular invasion after treatment (ymrEMVI)				
Initially negative or returned negative (n = 43)	151.1 ± 5.5 (140.3–161.9)	<0.001	**0.003**	102.9 (4.6–2291.1)
Persistently positive (n = 9)	40.3 ± 10.0 (20.7–59.9)			
Mesorectal fascia invasion after treatment (ymrMRF)				
Absent (n = 32)	143.4 ± 8.1 (127.5–159.3)	0.032	0.260	
Present (n = 20)	81.9 ± 10.2 (62.0–101.8)			
Persistent lymph node after CRT on MRI				
Absent (n = 40)	142.1 ± 7.8 (126.9–157.3)	0.004	0.945	
Present (n = 12)	86.3 ± 18.3 (50.4–122.2)			
T clinical				
T3 (n = 42)	137.2 ± 8.1 (121.3–152.1)	0.035	0.359	
T4 (n = 10)	61.0 ± 12.4 (36.7–85.3)			
Differentiation				
Well-moderate (n = 43)	139.7 ± 8.0 (124.1–153.3)	0.008	0.079	
Poor (n = 9)	67.0 ± 17.8 (38.0–96.0)			
Venous invasion				
Absent (n = 23)[a]	–	0.001	0.816	
Present (n = 29)	91.8 ± 9.8 (72.6–110.9)			
N metastasis (yN)				
Absent (n = 36)	140.0 ± 8.6 (123.2–156.7)	0.061	0.926	
Present (n = 16)	102.2 ± 15.4 (72.1–132.3)			
CRM				
Negative (n = 51)	132.5 ± 8.0 (116.9–148.2)	0.005	0.434	
Positive (n = 1)	22.5 ± 0.0 (22.5–22.5)			

*Log-rank test. †p value for multivariate analysis (Cox proportional hazard model).
[a] None of the patients without venous invasion died during follow-up; thus, mean survival could not be calculated. Survival data presented as mean overall survival ±standard error of the mean (95% confidence intervals). HR, hazard ratio; CI, confidence interval; CRM, circumferential resection margin.

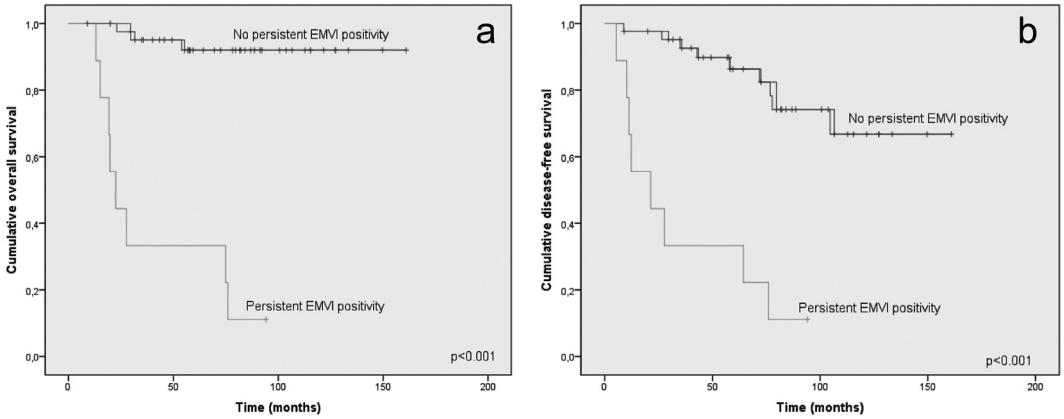


Fig. 2. Overall survival (left, a) and disease-free survival (right, b) Kaplan–Meier curves for persistent EMVI positivity on post-nCRT MRI. P values are from log rank test. EMVI, extramural vascular invasion; nCRT, neoadjuvant chemoradiotherapy.

potential benefit needs to be investigated in further large scale adequately designed trials.

Another important finding of the present study is that mesorectal fascia (MRF) invasion on post-neoadjuvant MRI was an independent predictor of disease-free survival, but not overall survival. This is somewhat expected finding since MRF invasion on MRI reflects CRM involvement on postoperative pathological examination of surgical specimen,[6,8,27,33–35] which is an important predictor of worse prognosis after rectal cancer surgery.[36,37] Thus, MRF on MRI is important for the determination of circumferential

Table 4
Potential predictors of disease-free survival on univariate and multivariate analysis.

	Disease-free survival	Univariate	Multivariate	HR (95% CI)
	Months (95% CI)	*p* value*	*p* value†	
All patients (n = 52)	112.5 ± 9.3 (94.4–130.7)			
Distance from anal verge				
≤4 (median) (n = 32)	84.1 ± 9.6 (65.3–102.9)	0.022	0.126	
>4 (n = 20)	141.0 ± 10.2 (120.9–161.0)			
Pretreatment extramural vascular invasion (mrEMVI)				
Negative (n = 19)	145.7 ± 10.0 (126.1–165.4)	0.008	0.427	
Positive (n = 33)	82.5 ± 9.2 (94.4–130.7)			
Extramural vascular invasion after treatment (ymrEMVI)				
Initially negative or returned negative (n = 43)	129.4 ± 9.8 (111.8–147.0)	<0.001	**0.002**	17.0 (2.7–106.0)
Persistently positive (n = 9)	35.9 ± 10.5 (15.4–56.4)			
Mesorectal fascia invasion after treatment (ymrMRF)				
Absent (n = 32)	138.6 ± 9.0 (120.9–156.4)	<0.001	**0.017**	8.0 (1.5–43.8)
Present (n = 20)	62.5 ± 9.3 (44.3–80.8)			
Persistent lymph node involvement after CRT on MRI				
Absent (n = 40)	122.6 ± 9.8 (103.4–141.8)	0.015	0.207	
Present (n = 12)	74.8 ± 18.4 (38.9–111.0)			
T clinical				
T3 (n = 42)	122.8 ± 9.5 (104.3–141.4)	0.003	0.248	
T4 (n = 10)	49.6 ± 12.1 (25.9–73.3)			
Differentiation				
Well-moderate (n = 43)	125.6 ± 9.5 (107.1–144.1)	0.003	**0.012**	10.3 (1.7–63.6)
Poor (n = 9)	54.2 ± 13.7 (27.3–81.1)			
Venous invasion				
Absent (n = 23)	136.1 ± 10.6 (115.4–156.8)	0.017	0.314	
Present (n = 29)	82.7 ± 10.2 (62.6–102.8)			
Lymphatic invasion				
Absent (n = 39)	123.1 ± 9.9 (103.7–142.5)	0.029	0.114	
Present (n = 12)	60.4 ± 12.3 (36.3–84.4)			
N metastasis (yN)				
Absent (n = 36)	125.7 ± 10.3 (105.5–146.0)	0.018	0.600	
Present (n = 16)	81.2 ± 15.3 (51.2–111.1)			
CRM				
Negative (n = 51)	114.4 ± 9.3 (96.2–132.6)	0.012	0.548	
Positive (n = 1)	21.4 ± 0 (21.4–21.4)			

*Log-rank test. †p value for multivariate analysis (Cox proportional hazard model). Survival data presented as mean overall survival ±standard error of the mean (95% confidence intervals). HR, hazard ration; CI, confidence interval, CRM, circumferential resection margin.

resection margin (CRM) in total mesorectal excision.[38] In the study by the MERCURY group, MRF involvement was associated with worse disease-free survival and high local recurrence rate.[10,27] Our findings regarding MRF involvement is in line with the findings of the previous studies.

Low sample size and retrospective design are the main limitations of this study. Low sample size might have precluded the achievement of statistical significance for certain parameters, e.g. the role of pre-neoadjuvant EMVI on MRI. However, we believe that opportunity of accurate retrospective review of archived MRI images seems to partly offset the disadvantages of retrospective design.

5. Conclusion

Persistent EMVI positivity after neoadjuvant therapy appears to be an independent factor for poor overall survival; and persistent EMVI positivity as well as mesorectal fascia involvement on post neoadjuvant therapy MRI and poor differentiation appears to be important predictors of poor disease-free survival in rectal cancer patients. This may reflect inadequate response to neoadjuvant treatment and has the potential in aiding the treatment planning of different subgroups in this regard. Although findings of this study provide a hint in the utility of looking specifically at persistent EMVI positivity after neoadjuvant treatment, the small sample size precludes generalizability and further conclusions. Therefore, further large-scale prospective studies would provide robust evidence on the relative significance of pre-neoadjuvant versus persistent EMVI positivity on survival outcomes.

Author contributions

Both authors fully contributed to the study conception and design, material preparation, data collection and analysis, OSG drafted and developed the manuscript and LVT critically reviewed and revised it, finally both authors read and approved the final manuscript.

Declaration of competing interest

All authors declare that they have no conflict of interest. All authors also declare that they have received no financial support.

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