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ORIGINAL ARTICLE

Can CRM Status on MRI Predict Survival in Rectal Cancers: Experience from the Indian Subcontinent

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Abstract

To determine the role of MRI as a predictor of circumferential resection margin (CRM) involvement. To study the impact of CRM status on MRI on recurrence and survival, in correlation with pathology. Analysis of a prospective database was performed over a period of 1 year. All patients with adenocarcinoma of rectum were included in the study. The MRI at presentation for all patients irrespective of stage (MRIT), pre-NACTRT MRI (MRI_1) for patients with locally advanced tumours, and post-NACTRT MRI (MRI_2) of these patients were analysed separately. The status of CRM on MRI was compared to that on histopathology and as a predictor of recurrence and survival. Two hundred twenty-one patients were included with a median follow-up 30 months. Sensitivity, specificity, positive predictive value, negative predictive value (NPV) and accuracy were 50%, 65.46%, 5.63%, 96.95% and 64.85% for MRIT; 50%, 55.32%, 5.97%, 95.12% and 55.03% for MRI1; and 77.78%, 63.29%, 10.77%, 98.04% and 64.07% for MRI2, respectively. On multivariate analysis, pathological positive margin alone predicted a poor overall survival (OS) whereas involved CRM on pathology and MRIT predicted poorer disease-free survival (DFS) and local recurrence. Pre-treatment and post-treatment MRI scans have a moderate sensitivity, specificity and accuracy and a high negative predictive value to predict CRM status on pathology. Pathological CRM status is the only factor to impact OS, DFS and LR on multivariate analysis. CRM status on MRI at presentation (MRI_T) does impact DFS and local recurrence but not OS.

Keywords Circumferential resection margin (CRM) · MRI · Adenocarcinoma

Introduction

Rectal cancer is presently the third most common cancer worldwide and is the fourth leading cause of cancer-related death [1]. The last two decades have seen a paradigm shift in the management of rectal carcinoma and a reduction in mortality rates [2]. Local recurrence (LR) rates after surgery for rectal carcinoma traditionally varied from 3 to 30% in the 1980s [3, 4]. The concept of total mesorectal excision (TME) to achieve a negative pathological circumferential resection margin (CRM) reduced these to less than 10% [5–7]. Neoadjuvant therapy trials have demonstrated better disease-free survival (DFS) and sphincter preservation rates as compared to adjuvant treatment approach. Neoadjuvant chemoradiation therapy (NACTRT) has become the standard approach for locally advanced rectal adenocarcinoma [8, 9]. Thus,

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accurate pre-operative staging to decide on treatment approach is of utmost importance. Though not conclusively demonstrated, both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) (for early disease) are fairly accurate for pre-treatment staging of rectal cancer [10–13].

Pathological CRM status has emerged as the most significant prognostic factor determining recurrence and survival of patients with rectal adenocarcinoma. Initially proven by studies from Heald and Quirke, numerous subsequent reports have confirmed the same [3, 4, 14–16]. However, it can be determined only once the surgery has been performed. MRI accurately predicts CRM positivity in the pre-treatment setting [11, 17–19]. Some reports have suggested a lower accuracy of MRI to determine the T- and N-stage of tumours after neoadjuvant treatment[20, 21]. On the other hand, MRI has stood its place in being a strong predictor of CRM status even after neoadjuvant therapy [21–26]. Recent studies have also looked into CRM status on MRI as a predictor of LR and survival [27–29].

We confirm the role of MRI to predict the CRM status taking pathological CRM as the gold standard. We also report on the CRM status on MRI as a predictor of LR and survival.

Materials and Methods

A prospective database of all patients with carcinoma rectum was analysed. Patients diagnosed with adenocarcinoma of rectum from 1 July 2013 to 30 June 2014 were included in the study. Other inclusion criteria were distance of the tumour within 15 cm from anal verge, treatment with a curative intent, locally resectable cancers upfront or after neoadjuvant treatment, and at least one MRI scan done as a part of workup. Patients with a past history of cancer at any site, patients with a locally advanced inoperable cancer or metastatic disease treated with a palliative intent were excluded from the analysis. At initial presentation, clinical examination, serum carcinoembryonic antigen (CEA) levels and MRI of lower abdomen and pelvis were performed for all patients.

High-resolution multiplanar MRI using T2-weighted images was performed in three orthogonal planes—sagittal, axial and coronal with respect to the tumour. In low rectal tumours, coronal and axial sections were obtained parallel and perpendicular to the anal canal. Rectal contrast, fat-suppressed sequences and post-gadolinium images were not used. Both

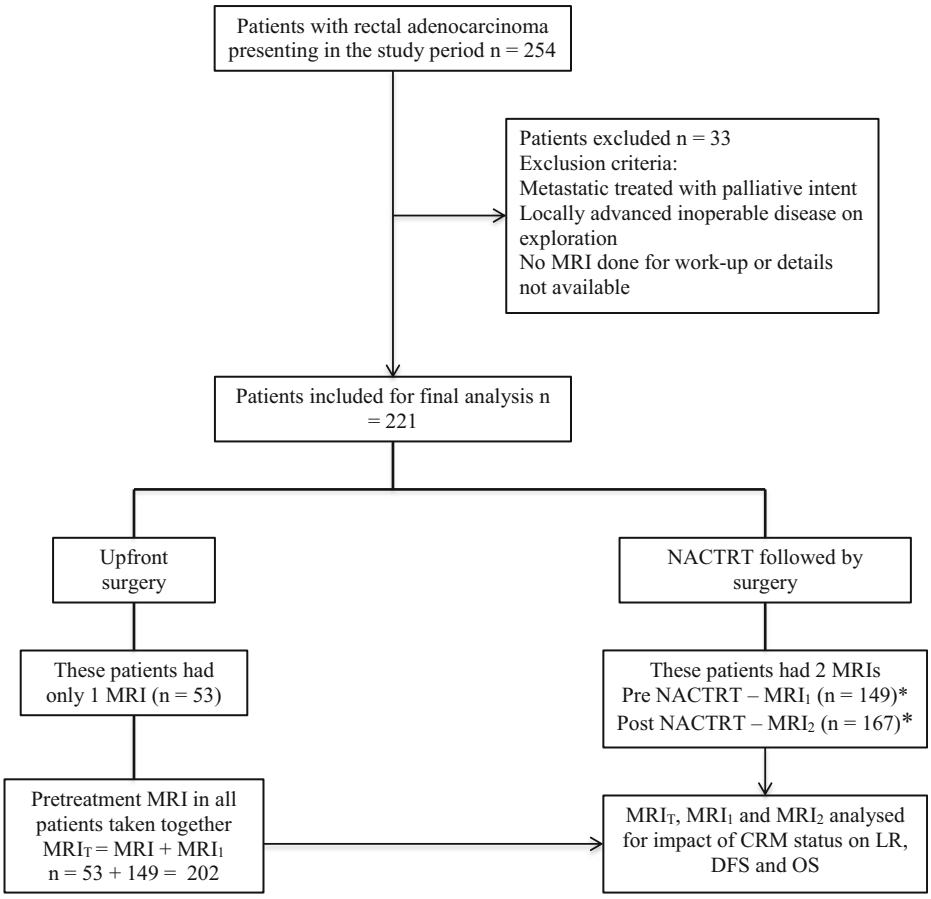

Fig. 1 Study flowchart

*Patients had at least one MRI and thus were included in the study

small field-of-view (FOV) and large FOV axial T2-weighted sections were obtained to evaluate the primary tumour and nodes. A multidetector contrast-enhanced computed tomography scan of the thorax, abdomen and pelvis was done to stage for distant metastases.

Consultant radiologists from the Gastrointestinal Disease Management Group reported the MRI scans. The reporting radiologists had an experience of reporting at least 50 rectal MRI scans. A positive CRM was defined as involvement of mesorectal fascia or tumour within 1 mm of the mesorectal fascia for upper and mid-rectal tumours. Disease involving or within 1 mm of inter-sphincteric plane or levator ani muscle was considered as involved CRM for low rectal tumours. Nodes measuring more than 9 mm in short axes were considered to be positive. Smaller nodes were evaluated for three characteristics—round shape, irregular border and heterogeneous signal intensity. Nodes measuring 5–9 mm with any two criteria and nodes measuring less than 5 mm with all three features were considered to be positive (Society of Abdominal Radiology criteria) [30].

A multidisciplinary tumour board involving a surgical oncologist, medical oncologist, radiation oncologist and a radiologist took further treatment decisions. Any disparity between the reporting radiologist and the tumour board decision was discussed, and the report was updated accordingly. Patients were treated either with upfront surgery or NACTRT. Indications of NACTRT included T-stage of T3 or T4, node positive disease or an involved CRM on MRI. NACTRT protocol included radiation dosage of 50Gy in 25 fractions over 5 weeks along with concurrent oral capecitabine (850 mg/m^2 twice daily from days 1–14 and 22–35). After 6–8 weeks of completion of NACTRT, a reassessment MRI was performed. Further treatment decision regarding surgery versus additional chemotherapy was taken at the tumour board meeting.

After treatment completion, patients were followed-up every 3 months for the first 2 years, then every 6 months for up to 5 years post-treatment and annually thereafter. A clinical examination and serum CEA levels were done at each follow-up. Further imaging was performed if a patient had symptoms suspicious of recurrence, increased or rising CEA levels, a suspicious finding on clinical examination, or annually. Recurrence was defined as biopsy-proven disease present locally or at a distant site. Anastomotic recurrences were also categorised as LR, and all other recurrences were considered to be distant.

Demographic details, tumour characteristics, surgical details, histopathology reports and details of adjuvant treatment were noted for each patient. The outermost resection margin was taken as the pathological CRM. This would be the mesorectal fascia in patients undergoing a TME but could be different than that defined on MRI for patients with more extensive resections. For analysis, MRI scans done for patients at presentation were labelled as MRI_T. This included all patients irrespective of further treatment received. Patients who were treated with NACTRT had two MRI scans. In this subset of patients, the MRI at the presentation was labelled as MRI_1 and the reassessment MRI after NACTRT was labelled as MRI_2. Thus, MRI_1 represented a subset of MRI_T with locally advanced tumours treated with NACTRT (Fig. 1). All sets of MRI scans were analysed separately for prediction of CRM involvement and for the effect of CRM status on MRI on LR and survival rates. The CRM status on pathology after resection was taken as the gold standard.

Table 1 Patient demography and treatment details

Factor	Number
Total patients (*n*)	221
Mean age (years)	48
Male:female	1.9:1
Recurrence rate	59/221 (26.7%)
Recurrence type	Number of cases
Local	8
Local + distant	6
Distant	45
Total	59
Total local recurrences	14/221 (6.33%)
Death rate	32/221 (14.5%)
NACTRT	
Yes	168 (76%)
No	53 (24%)
Total	221
T-stage	
Tis	2
T1	2
T2	46
T3	156
T4	15
Total	221
Nodal status	
Negative	54
Positive	167
Total	221
Surgical procedure	
AR	107
TPC	3
ISR	38
APR	39
Prone APR	20
Total pelvic exenteration	12
Transanal excision	2
Total	221

AR anterior resection, *TPC* total proctocolectomy, *ISR* intersphincteric resection, *APR* abdominoperineal resection

Table 2 CRM positivity on MRI_T, MRI_1, MRI_2 and pathology

CRM positivity			
CRM positivity at	Negative	Positive	Total
MRI_T	131	71 (35%)	202
MRI_1	82	67 (45%)	149
MRI_2	102	65 (39%)	167
Pathology	213	9 (4.1%)	221

CRM circumferential resection margin

Apart from CRM status on MRI and pathology, other factors studied to predict LR, DFS and overall survival (OS) included age and sex of the patients, body mass index (BMI), tumour grade, pre-treatment T- and N-stage, and effect of NACTRT.

Statistical Analysis

The demographic, clinical and disease-related variables were presented as frequency (percentage), mean or median as appropriate. Categorical variables were analysed using the chi-square test or Fischer's exact test (for binary variables) with a p value of less than 0.05 considered to be statistically significant. Survival analysis was done using the Kaplan–Meier method, and groups were compared using the log-rank test. Cox regression method was used for multivariate analysis. IBM SPSS version 24 was used for data management and analysis.

Results

A total of 254 patients were diagnosed with rectal adenocarcinoma in the study period. After excluding patients with inoperable or metastatic disease, those treated with palliative intent due to other factors and those who did not have at least a single MRI for workup, a total of 221 patients were included in the study. Of note, 19/168 patients treated with NACTRT did not have the baseline MRI (MRI_1) but did have the MRI_2 (post-NACTRT) available for evaluation and were included in the analysis (Fig. 1).

The mean age of the cohort was 48 years with a male to female ratio of 1.9:1. There were 168 (76%) of the patients that received NACTRT. Tumour characteristics and treatment details are summarised in Table 1. CRM positivity rate on MRI_T, MRI_1, MRI_2 and pathology was 35%, 45%, 39% and 4.1%, respectively (Table 2). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy to detect CRM positivity for MRI_T were 50%, 65.46%, 5.63%, 96.95% and 64.85% (95% CI 0.92–0.99), respectively. The corresponding values for MRI_1 were 50%, 55.32%, 5.97%, 95.12% and 55.03% (95% CI 0.88–0.98) and for MRI2 were 77.78%, 63.29%, 10.77%, 98.04% and 64.07% (95% CI 0.93–0.99), respectively.

Median follow-up was 30 months. Predicted OS at 1 year and 3 years was 98.1% and 81.2%, respectively. Corresponding values for DFS were 94.2% and 68.1%, respectively (Fig. 2). CRM positivity on MRI_T, MRI_1 and pathology had a significant impact on OS, DFS and local LR on univariate analysis (Fig. 3). MRI_2 did not impact OS, DFS or LR. Of the other factors, grade of tumour (p = 0.020), sex (p = 0.039) and pre-operative T-stage (p = 0.016) had a significant impact on OS on univariate analysis. Tumour grade had a significant impact on DFS as well (p = 0.013). On multivariate analysis, CRM status on pathology was the only factor to have a significant impact on OS whereas CRM positivity on MRI_T and pathology had a significant impact on DFS and LR (Table 3).

Discussion

A positive CRM on pathology after resection has been observed as one of the most important prognostic factors for

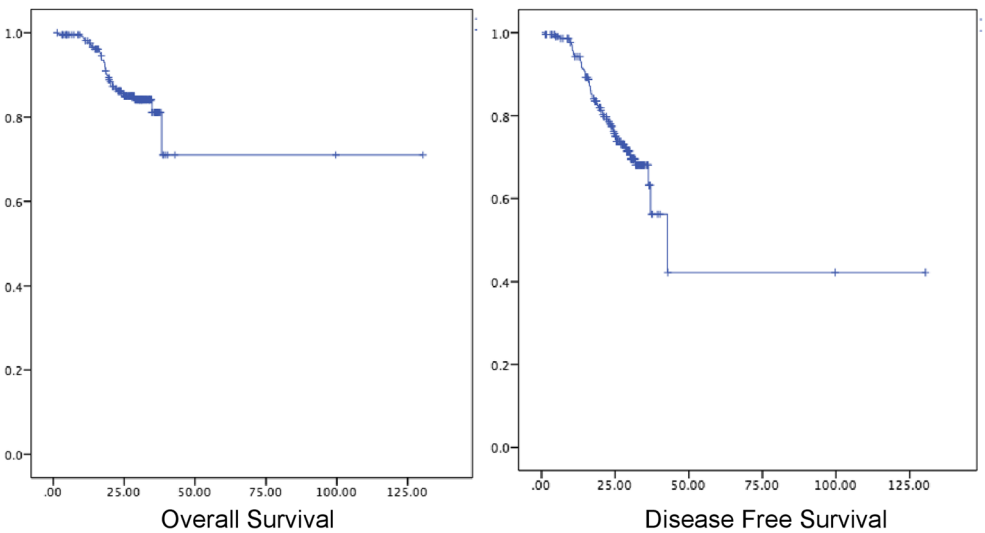

Fig. 2 Overall survival (OS) and disease-free survival (DFS)

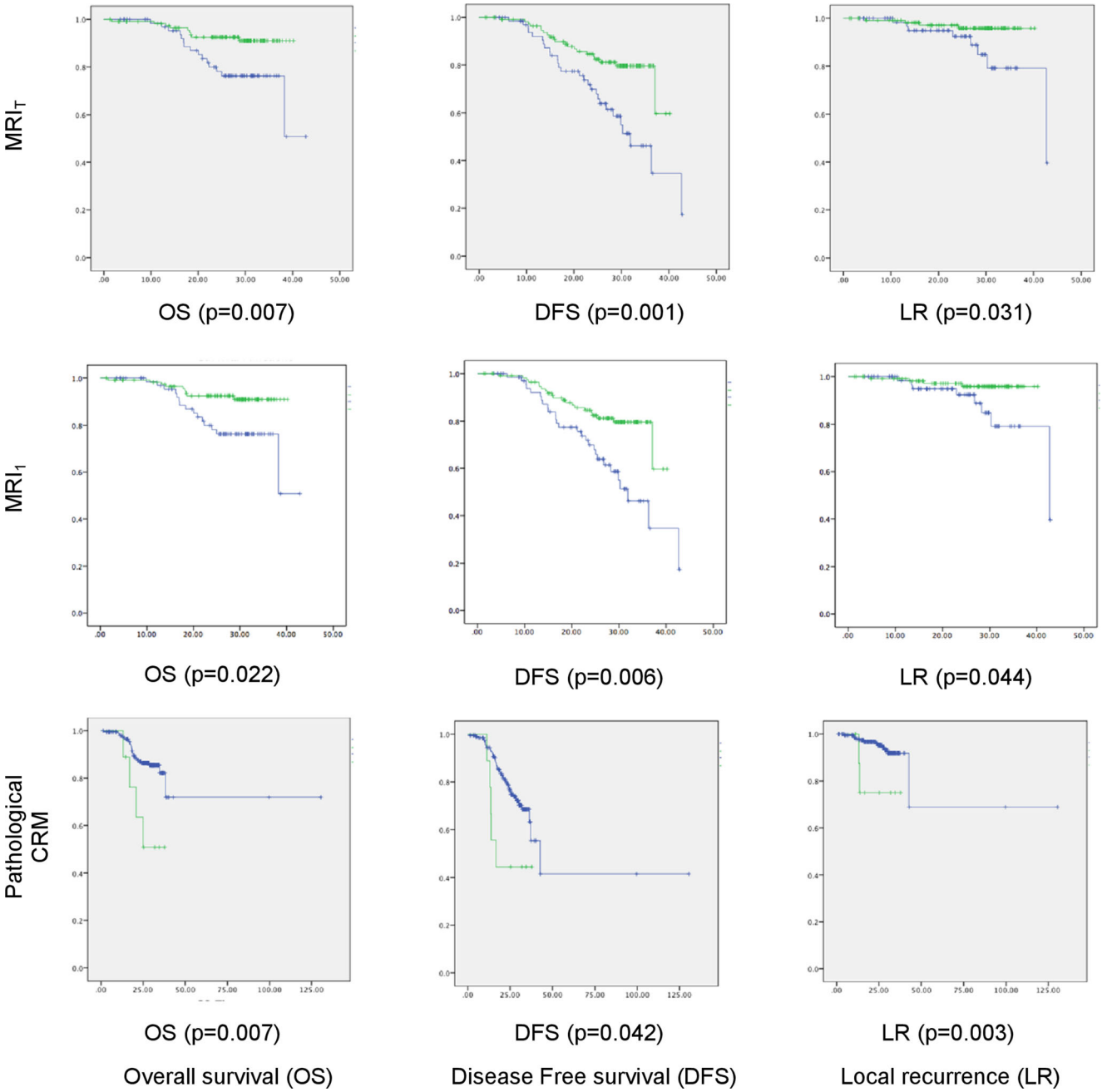

Fig. 3 Impact of CRM status on MRI T, MRI 1 and pathology on OS, DFS and LR

rectal carcinoma [14–16]. MRI has been shown to be a good modality to predict the involvement of CRM and for tumour staging pre-operatively [13, 17–19]. A meta-analysis of 21 studies by Al-Sukhni et al. concluded that MRI is highly specific to rule out CRM involvement and has moderate sensitivity for the same [13]. The accuracy of MRI after neoadjuvant treatment is shown to be slightly lower as compared to pre-treatment MRI. However, MRI remains a good predictor of CRM status, especially with regard to NPV and specificity [13, 21–26]. Systemic meta-analyses conclude MRI to be a good modality to exclude CRM involvement with the possibility of under-staging as well as over-staging for T and N status [21, 24, 26]. In our series, we had a reasonably high NPV and moderate sensitivity, specificity and accuracy for MRI_T, MRI_1 and MRI_2. The PPV for MRI_T, MRI_1 and MRI_2 was 5.63%, 5.97% and 10.77%, respectively. These values may appear unacceptably low. However, we often modified our surgical approach in patients with CRM

Table 3 Univariate analysis with impact on OS, DFS and LR

Factor	*p* value		
	Impact on OS	Impact on DFS	Impact on LR
MRI_T	0.007	0.001	0.031
MRI_1	0.022	0.006	0.044
MRI_2	0.154	0.096	0.151
Path CRM	0.007	0.042	0.03
Grade	0.020	0.013	0.113
Age	0.297	0.518	0.726
Sex	0.039	0.402	0.95
BMI	0.074	0.181	0.072
Pre-op T	0.016	0.271	0.268
Pre-op N	0.374	0.675	0.263
NACTRT	0.969	0.545	0.178

Path CRM pathological circumferential resection margin, *BMI* body mass index, *NACTRT* neoadjuvant chemoradiation

positivity on MRI to dissect beyond the mesorectal fascia. This would entail taking a shave of the prostate or a part of the levator ani muscle in order to achieve a negative pathological CRM. As the PPV was calculated taking pathological CRM as gold standard, this would eventually reflect as a low PPV for CRM positivity on MRI. This indicates that MRI has a potentially very important role in planning appropriately aggressive surgery in locally advanced cases in order to achieve a pathological negative CRM.

Few studies have reported on the impact of CRM status on MRI on LR and survival, with no reports from the Indian subcontinent. In a study of 115 rectal cancer patients, Martling et al. reported on the impact of post-neoadjuvant treatment MRI on survival and recurrence. Patients with a positive CRM on post-treatment MRI had a poor recurrence-free survival. However, the difference was due to the incidence of distant metastases in the two groups, LR and OS rates being similar. In their study, 61% of the patients had early rectal cancers and 70% of the patients received neoadjuvant treatment in the form of short-course radiotherapy. CRM status on MRI did not affect OS [28]. Weider et al. analysed 68 patients with locally advanced rectal adenocarcinoma treated with NACTRT followed by surgery. They found pre-treatment negative CRM status on MRI to be a significant predictor of LR on multivariate analysis, but not affecting OS [29]. We cannot explain the difference in outcome in comparison to our results, with CRM status on MRI_1 (pre-treatment MRI in locally advanced cancers) affecting DFS and not LR or OS. However, our study has a larger sample size.

Taylor et al. from the MERCURY (Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study) group have reported survival outcomes of 374 patients (58% of them were 65 years or older) with rectal cancer based on CRM status on MRI and concluded that it was the only pre-operative staging parameter to impact OS, DFS and LR on multivariate analysis [27]. Fifty-eight percent of the patients in their study were treated by upfront surgery. This contrasts with the patients in our series, 76% of whom received NACTRT. The neoadjuvant protocol in MERCURY study varied among the 11 centres included, from NACTRT, neoadjuvant radiation or short-course radiotherapy. Importantly, in patients treated with neoadjuvant protocols, only the post-treatment MRI was used for analysis. Thus, the cohort of MRI scans analysed included a mixture of pre-treatment (58%) and post-treatment (42%) scans. In contrast to the MERCURY study report, the pre- and post-treatment MRI scans in our study were analysed separately, and the neoadjuvant treatment protocols were uniform. Also, our series is representative of patients in the Indian subcontinent where a higher proportion of younger patients present with advanced tumours. Of our patients, 88% were below 65 years, with 58% below 55 years of age.

About three fourths of the patients diagnosed with adenocarcinoma of rectum in the Indian subcontinent present at a relatively younger age, with high-grade disease and locally advanced stage. These are markers of poor prognosis. The role of CRM status on MRI to predict recurrence and survival in this cohort of patients needs to be reported. To our knowledge, this study is the first such report from the Indian subcontinent. The post-treatment MRI (MRI_2) helped to modify the surgical approach and to adapt a more radical approach in patients deemed to have a positive CRM on MRI. The authors appreciate that this was not the aim of the study but is an important outcome of the analysis and needs further assessment. Also, the post-treatment MRI scan (MRI_2) helps us to evaluate the treatment response to neoadjuvant chemoradiation therapy. In patients with a stable or progressive disease, further consolidation chemotherapy with salvage surgery can be considered [31]. A pathological CRM positivity rate of 4.1% in the operated patients is acceptable.

Our study does have some limitations. Although it is an analysis of a prospectively maintained database, there is a potential of referral bias and the patient population may not be representative of the general population as these are patients referred to a tertiary care cancer centre. Patients with inoperable locally advanced tumours were not included in the analysis, as they did not have surgery as part of their treatment and thus a pathological CRM was not available. About 76% of the patients with operable disease had locally advanced cancers. Role of MRI in early rectal cancers should probably be analysed separately. However, this could not be done as the sample size was small and further analysis on the same is planned. The definition of pathological CRM and that on MRI would have been different for patients undergoing more extensive resections. These patients could not be excluded from the analysis so as to avoid a selection bias.

Conclusion

Pre-treatment and post-treatment MRI scans have a moderate sensitivity, specificity and accuracy, and a high negative predictive value to predict CRM status on pathology. Pathological CRM status is the only factor to impact OS, DFS and local recurrence on multivariate analysis. CRM status on MRI at presentation (MRI_T) does impact DFS and local recurrence but not OS.

Compliance with Ethical Standards

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

Informed Consent Informed consent was obtained from all individual participants in the study.

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