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MRI morphologic and clinicopathologic characteristics for predicting outcomes in patients with locally advanced rectal cancer

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Abstract

Purpose The aim of this study was to investigate the value of MRI morphologic and clinicopathologic factors for predicting 3-year disease-free survival (DFS) in patients with locally advanced rectal cancer (LARC).

Method In this retrospective study, pre- and post-neoadjuvant chemoradiotherapy (nCRT) MRI morphologic (e.g., pre-nCRT MRI-detected extramural venous invasion) and clinicopathologic variabilities (e.g., pathological complete response) were evaluated in all patients. Three-year DFS was estimated using Kaplan–Meier product-limit method, and Cox proportional hazards models were used to determine associations between morphologic or clinicopathologic variabilities and survival outcomes.

Results A total of 115 patients (39 females and 76 males; median age, 54 years; age range, 28–82 years) with LARC treated with nCRT were enrolled. With a median follow-up of 48.0 months, the 3-year DFS was 79.0% for all patients. During follow-up, 18 patients died, 28 patients experienced relapse (26 distant, one local, and one both), and 69 patients were censored. MRI-detected extramural venous invasion (mrEMVI) was the only significantly independent factor of long-term survival, while HR was 2.308 (95% CI 1.151–4.629, $P = 0.018$) on univariate and 2.495 (95% CI 1.243–5.012, $P = 0.010$) on multivariate analysis. The 3-year cumulative survival rate in patients with mrEMVI negativity compared with positivity were 86.6% versus 65.0% ($P = 0.015$), respectively.

Conclusion In conclusion, pre-nCRT mrEMVI status was the independent significant risk factor for long-term outcomes in LARC patients treated with nCRT, while the other morphologic and clinicopathologic characteristics were not related to the patient survival.

Keywords Locally advanced rectal cancer · Neoadjuvant chemoradiotherapy · Magnetic resonance imaging · Morphologic characteristics · Outcomes

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide [1, 2]. In the United States in 2017, there were 135,430 individuals newly diagnosed with CRC and 50,260 CRC-related death cases. The annual age-standardized incidence rate for CRC during 2009 through 2013 was 40.7 per 100,000 population, and the mortality rate (2010-2014) was 14.8 per 100,000 population in the United States [3]. Neoadjuvant chemoradiotherapy (nCRT) and total mesorectal excision (TME) have become a standard treatment for patients with locally advanced rectal cancer (LARC) [4, 5]. These therapeutic strategies have reduced local recurrence rate of the disease, but have not significantly improved long-term outcomes; the 5-year survival

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rates for stage III and IV rectal cancer patients still remain low, i.e., 69.5% and 12.9%, respectively [1]. Distant metastasis is the main cause of treatment failure in patients with LARC who undergo nCRT [6]. Therefore, accurate identification of the adverse prognostic factors that influence cancer therapy or patient survival can be helpful to modify the treatment strategy and to improve the prognosis of LARC.

High-resolution magnetic resonance imaging (MRI) has emerged as a standard technique for staging rectal cancer and predicting the treatment response. Several studies have investigated the correlation between MRI characteristics and patient survival. Mesorectal fascia (MRF) involvement detected on pre-nCRT MRI (mrMRF) is considered as a poor prognostic factor in mid and lower rectal cancer [7]. In addition, extramural venous invasion (EMVI) positivity evaluated by MRI has been reported as a significant risk factor in patients with rectal cancer [8, 9]. The tumor depth of invasion that goes beyond the outer border of the muscularis propria > 5 mm has shown to be an adverse prognostic factor for disease-free survival (DFS) [10, 11]. Nevertheless, when stratified analysis was performed to investigate the impact of these parameters on patient survival, the results have shown to be variable and controversial [11–15]. Furthermore, other MRI morphologic factors (e.g., tumor length, thickness, or circumference ratio) used as predicting values for survival were limited in previous studies. Therefore, more studies are required to investigate the value of those MR morphologic characteristics together with clinicopathologic features for predicting patient survival before clinical application.

The following study investigates the value of MRI morphologic and clinicopathologic factors for predicting 3-year DFS in patients with LARC.

Materials and methods

Patients

A total of 170 consecutive patients with LARC who were in line for treatment with nCRT followed by TME between October 2010 and December 2013 were enrolled in the present study. MRI of the pelvis and computed tomography (CT) scans of the chest and abdomen were performed for tumor staging before treatment. Patients were excluded if they met the following criteria: (1) tumor with mucinous adenocarcinoma (n = 8). Mucinous adenocarcinoma represents a poor response and an adverse prognostic biomarker to nCRT [16, 17]. In this study, we excluded the effect of mucinous adenocarcinoma on prognosis and only analyzed the long-term prognosis of the rectal adenocarcinoma subgroup; (2) history of other malignancy (n = 6); (3) pre- or post-nCRT MRI data not available (n = 41). Finally, a total of 115 patients (median age, 54 years; range 28–82 years) with full pre- and post-nCRT MRI examinations were included in the study.

Our Institutional Review Board with a waiver of informed consent approved this retrospective study.

MR image acquisition

Pre-nCRT MRI was preformed within 2 weeks before treatment and 6–8 weeks after nCRT in all patients. MR imaging was performed using a 3-T scanner (Signa HDx, General Electrics, Milwaukee, WI, USA) with a phased-array body coil. MRI sequences and parameters used in this study are described in Supplementary S1.

MR image analysis

The pre- and post-nCRT MR images were analyzed based on the consensus of two experienced radiologists (H.M.Z and C.W.Z.) (20 and over 30 years of experience in gastrointestinal MR imaging), who were blinded to the clinical and histological data. The high-resolution T2-weighted imaging was used as the key sequence for evaluation, and the others were used for assistance. All analysis data were recorded in Excel table.

The maximum length of the tumor was defined as the distance of the upper and lower margin of the tumor on the sagittal plane. The maximum thickness of the tumor was measured at the thickest section of the tumor on the oblique axial plane. Tumor circumference ratio was defined as the proportion of tumors involving the intestinal circumference. The distance of the tumor from the anal margin was measured from the lowest edge of the tumor to the anal verge [18].

T3 rectal cancer was clinically subclassified based on the T2-weighted images from the outer edge of the low-signal-intensity longitudinal muscularis propria to the outermost edge of the tumor (T3a, tumor extending < 1 mm, T3b, tumor extending 1–5 mm, T3c, tumor extending 6–15 mm, and T3d, tumor extending > 15 mm beyond the muscularis propria) [19].

Pre- and post-nCRT lymph node status was based on interpretation of lymph node border characteristics and signal intensity. As a reference, margin irregularity and/or internal heterogeneity were recorded as malignant features [15].

EMVI was evaluated on baseline high-resolution T2WI and referencing multi-phase contrast-enhanced imaging using a previously described scoring system of 0–4 [20]. EMVI status was recorded as either positive or negative: EMVI 0, no vessels adjacent to areas of tumor penetration; EMVI 1, minimal extramural stranding/nodular extension

but not near any vascular structures; EMVI 2, stranding near extramural vessels but with normal caliber and no definite tumor signal within the vessel; EMVI 3, apparent intermediate tumor signal intensity within vessels with the contour and caliber of these vessels only slightly expanded; EMVI 4, obvious irregular vessel contour or nodular expansion of a vessel by a definite tumor signal. An EMVI of 0, 1, or 2 was considered as negativity, while EMVI 3 or 4 as positivity (Fig. 1).

mrMRF involvement was defined as the distance from tumor, a tumor deposit, or a positive lymph node to the mesorectal fascia/levator muscle < 1 mm. If tumor was present at or below the level of the puborectalis sling, mrMRF was predicted as involved if there was invasion into the intersphincteric plane or beyond [21].

MRI assessment of tumor regression grading (mrTRG) using a 5-point scale was based on similar principles to the pathologic TRG originally described by Mandard et al. [22]. Scans were reviewed to determine the degree of

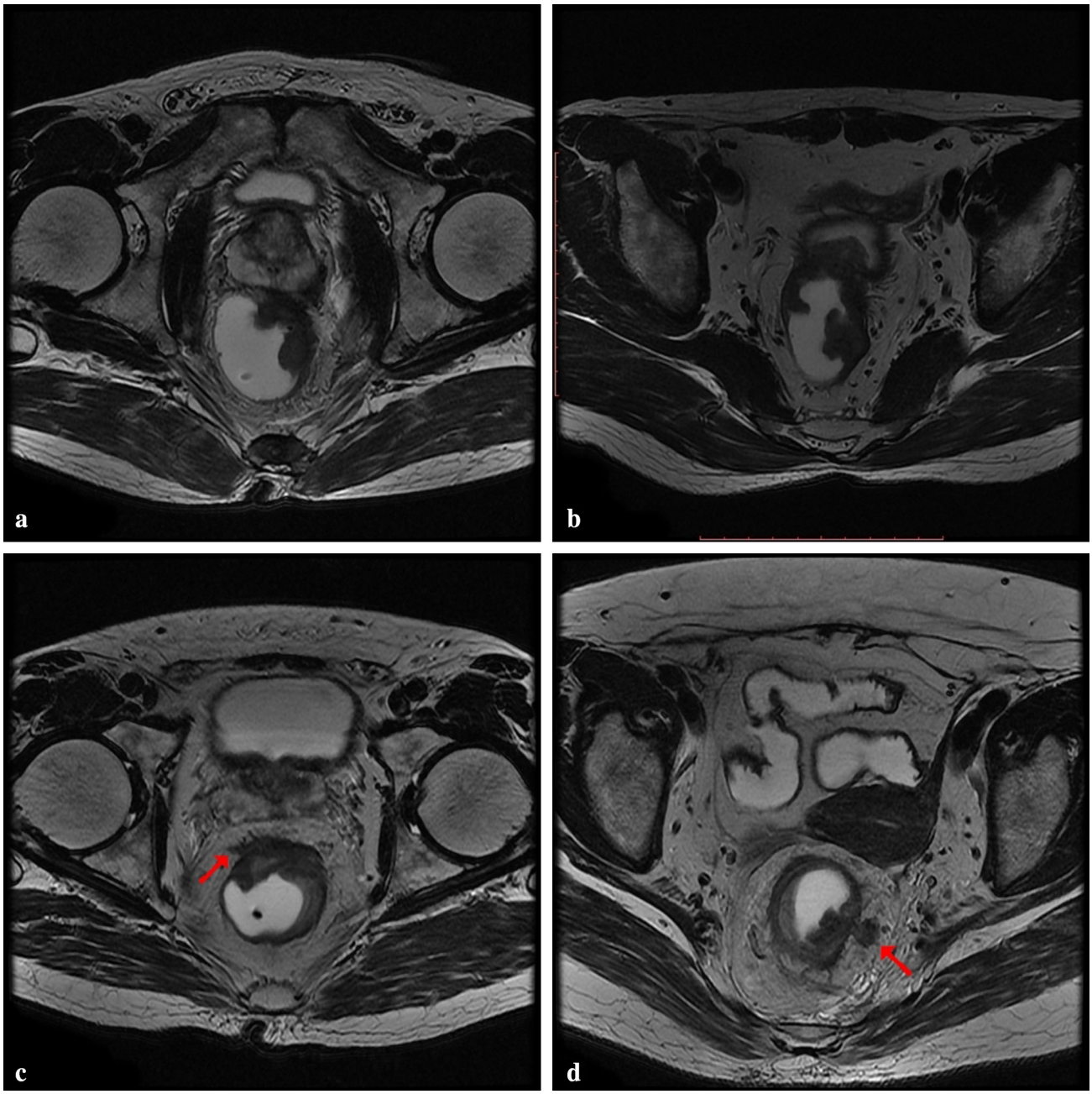

Fig. 1 **a** Fifty-eight-year-old male pre-nCRT mrEMVI negativity (EMVI 1), **b** 44-year-old male pre-nCRT mrEMVI negativity (EMVI 2), **c** 63-year-old female pre-nCRT mrEMVI positivity (EMVI 3), **d** 65-year-old female pre-nCRT mrEMVI positivity (EMVI 4)

tumor replacement by fibrotic stroma [23]. Lower mrTRG refers to greater regression and the system also divides the categories into type of response (complete, good, moderate, slight, and none). mrTRG 1 was defined as radiological complete response: only fibrosis/acellular mucin but no residual intermediate tumor signal; mrTRG 2 was defined as good response: a predominance of fibrosis/acellular mucin with minimal residual intermediate tumor signal; mrTRG 3 was defined as moderate response: substantial intermediate tumor signal was present but it did not predominate the fibrosis/acellular mucin; mrTRG 4 was defined as slight response: a predominance of intermediate tumor signal with minimal low signal fibrosis/high signal mucin; mrTRG 5 was defined as none response: the tumor with intermediate signal appears unchanged from baseline. mrTRG 1–3 were classified as good response, while mrTRG 4–5 as poor response.

Treatment protocol

All patients received nCRT and TME surgery. Some patients underwent adjuvant chemotherapy after surgery. Treatment protocols are described in Supplementary S2.

Reference standard for pathology

The resected gross specimens were processed and evaluated by a single pathologist with 15 years of experience in interpreting rectal cancer pathology (S.M.Z.). The specimens were examined according to the criteria of the Union for International Cancer Control/American Joint Committee on Cancer TNM staging system (7th edition).

Pathological tumor regression grading (pTRG) was evaluated with five grades according to the study of Mandard et al. [22]. Grades 4 and 5 were classified as 'unfavorable response,' and grade 1–3 as 'favorable response.' Pathological complete response (pCR) was defined as the absence of any tumor cells in the pathology specimen (ypT0N0).

Post-nCRT pathologic MRF (ypMRF) positivity was defined as a primary tumor, a tumor deposit, or a positive lymph node abutting or extending through or within 1 mm of the MRF [15]. The negative conversion of MRF was defined as pre-nCRT mrMRF positivity converted to ypMRF negativity.

Follow-up

According to the protocol at our institution, all patients were followed up for at least 3 years after surgery, starting with follow-up at 3-monthly intervals in the first year, and every 6 months in the next 2 years. Follow-up included physical examination, serum carcinoembryonic antigen (CEA) testing, chest and abdominopelvic computed tomography (CT). Colonoscopy and pelvic MRI examinations were performed according to the doctor's advice. The study endpoint was DFS, defined as the interval between TME surgery and disease progression, which included tumor local recurrence, distant metastasis, or death from any cause, or the date of the last follow-up visit (censored). Local recurrence was defined as a recurrence in the pelvis and distant metastasis was defined as a recurrence outside the pelvis. Local recurrence and distant metastasis were diagnosed by a multidisciplinary team based on clinical examination, serum CEA level measurement, chest and abdominopelvic CT, and/or abdominopelvic MRI, endoscopy, and biopsy. Follow-up information was recorded in the database. A minimum follow-up of 36 months was needed to confirm the patients' 3-year DFS status.

Statistical analysis

DFS was measured from the date of examination until progression at any site (local and/or distant), second tumor, or death from any cause, which ever happened first. Patients who were alive and disease free were censored at last follow-up. Cumulative incidence of recurrence was measured from enrolment date until progression at any site (local and/or distant). All the other events were censored at last follow-up.

Univariate analysis was performed for the association between DFS and MRI morphologic/clinicopathologic variables. In the univariate analysis, variables at $P < 0.10$ were included in the multivariate analysis using a forced entry method. Multivariate Cox proportional hazards ratios regression model for DFS was used to identify significantly independent predictors. Hazard ratios (HRs) were reported in the final analysis. Survival curves were calculated for each variable using the Kaplan–Meier product-limit method with univariate log-rank analysis testing for differences in survival rates. SPSS 19.0 was used for calculations. P value < 0.05 was considered to be statistically significant.

Results

Demographic characteristics

A total of 115 patients were included in the study: 76 males (66.1%) and 39 females (33.9%); median age, 54 years; age range 28–82 years. From May 2017, patients had been followed for a median of 48.0 months (range 1.7–76.7 months). 69 (60.0%) patients were censored, among which only three (2.6%) patients (one male and two females) were lost during full follow-up (follow-up less

Table 1 Demographic, radiologic, and clinicopathologic characteristics of patients enrolled in this study (n = 115)

	Frequency	%
Age		
< 65	91	79.13
≥ 65	24	20.87
Sex		
Female	39	33.91
Male	76	66.09
Pre-nCRT CEA (median 4.49 ng/ml)		
< 4.49	56	48.70
≧ 4.49	57	49.57
Missing	2	1.73
Post-nCRT CEA (median 1.91 ng/ml)		
< 1.91	56	48.70
≧ 1.91	54	46.95
Missing	5	4.35
Pre-nCRT T stage		
T3a	20	17.39
T3b	49	42.60
T3c	27	23.48
T3d	7	6.09
T4	12	10.44
Pre-nCRT N stage		
N0	34	29.57
N1	41	35.65
N2	40	34.78
ypMRF		
Non-involvement	113	98.26
Involvement	2	1.74
ypT stage		
T0	28	24.35
T1	2	1.74
T2	23	20.00
T3	59	51.30
T4	3	2.61
ypN stage		
N0	70	60.87
N1	32	27.83
N2	13	11.30
ypTRG (Mandard criteria)		
1	27	23.48
2	37	32.17
3	39	33.91
4	12	10.44
5	0	0.00
pCR		
No	92	80.00
Yes	23	20.00
Adjuvant chemotherapy		
No	67	58.26
Yes, incomplete course	6	5.22
Yes, full course (4–6 cycle)	42	36.52
Follow-up		
Died	18	15.65
Distant metastasis	26	22.61
Local recurrence	1	0.87
Distant metastasis and local recurrence	1	0.87

CEA carcinoembryonic antigen, *nCRT* neoadjuvant chemoradiotherapy, *ypT and ypN stage* post-nCRT treatment pathologic T and N stage, *pTRG (Mandard Criteria)* post-nCRT treatment pathologic tumor regression grade according with the Mandard criteria

than 3 years). The other 66 censored patients all had follow-up of 3 years or greater. These censored patients did not experience any end point event (local recurrence, distant metastasis, or death from any cause) during the last follow-up visit. The demographic characteristics of the 115 patients enrolled in the study are shown in Table 1.

Clinicopathologic characteristics

ypMRF was positive only in 2 (1.7%) patients. The negative conversion of MRF was 25 (21.7%) after nCRT. According to the reference standards, TRG 1–3 and TRG 4–5 were found in 103 (89.6%) and 12 (10.4%) patients, respectively. In addition, 23 (20.0%) patients reached pCR after treatment. Forty-two (36.5%) patients had undergone full course adjuvant chemotherapy after surgery, while 67 (58.3%) patients did not (Table 1).

Pre- and post-nCRT MRI characteristics

There were 69 (60.0%) patients who had rectal tumors with T3a or T3b, and 46 patients (40.0%) who had tumors with T3c, T3d, or T4 before treatment. Regional lymph node negativity was found in thirty-four (29.6%) patients on pre-nCRT MRI (Table 1).

Survival analysis

Tables 2, 3, and 4 summarize the results of univariate and multivariate analyses of MRI morphologic and clinicopathologic variables against 3-year DFS. The 3-year DFS for all patients was 79.0% (Fig. 2). During the follow-up, 18 patients died, 28 patients experienced local recurrence and distant metastasis (26 distant, one local, and one both), and 69 patients were censored. Lung, lymph node, liver,

Table 2 Clinicopathologic characteristics of univariate and multivariate analyses

Variable	*n*	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age (year)					
< 65	91	Ref			
≥ 65	24	1.196 (0.536, 2.667)	0.663	Not included	
Sex					
Female	39	Ref			
Male	76	0.672 (0.332, 1.362)	0.270	Not included	
Pre-nCRT CEA[a]					
< 4.49	56	Ref			
≧ 4.49	57	1.535 (0.756, 3.117)	0.236	Not included	
Post-nCRT CEA[b]					
< 1.91	56	Ref			
≧ 1.91	54	0.806 (0.396, 1.640)	0.552	Not included	
Adjuvant chemotherapy					
No	67	Ref			
Yes, incomplete course	6	0.931 (0.217, 3.996)	0.923		
Yes, full course (4–6 cycle)	42	0.725 (0.339, 1.551)	0.407	Not included	
ypMRF					
Non-involvement	113	Ref			
Involvement	2	2.282 (0.309, 16.869)	0.419	Not included	
pTRG (Mandard criteria)					
Unfavorable	12	Ref			
Favorable	103	0.508 (0.121, 2.133)	0.355	Not included	
pCR					
No	92	Ref		Ref	
Yes	23	0.348 (0.106, 1.142)	**0.082**	0.699 (0.166, 2.939)	0.625

Bold value indicates statistically significant ($P < 0.1$)

CEA carcinoembryonic antigen, *ypMRF* post-neoadjuvant chemoradiotherapy pathologic mesorectal fascia, *ypTRG* post-neoadjuvant chemoradiotherapy pathologic tumor regression grade, *pCR* pathologic complete response, *Ref* reference

[a]indicate that pre-nCRT CEA data missing

[b]indicate that post-nCRT CEA data missing

and other sites distant metastasis were observed in 16, 3, 2, and 5 patients, respectively.

Clinicopathologic variables

According to univariate analysis, pCR was a factor for increased 3-year DFS (HR 0.348, 95% CI 0.106–1.142, $P = 0.082$). The HR was 0.699 (95% CI 0.166–2.939, $P = 0.625$) on multivariate analysis. The 3-year DFS of the patients with adjuvant chemotherapy after surgery was higher compared to those without adjuvant chemotherapy, but there was no significant difference. ypMRF involvement was not significantly adverse factor for 3-year DFS (HR 2.282, 95% CI 0.309-16.869, $P = 0.419$) (Table 2).

Pre-nCRT MRI variables

Among 115 patients, 40 (34.8%) had pre-nCRT mrEMVI positivity. Among the mrEMVI-positive group, there were fifteen (37.5%) patients that experienced tumor local recurrence and distant metastasis (14 distant, one local), while twelve out of the fifteen patients (30.0%) died during the 3-year follow-up. By contrast, among the 75 cases from mrEMVI-negative group, thirteen (17.3%) patients experienced local recurrence and distant metastasis (12 distant, 1 both), while six of those thirteen (8.0%) patients died.

Pre-nCRT mrEMVI status was the only independent predictor for 3-year survival on pre-nCRT MRI variables. In univariate and multivariate analyses, mrEMVI positivity was a significant factor for worse 3-year DFS with the HR of 2.308 (95% CI 1.151–4.629, $P = 0.018$) in univariate

Table 3 Univariate and multivariate analyses of pre-nCRT MRI characteristics

Variable	*n*	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Maximum diameter (mm)					
< 40	56	Ref			
≧ 40	59	1.005 (0.500, 2.018)	0.990	Not included	
Thickness (mm)					
< 14	51	Ref			
≥ 14	64	1.032 (0.513, 2.076)	0.930	Not included	
Circumference ratio					
< 50%	20	Ref			
≥ 50%	95	1.494 (0.523, 4.265)	0.453	Not included	
Tumor from anal margin (mm)					
< 50	38	Ref			
≧ 50	77	0.958 (0.453, 2.029)	0.912	Not included	
Tumor invasion depth					
Unfavorable (T3c–d, T4)	46	Ref			
Favorable (T2, T3a–b)	69	0.972 (0.474, 1.993)	0.938	Not included	
MRF					
Non-involvement	88	Ref			
Involvement	27	1.664 (0.787, 3.519)	0.183	Not included	
Pre-nCRT N stage					
N0	34	Ref			
N1	41	1.157 (0.440, 3.044)	0.767		
N2	40	1.913 (0.779, 4.694)	0.157	Not included	
mrEMVI					
Negativity	75	Ref		Ref	
Positivity	40	2.308 (1.151, 4.629)	**0.018**	2.495 (1.243, 5.012)	**0.010**

Bold values indicate statistically significant ($P < 0.1$)

MRF mesorectal fascia, *mrEMVI* pre-nCRT MRI extramural venous invasion, *Ref* reference

and 2.495 (95% CI 1.243–5.012, $P = 0.010$) in multivariate analysis (Table 3).

The cumulative survival rate for 3 year DFS in patients with mrEMVI negativity was 86.6% compared to 65.0% in mrEMVI positivity group. In addition, there was a significant difference in DFS using the Mantel Cox log-rank test with P value of 0.015 (Fig. 3).

MRF involvement was detected on pre-nCRT MRI in 27 (23.5%) patients. The 3-year DFS was not significantly different in MRF involvement and non-involvement groups ($P = 0.183$).

Post-nCRT MRI variables

According to univariate analysis, post-nCRT lymph node status was significant with the HR of 2.251 (95% CI 1.121–4.520, $P = 0.023$), while other variables (circumference ratio, MRF, and mrTRG) were not significant for DFS in univariate Cox analysis, but with the P values less than 0.1, consequently all were analyzed in multivariate analysis. However, the variable of mrTRG had borderline significance in multivariate analysis with P value of 0.067 (HR 0.260, 95% CI 0.062–1.096). These results are listed in Table 4. The 3-year DFS for patients with good response evaluated by MRI was 100% and for those with poor response was 75.3% (Fig. 4).

All multivariate Cox analysis data (HRs and P values) are shown in Fig. 5. mrEMVI was the most significant adverse factor for 3-year DFS.

Discussion

This study aimed to determine the prognostic significance of MRI morphological characteristics and clinicopathologic findings in LARC patients treated with TME following nCRT. In the study, pre-nCRT mrEMVI status was an independent prognostic factor in univariate analyses for 3-year DFS, which remained significant after multivariate adjustment (HR = 2.495 95% CI 1.243, 5.012, $P = 0.010$).

Table 4 Univariate and multivariate analyses of post-nCRT MRI characteristics

Variable	*n*	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Maximum diameter (mm)					
< 24	52	Ref			
≧ 24	63	0.870 (0.435, 1.740)	0.693	Not included	
Thickness (mm)					
< 9	56	Ref			
≥ 9	59	0.968 (0.483, 1.942)	0.927	Not included	
Circumference ratio					
< 50%	63	Ref			
≥ 50%	52	1.933 (0.953, 3.921)	0.068	0.622 (0.298, 1.297)	0.205
Tumor from anal margin (mm)					
< 50	29	Ref			
≧ 50	86	0.766 (0.353, 1.664)	0.501	Not included	
Tumor invasion depth					
T0–2	38	Ref			
T3–4	77	2.007 (0.867, 4.646)	0.104	Not included	
Post-nCRT N stage					
N−	79	Ref			
N+	36	2.251 (1.121, 4.520)	**0.023**	1.409 (0.644, 3.081)	0.391
MRF					
Non-involvement	105	Ref			
Involvement	10	2.290 (0.877, 5.978)	0.091	1.168 (0.409, 3.334)	0.771
mrTRG					
Poor response	98	Ref			
Good response	17	0.296 (0.071, 1.244)	0.097	0.260 (0.062, 1.096)	0.067

Bold value indicate statistically significant ($P < 0.1$)

MRF mesorectal fascia, *mrTRG* MRI tumor regression grading, *Ref* reference

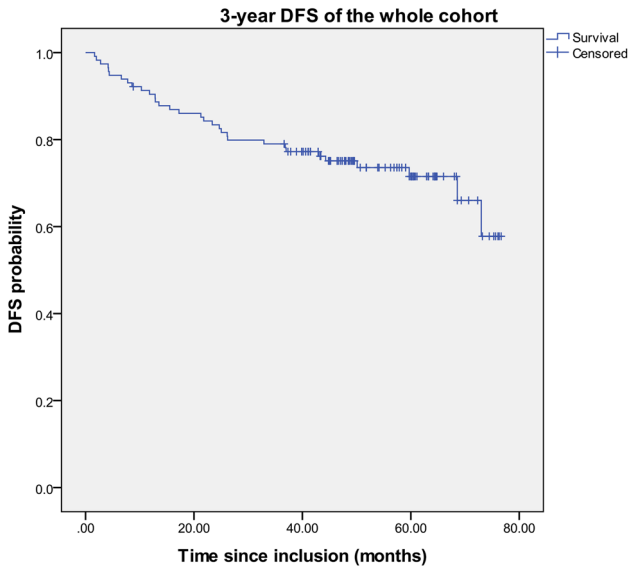

Fig. 2 Kaplan–Meier disease-free survival curve for the whole cohort of 115 patients

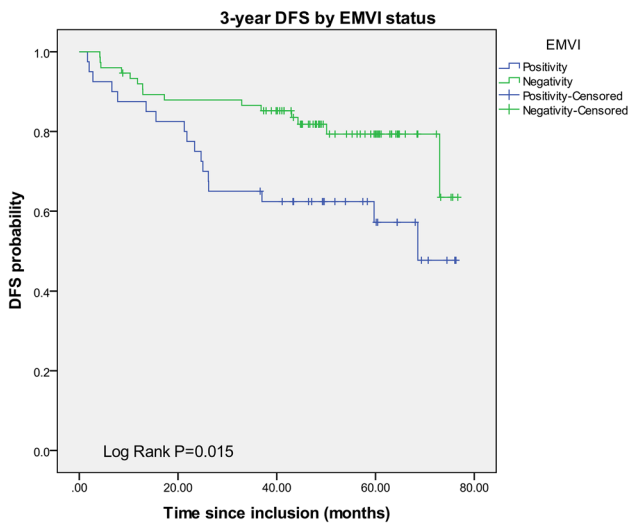

Fig. 3 Three-year DFS by mrEMVI status

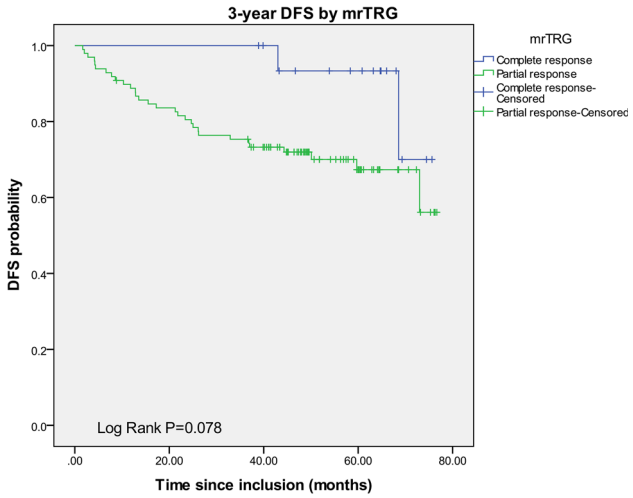

Fig. 4 Three-year DFS by post-nCRT mrTRG

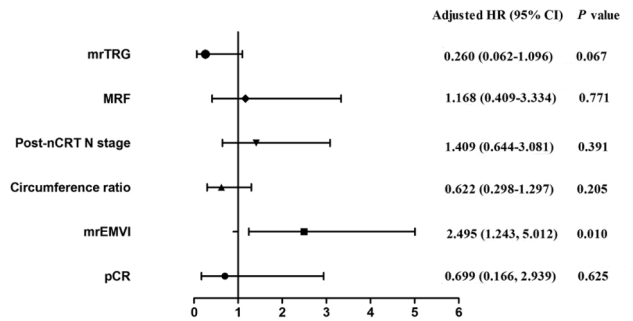

Fig. 5 HRs and P values of all factors for 3-year DFS on multivariate Cox analysis

Previous studies have reported that pre-nCRT mrEMVI positivity is an independent significant adverse predictor for metastases [24, 25]. In our study, the patients with pre-nCRT mrEMVI positive were at a higher risk of local recurrence and distant metastasis than those with negative. These results were consistent with the previous studies [24, 25], which argued that EMVI positivity was significantly poor prognostic factor during long-term follow-up. Since EMVI was defined as the presence of tumor cells in the venous beyond the muscularis propria, it is possible that there were micrometastatic foci in the body beyond the pelvis in EMVI-positive patients, which were not detected by current imaging modality. Therefore, clinicians should adopt a more intensive follow-up strategy for EMVI-positive patients.

Nevertheless, Kamran et al. have reported that pre-nCRT EMVI status evaluated by MRI is not a significant prognostic factor for patient survival, while ypEMVI is useful for predicting distant metastasis [13]. Kamran et al. have conducted a study on 70 patients (38.9%) with pre-nCRT mrEMVI positivity, in which 22 patients (12.2%) had post-nCRT pathologic EMVI (ypEMVI) positivity. Their preliminary results showed that ypEMVI was superior pre-nCRT mrEMVI as a predictor for survival outcomes. The ypEMVI may more intuitively reflect the residual of intravascular tumors post-nCRT. Further analysis is necessary to verify the relationship between pre-/-post-nCRT mrEMVI conversion (reference ypEMVI) and outcomes. Furthermore, Kamran et al. have conducted a study in which eighty percent of patients received adjuvant chemotherapy (AC) following surgery and AC improved patients' overall survival (OS). Treatment regimen bias may also cause the variation in two studies.

Although post-nCRT lymph node status was the significant factor that correlated with 3-year DFS in univariate analysis, in the present study it did not remain independent in multivariate adjustment. mrEMVI has been reported to be correlated with lymph node metastasis [26]. Consequently, the confounding effect from pre-nCRT mrEMVI may decline the factor weight of lymph node status in multivariate analysis. Furthermore, it is slightly difficult to evaluate lymph node only based on nodal border or signal intensity on routine post-nCRT MRI, since treatment-related edema and inflammation may disturb the judgment [27]. Some new MRI technologies, such as chemical shift effect, have shown promising predicting values in assessing metastatic lymph nodes [28–30]. In our study, pre-nCRT T and N staging revealed no significant correlation with patient outcomes, which was in line with results reported by Wen et al. [31]. Consequently, only T and N stages appeared as less than optimum predictors for survival, while other factors (e.g., mrEMVI) may be efficiently used to improve predicting accuracy.

According to Taylo et al., pre-nCRT MRF status is a useful factor for predicting tumor outcomes [21]. MRF positivity before treatment and ypMRF involvement have all been reported as adverse factors for long-term survival in that study. However, in the present study, the relevance of pre-nCRT MRF and long-term survival were not so significant. In Taylo et al. study, more than one half of the patients only underwent surgery, while in our study all patients received long-course concurrent chemoradiotherapy and TME. Accordingly, the difference in patient enrollment bias may cause the inconsistency of the results. On the other hand, it has been reported that patients with negative conversion of MRF through nCRT have a significant survival benefit compared to those patients with persistent MRF involvement [32]. In our study, 21.7% of patients had negative conversion of MRF, while there were only two patients with ypMRF positivity after treatment. Relatively smaller cases of ypMRF involvement and higher percentage of negative conversion of MRF may cause the negative result.

The mrTRG has been reported as a non-operative surrogate that provides complementary information for better

stratification of LARC patients with improved outcomes [15]. Nonetheless, in the present study no positive results were observed for the predictor of mrTRG. The possible subjectivity exists in evaluating TRG status by different observers based on pre- and post-nCRT MRI. Multi-parametric MRI and analysis combining T2WI, DWI, and DCE may improve the accuracy of prediction [33]. Furthermore, radiomics, which is as an advanced computational method that extracts a large number of quantitative features from traditional medical images, has shown enormous potential in tumor diagnosis, treatment evaluation, and outcomes [34]. The utility of radiomics combining traditional imaging method may increase the prediction performance for mrTRG evaluation.

There is a limited research on the correlation between the other predictors (i.e., maximum length, thickness, and circumference ratio) and the prognosis of patients with LARC [35]. In our study, these morphological factors showed insignificant correlation with patient outcomes (P = 0.068–0.930).

Adjuvant chemotherapy after surgery was not a significant predictor for patient survival in our study, which was in accordance with Breugom et al. results [36]. Breugom and his team revealed that the postoperative adjuvant chemotherapy could not improve the survival in patients with LARC.

The present study has some limitations that need to be pointed out. First, the retrospective analysis was performed in one institution, while the external validation was not performed. Second, the exclusion of 41 patients who did not receive the pre- or post-nCRT MRI represents a sizable portion of the study cohort. Selection bias exists where they may be an unrecognized factor which potentially impacts the results in some fashion. Third, the pre-nCRT mrEMVI consensus of two radiologists was not evaluated in this study. Fourth, post-nCRT EMVI status was not assessed as there was slightly lower sensitivity and poorer reproducibility compared to pre-nCRT, due to the presence of increased amounts of fibrotic strands and reactive edema [37, 38]. Fifth, the utility of other parameters extracted from advanced imaging method, such as intravoxel incoherent motion (IVIM) or diffusion kurtosis imaging (DKI) was not investigated.

In conclusion, pre-nCRT mrEMVI status can be used as a useful independent factor for predicting long-term outcomes in LARC patients. Precise evaluation of EMVI status before therapy may contribute in designing individualized treatment and improving patient outcomes.

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest were disclosed.

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