

Research Article

Response of MRI-detected Extramural Venous Invasion and Tumor Deposits to Neoadjuvant Chemo-radiotherapy in Locally Advanced Rectal Cancer: A Prospective Evaluation using mr-vTRG Score

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Abstract: **Introduction:** Extramural venous invasion (EMVI) and tumor deposits (TDs) detected on magnetic resonance imaging (MRI) are established adverse prognostic factors in locally advanced rectal cancer (LARC). This prospective study evaluated the response of MRI-detected EMVI (mrEMVI) and MRI-detected tumor deposits (mrTDs) to neoadjuvant chemo-radiotherapy (NACRT) using the MRI-based venous tumor regression grade (mr-vTRG). **Materials and Methods:** Thirty-three patients with cT3/cT4 rectal adenocarcinoma without distant metastasis were enrolled between July 2022 and January 2024 at a tertiary cancer centre in Bangalore, India. All patients received 50.4 Gy in 28 fractions with concurrent oral capecitabine, followed by restaging MRI at six weeks. Pre- and post-treatment MRIs were compared for T/N stage, cranio-caudal length, circumferential extent, mesorectal nodes, mrEMVI, mrTDs and prognostic group. Response was graded using mr-TRG and mr-vTRG. **Results:** Baseline mrEMVI was present in 42.4% and mrTDs in 30.3% of patients. Post NACRT, 43.8% had complete disappearance and 50% had reduction of mrEMVI (Stuart–Maxwell $\chi^2 = 15.00$; $p = 0.002$); mr-vTRG 1 was achieved in 43.8%, mr-vTRG 2 in 43.8%, and only 6.2% had mr-vTRG 4 (poor response). All patients with baseline mrTDs demonstrated complete (60%) or significant (40%) regression ($p = 0.019$). Mean cranio-caudal length decreased from 5.51 to 2.51 cm and mean mesorectal nodes from 5.73 to 1.94 (both $p < 0.001$). Substantial AJCC prognostic-group downstaging occurred in 82% of patients. **Conclusion:** NACRT produces significant regression of mrEMVI and mrTDs in locally advanced rectal cancer. The mr-vTRG is a simple, reproducible imaging biomarker for identifying poor responders who may benefit from treatment intensification.

Keywords: rectal cancer, EMVI, tumor deposits, MRI, neoadjuvant chemoradiotherapy, mr-vTRG.

INTRODUCTION

Colorectal cancer (CRC) remains one of the most common malignancies worldwide. According to GLOBOCAN 2022 estimates, CRC ranked as the third most frequent cancer globally, with rectal cancer alone accounting for approximately 730,000 new cases and 340,000 deaths.¹ In India, rectal cancer contributed nearly 30,800 new cases and 17,700 deaths in 2022, and its incidence continues to rise in urban populations.² Locally advanced rectal cancer (LARC), typically defined as cT3/cT4 or node-positive disease without distant metastasis, requires a multidisciplinary approach combining neoadjuvant chemo-radiotherapy (NACRT), total mesorectal excision (TME) and adjuvant systemic therapy.^{3, 4}

Magnetic resonance imaging (MRI) has become the reference standard for local staging and restaging of rectal cancer because of its high soft-tissue resolution and reproducibility.⁵ Beyond the assessment of T stage, nodal status and involvement of the mesorectal fascia (MRF), MRI reliably identifies two critical adverse

prognostic features: extramural venous invasion (EMVI) and tumor deposits (TDs).^{6, 7}

EMVI was first characterized on MRI by Brown et al. as a serpiginous extension of tumor signal within the extramural vasculature and has since been validated as an independent predictor of distant metastasis and reduced disease-free survival (DFS).^{8, 9} A meta-analysis by Siddiqui et al. reported a pooled prevalence of MRI-detected EMVI (mrEMVI) of 34.6% in rectal cancer and demonstrated a nearly five-fold higher risk of synchronous metastases in mrEMVI-positive patients.¹⁰ The MERCURY collaboration further confirmed the reproducibility of mrEMVI scoring and its correlation with histopathological EMVI.¹¹

Tumor deposits, defined by the AJCC as discrete tumor foci in the pericolic or perirectal fat without histological evidence of residual lymph node, vascular or neural structures, have also emerged as strong prognostic markers.¹² A systematic review and meta-analysis by Lord et al. showed that extranodal tumor deposits are associated with worse overall and disease-free survival

in colorectal cancer and are strongly linked with EMVI.¹³ Nagtegaal et al. further demonstrated that incorporation of TDs into TNM staging refines prognostic accuracy.¹⁴

Because both EMVI and TDs are dynamic imaging biomarkers, their behaviour after NACRT is of therapeutic interest. Chand et al. proposed the MRI-based venous tumor regression grade (mr-vTRG), a five-point scale analogous to the tumor regression grade (mr-TRG) used for the primary tumor.¹⁵ Patients with mr-vTRG 1–3 (good responders, $\geq 50\%$ fibrosis) had significantly better three-year DFS than mr-vTRG 4–5 (poor responders).¹⁵ Subsequent studies by Lee et al., Prampolini et al. and Schaap et al. confirmed that regression of mrEMVI following NACRT correlates with improved distant-metastasis-free survival, whereas persistent mrEMVI or TDs identifies a high-risk cohort in whom treatment intensification, such as total neoadjuvant therapy (TNT), may be warranted.^{16–18} Despite this evidence, prospective Indian data on the response of mrEMVI and TDs to NACRT remain limited. In this study, we prospectively evaluated the prevalence of mrEMVI and mrTDs in cT3/cT4 rectal cancer patients and quantified their regression after NACRT using the mr-vTRG score, with the aim of identifying "high-risk" poor responders who might benefit from intensified therapy.

MATERIALS AND METHODS

Study design, setting and population

This was a prospective analytical study conducted in the Department of Radiation Oncology at Apollo Hospitals, Bangalore, India, from July 2022 to January 2024. Approval from the institutional ethics committee was obtained, and written informed consent was taken from all participants.

Consecutive patients with biopsy-proven rectal adenocarcinoma, staged as cT3 or cT4 on baseline high-resolution MRI, and scheduled for neoadjuvant chemo-radiotherapy, were considered for inclusion.

Inclusion criteria: (i) age ≥ 18 years, (ii) histologically confirmed rectal adenocarcinoma, (iii) cT3 or cT4 stage on pre-treatment MRI, (iv) no evidence of synchronous distant metastasis.

Exclusion criteria: (i) presence of distant metastasis, (ii) patients receiving only post-operative adjuvant radiotherapy, (iii) absence of baseline MRI evaluation.

Sample size

Using an expected proportion of good response (25%) after NACRT (as reported by Schaap et al.),¹⁸ with an absolute precision of 15% at a 95% confidence level, the minimum required sample size was 33 patients. This number was accrued during the study period.

Imaging protocol

All patients underwent baseline high-resolution pelvic MRI on a 1.5-T or 3-T scanner. Sequences included sagittal, axial and coronal T2-weighted (T2W), oblique T2W (perpendicular and parallel to the tumor axis) and diffusion-weighted imaging (DWI). All scans were reported by an experienced abdominal radiologist and analysed for tumor location, cranio-caudal length, circumferential extent (clock-hour method), T and N stage, mesorectal and extramesorectal nodes, involvement of the mesorectal fascia, presence and score of EMVI (using the five-point Smith/MERCURY scoring system: 0 = absent, 4 = large vessel with irregular contour and tumor signal),^{9,11} presence of tumor deposits, and TNM/AJCC 8th edition prognostic grouping.¹⁹

Neoadjuvant chemo-radiotherapy

All patients received long-course chemo-radiotherapy: external beam radiation of 50.4 Gy in 28 fractions (1.8 Gy/fraction, five fractions/week) delivered to the pelvis using IMRT (n = 14), IGRT (n = 14), Rapid Arc (n = 3) or 3D-CRT (n = 2). Concurrent chemotherapy consisted of oral capecitabine 650 mg/m² twice daily on radiation days, in accordance with the German CAO/ARO/AIO-04 and NSABP R-04 protocols.^{20,21}

Response assessment

Restaging pelvic MRI was performed six weeks after completion of NACRT, using the same protocol. Variables reassessed included cranio-caudal length, circumferential extent, T and N stage, mesorectal nodes, prognostic group, MRI tumor regression grade (mr-TRG, scale 1–5)²² and MRI venous tumor regression grade (mr-vTRG) as originally described by Chand et al.¹⁵

mr-vTRG scale: mr-vTRG 1 = tumor signal replaced entirely by vessel fibrosis; mr-vTRG 2 = 50–75% fibrosis; mr-vTRG 3 = 25–49% fibrosis; mr-vTRG 4 = $<25\%$ fibrosis; mr-vTRG 5 = minimal or no fibrosis. Patients with mr-vTRG 1–3 were classified as "good venous responders," and mr-vTRG 4–5 as "poor venous responders." TDs on restaging were categorized as complete regression, significant regression, or persistent.

Statistical analysis

Data were entered in Microsoft Excel and analysed using SPSS version 23.0. Continuous variables were expressed as mean $\pm$ SD or median (IQR), and categorical variables as frequency and percentage. Given the non-normal distribution of most continuous variables, the paired Wilcoxon signed-rank test was used to compare pre- and post-treatment values. Categorical shifts across stages were assessed with the Stuart–Maxwell test. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 33 patients (18 males, 15 females) with cT3/cT4 rectal cancer completed neoadjuvant chemo-radiotherapy and restaging MRI. The mean age was 55.94 ± 14.03 years, with the largest subgroups in the 50–59-year (27.3%) and 60–69-year (27.3%) age brackets (Table 1). Baseline T stage was T3 in 22 (66.7%), T4a in 10 (30.3%) and T4b in 1 (3.0%). N stage was N1a in 6.1%, N1b in 30.3%, N2a in 24.2% and N2b in 39.4%. All patients were M0 at enrolment. The AJCC prognostic group was IIIB in 19 (57.6%) and IIIC in 14 (42.4%). The most frequent tumor location was low or mid-low rectum (24.2% each), followed by mid rectum (21.2%), upper–mid rectum (15.2%) and upper rectum (15.2%).

Table 1. Baseline demographic and MRI characteristics of the study population (n = 33)

Parameter	Value
Mean age (years)	55.94 ± 14.03
Male : Female	18 : 15
Mean cranio-caudal length (cm)	5.51 ± 1.30
Mean circumferential extent (clock hours)	8.70 ± 2.48
Mean mesorectal nodes	5.73 ± 2.99
mrEMVI present, n (%)	14 (42.4%)
mrEMVI equivocal, n (%)	3 (9.1%)
MRI tumor deposits present, n (%)	10 (30.3%)
Extramesorectal nodes present, n (%)	10 (30.3%)
Mesorectal fascia involvement, n (%)	9 (27.3%)
Prognostic group IIIB / IIIC, n	19 / 14
T3 / T4a / T4b, n	22 / 10 / 1

Response of the primary tumor

The mean cranio-caudal length decreased from 5.51 ± 1.30 cm to 2.51 ± 1.17 cm, an absolute reduction of 3.00 cm (55.5%) (Wilcoxon V = 561.0; $p < 0.001$). The mean circumferential extent decreased from 8.70 to 5.67 clock hours (Wilcoxon V = 412.0; $p < 0.001$) (Figure 1).

Post-treatment T stage improved substantially: T2 in 20 (60.6%), T3 in 10 (30.3%) and T4a in 3 (9.1%). Twenty of 22 T3 patients (91%) downstaged to T2, and 8 of 10 T4a patients (80%) downstaged to T3. The overall T-stage migration was highly significant (Stuart–Maxwell $\chi^2 = 29.00$; $p < 0.001$) (Figure 2).

Mesorectal nodes decreased from a mean of 5.73 ± 2.99 to 1.94 ± 2.30 (absolute change -3.79 ; $p < 0.001$). Nine patients (27.3%) achieved a nodal complete response (ypN0). The overall change in N stage was also statistically significant (Stuart–Maxwell $\chi^2 = 24.83$; $p < 0.001$) (Figure 2).

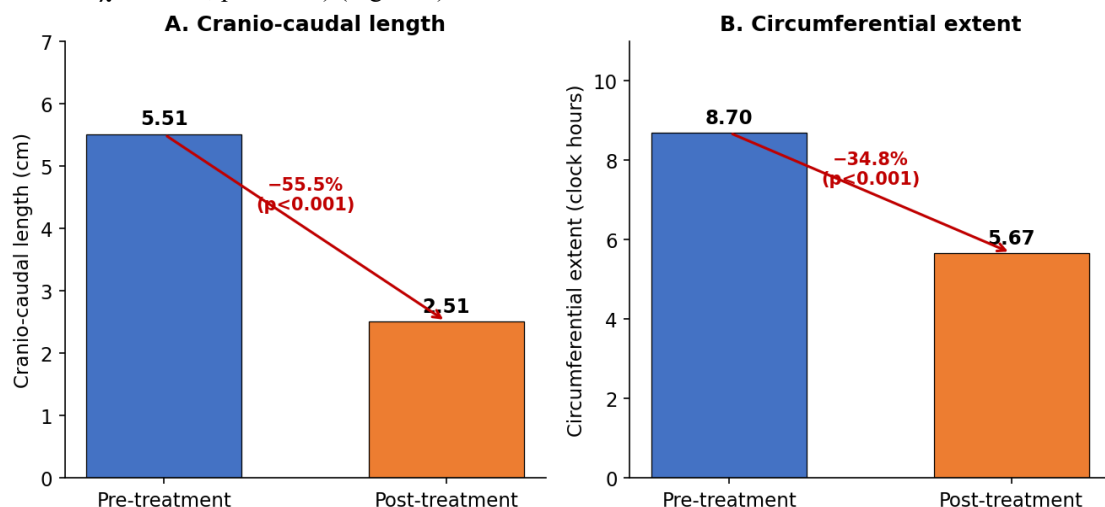


Figure 1. Change in mean cranio-caudal length (A) and circumferential extent (B) of the primary tumor between pre- and post-treatment MRI. Both changes are statistically significant (Wilcoxon signed-rank, $p < 0.001$).

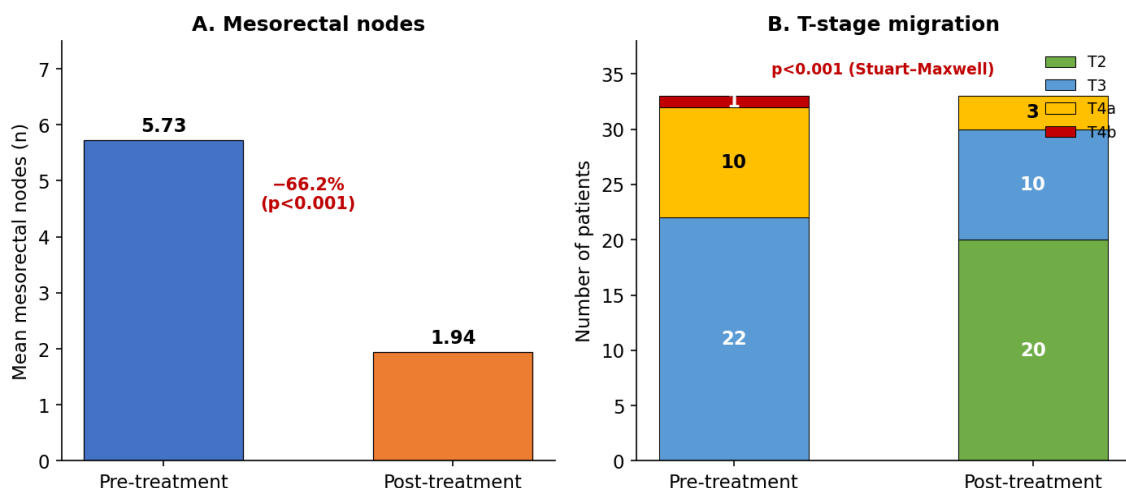


Figure 2. Reduction in mean mesorectal nodes (A) and migration of T stage (B) after NACRT. Twenty of 22 cT3 patients (91%) downstaged to ypT2; 8 of 10 cT4a to ypT3 (Stuart–Maxwell $p < 0.001$).

Response of MRI-detected EMVI

Of the 33 patients, 14 (42.4%) were mrEMVI-positive and 3 (9.1%) equivocal at baseline (mean mrEMVI score 1.61 ± 1.66). On restaging, 8 of 16 evaluable patients (50%) demonstrated a reduction and 7 (43.8%) complete disappearance of mrEMVI; only 1 patient (6.2%) had persistent frank mrEMVI (Figure 3A). The overall change in mrEMVI category was statistically significant (Stuart–Maxwell $\chi^2 = 15.00$; $p = 0.002$).

When response was graded using mr-vTRG, 7 patients (43.8%) achieved mr-vTRG 1 (complete vessel fibrosis), 7 (43.8%) mr-vTRG 2, 1 (6.2%) mr-vTRG 3, and 1 (6.2%) mr-vTRG 4 (Table 2, Figure 3B). No patient scored mr-vTRG 5. Overall, 15 of 16 patients (93.8%) were classified as good venous responders (mr-vTRG 1–3), and 1 of 16 (6.2%) as poor responders (mr-vTRG 4–5).

Table 2. Distribution of mr-vTRG on restaging MRI (n = 16 evaluable for EMVI)

mr-vTRG score	Description	Frequency (%)
1	Tumor signal replaced by vessel fibrosis	7 (43.8%)
2	50–75% fibrosis	7 (43.8%)
3	25–49% fibrosis	1 (6.2%)
4	<25% fibrosis	1 (6.2%)
5	No or minimal fibrosis	0 (0.0%)

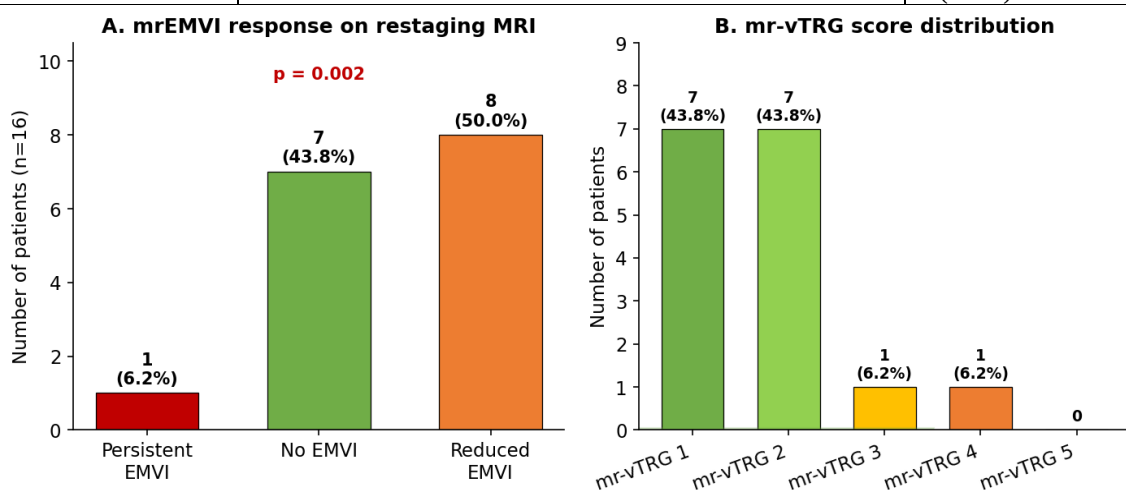


Figure 3. Response of MRI-detected EMVI on restaging MRI. (A) 43.8% of patients had complete disappearance and 50% had reduction of mrEMVI; only 6.2% had persistent EMVI. (B) mr-vTRG score distribution: 87.6% of patients scored mr-vTRG 1–2 (good venous responders); only 6.2% scored mr-vTRG 4 (poor responder). No patient scored mr-vTRG 5.

Response of tumor deposits

Ten patients (30.3%) had MRI-detected tumor deposits at baseline. On restaging MRI, 6 (60%) showed complete regression and 4 (40%) significant regression of TDs. No patient had persistent or progressive TDs (Stuart–Maxwell $\chi^2 = 10.00$; $p = 0.019$) (Figure 4).

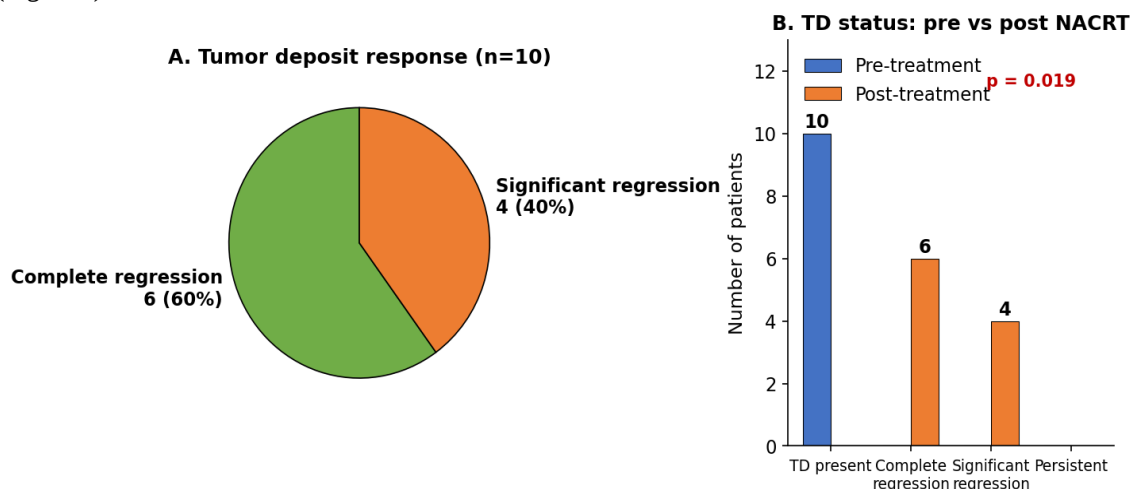


Figure 4. Response of MRI-detected tumor deposits ($n = 10$) to NACRT. (A) 60% of patients had complete regression and 40% significant regression; no patient had persistent TDs. (B) Pre- versus post-treatment TD distribution (Stuart–Maxwell $p = 0.019$).

mr-TRG of the primary tumor

Overall tumor regression on the mr-TRG scale showed: score 2 (good response) in 8 patients (24.2%), score 3 (moderate response) in 22 (66.7%) and score 4 (slight response) in 3 (9.1%). No patient achieved mr-TRG 1 (complete radiological response) or mr-TRG 5 (no response) at the six-week post-treatment MRI (Table 3).

Table 3. Distribution of mr-TRG (primary tumor) on restaging MRI

mr-TRG score	Interpretation	Frequency (%)
2	Good response	8 (24.2%)
3	Moderate response	22 (66.7%)
4	Slight response	3 (9.1%)

Migration of prognostic groups

Post-treatment AJCC prognostic groups were: group I in 7 (21.2%), IIA in 1 (3.0%), IIB in 1 (3.0%), IIIA in 12 (36.4%), IIIB in 10 (30.3%) and IIIC in 2 (6.1%) (Figure 5). Of the 19 patients initially in group IIIB, 7 downstaged to group I, 1 to IIA and 7 to IIIA. Among the 14 patients initially in group IIIC, 1 downstaged to IIB, 5 to IIIA and 6 to IIIB. The overall change in prognostic grouping was highly significant (Stuart–Maxwell $\chi^2 = 25.04$; $p < 0.001$).

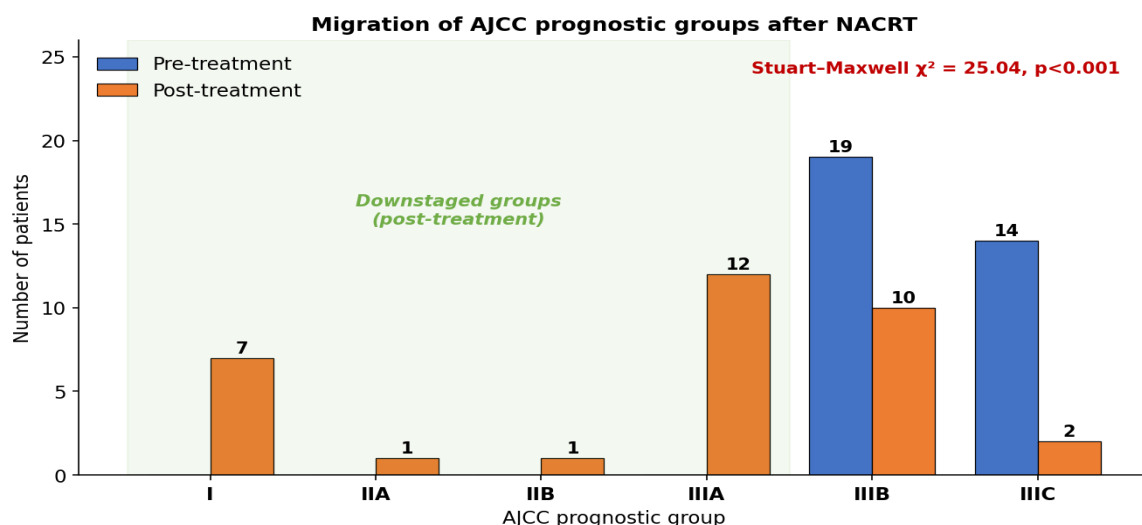


Figure 5. Migration of AJCC prognostic groups from pre-treatment to post-treatment. At baseline all patients were in group IIIB ($n = 19$) or IIIC ($n = 14$); after NACRT, 82% downstaged to groups I–IIIA (Stuart–Maxwell $\chi^2 = 25.04$, $p < 0.001$).

DISCUSSION

Locally advanced rectal cancer has undergone a paradigm shift in management with the widespread integration of pre-treatment MRI, which allows accurate stratification of high-risk features that guide the intensity of neoadjuvant therapy.^{5,22} Among these features, EMVI and tumor deposits have consistently emerged as the strongest MRI-based predictors of distant metastasis, over and above conventional T and N staging.^{10,13,23}

Our prospective series of 33 patients with cT3/cT4 rectal cancer demonstrated a baseline mrEMVI prevalence of 42.4% and mrTD prevalence of 30.3%. These figures are consistent with the range reported in previous literature. Siddiqui et al. found a pooled mrEMVI prevalence of 34.6% across 1262 patients from six studies,¹⁰ Schaap et al. reported 58.8% mrEMVI positivity in a cT3/cT4 cohort,¹⁸ and Chandramohan et al. from an Indian cohort noted mrEMVI in 49.5% and TDs in 47.5% of LARC.²⁴ The relatively lower prevalence in our study likely reflects both the smaller sample size and strict inclusion of only patients staged as cT3/cT4 without metastatic disease.

After NACRT with 50.4 Gy in 28 fractions and concurrent capecitabine, the primary tumor showed substantial regression, with a mean 55.5% reduction in crano-caudal length and 34.8% reduction in circumferential extent (both $p < 0.001$), 91% of T3 tumors downstaged to T2, and a 66.7% reduction in mesorectal nodes. These findings mirror the historical downstaging rates reported in the German CAO/ARO/AIO-94/04 trials, in which preoperative chemo-radiotherapy resulted in ypT downstaging in over 60% of patients and significantly reduced local recurrence.²⁰

The most clinically relevant finding of our study relates to the behaviour of mrEMVI and TDs. Reduction or complete disappearance of mrEMVI occurred in 93.8% of patients, with mr-vTRG 1–3 (good responders) achieved in 15 of 16 evaluable patients. This regression rate compares favourably with that reported by Chand et al., who found >50% fibrosis of mrEMVI in 35 of 62 patients (56%) after CRT and showed that mr-vTRG 4–5 (poor responders) had 3-year DFS of only 45.8%, versus 87.8% in good responders ($p < 0.0001$).¹⁵ Similarly, Prampolini et al. observed that regression of mrEMVI on post-CRT MRI was independently associated with lower distant metastasis and better DFS.¹⁷ Lee et al. reported that persistent mrEMVI on restaging MRI carried a significantly increased hazard of distant metastasis compared with mrEMVI-negative patients.¹⁶

Schaap et al. specifically evaluated the mr-vTRG in 277 patients with cT3/cT4 rectal cancer and demonstrated that poor mr-vTRG responders (grade 3–5) had a 5-year

distant metastasis rate of 46.1%, compared with 25.7% in good responders and mrEMVI-negative patients—a difference that persisted after multivariable adjustment.¹⁸ This is the clinical rationale underpinning our study: patients with mr-vTRG 4–5 or persistent TDs represent a high-risk subgroup in whom treatment intensification (e.g., total neoadjuvant therapy with consolidation chemotherapy as in RAPIDO, or induction FOLFIRINOX as in PRODIGE-23) may translate into meaningful survival gains.^{25,26}

Regarding tumor deposits, all 10 patients with baseline mrTDs demonstrated regression—complete in 60% and significant in 40%. This aligns with a systematic review by Lord et al., which noted that although the prevalence of TDs after NACRT remains similar to untreated cases, most treated TDs represent responders and may reflect the biological aggressiveness of the primary tumor.²⁷ Nagtegaal et al. demonstrated that TDs independently predict distant metastasis and reduce disease-free survival, particularly liver metastasis.¹⁴ Ale Ali et al. reviewed the imaging and pathological correlates of TDs and highlighted their strong association with EMVI, supporting a common vascular origin.²⁸

The overall AJCC prognostic-group migration observed in our cohort (Stuart–Maxwell $\chi^2 = 25.04$; $p < 0.001$), with 21.2% achieving group I (ypT0–2 N0) and 82% showing at least one-stage downstaging, further confirms the efficacy of long-course NACRT. Feeney et al. summarized the evolution of neoadjuvant therapy in rectal cancer and emphasized that MRI-based restaging is now indispensable for identifying candidates for organ-preserving strategies such as watch-and-wait.²⁹

Several implications arise from our findings. First, mrEMVI and TDs should be routinely reported at both baseline and restaging MRI. Structured MRI reporting templates, such as those proposed by the ESGAR consensus and adopted by MERCURY, improve interobserver agreement.^{11,22} Second, the mr-vTRG offers a simple, reproducible five-point score that can be integrated into standard restaging reports and used for clinical decision-making. Third, patients with mr-vTRG 4–5 or persistent TDs deserve enrolment into trials evaluating TNT or additional chemotherapy, since existing evidence suggests they harbour occult micrometastatic disease refractory to standard CRT.^{15,18,26} Finally, the presence of regressing EMVI/TDs on restaging MRI may support consideration of organ-preservation approaches in selected patients, although longer follow-up and pathological correlation are needed before such an approach becomes standard.

Our study has several limitations. First, the small sample size limits the power for subgroup analyses, and only one patient exhibited an mr-vTRG 4 response, precluding

meaningful outcome analysis for poor responders. Second, we did not incorporate pathological correlation for EMVI and TD status, which would have added a gold-standard comparator; histopathology remains subject to inter-observer variability, but elastin staining, as recommended by Kirsch et al., substantially improves detection.³⁰ Third, the follow-up duration was insufficient to compute disease-free or overall survival, which are the ultimate outcomes of interest. Fourth, all patients received standard long-course CRT with capecitabine; the effect of intensified regimens such as short-course radiotherapy with consolidation chemotherapy (RAPIDO)²⁵ or FOLFIRINOX-based induction (PRODIGE-23)²⁶ on mr-vTRG could not be evaluated. Finally, single-institution data may not reflect broader Indian practice patterns.

Despite these limitations, our findings add to a growing body of prospective evidence that mrEMVI and mrTDs are dynamic imaging biomarkers whose response to NACRT can be quantified reliably using the mr-vTRG. This information can be readily incorporated into multidisciplinary decision-making without additional cost or invasive investigation.

CONCLUSION

MRI-detected EMVI and tumor deposits are important adverse prognostic features in locally advanced rectal cancer, present in 42.4% and 30.3% of cT3/cT4 patients, respectively, in our cohort. Neoadjuvant chemo-radiotherapy with 50.4 Gy in 28 fractions and concurrent capecitabine produces statistically significant regression of the primary tumor, mesorectal nodes, mrEMVI and mrTDs, together with substantial migration of AJCC prognostic groups. The mr-vTRG score is a simple, reproducible tool for grading mrEMVI response on restaging MRI and identifying poor venous responders (mr-vTRG 4–5), who represent a high-risk group that may benefit from treatment intensification through total neoadjuvant therapy or additional systemic chemotherapy. Good responders (mr-vTRG 1–3) may in turn be candidates for organ-preservation strategies. We recommend routine MRI evaluation of EMVI and TDs both at baseline and at restaging, and prospective incorporation of the mr-vTRG into standard reporting and clinical decision-making pathways for locally advanced rectal cancer.

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