Article published online: 2025-02-14

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Review Article

Response Assessment after Neoadjuvant Chemoradiotherapy in Rectal Cancer

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J Gastrointestinal Abdominal Radiol ISGAR

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Abstract

Management of locally advanced rectal cancer is complex, and magnetic resonance imaging (MRI) findings play a central role in treatment decisions. While neoadjuvant chemoradiotherapy significantly improved local recurrence rates, newer treatment modalities, such as total neoadjuvant chemotherapy, improved distant control. They significantly improved pathological complete response rates, enabling organ preservation in more patients. MRI is the best imaging modality to assess treatment response. MRI aids in assessing operability, predicts surgical outcomes following neoadjuvant treatment, and aids in identifying patients' eligible for organ preservation and their follow-up. In this review, we discuss imaging techniques and interpretation of rectal cancer MRI following neoadjuvant treatment, provide a structured reporting template for response assessment MRI, and detail how imaging findings influence treatment decisions.

Keywords
- MRI
- rectal cancer
- MDT
- restaging
- neoadjuvant chemoradiotherapy

Introduction

The management of locally advanced rectal cancer (stage III and above) has rapidly evolved since the first description of total mesorectal excision (TME) in 1986.[1] We saw a shift from traditional surgical management to neoadjuvant chemoradiotherapy (NACRT) and now to total neoadjuvant therapy (TNT). The complete response rates have increased from 10 to 15% to around 50% with improvements in the neoadjuvant treatment regimens.[2–5] Nonoperative management (NOM) of rectal adenocarcinoma is increasingly accepted as a standard practice. Rectal cancer magnetic resonance imaging (MRI) plays a pivotal role in assessing response to different neoadjuvant treatment regimens. In those with complete response (CR) or near-complete response (nCR), MRI aids in identifying patients eligible for NOM and their subsequent follow-up.[5,6] In patients with incomplete response (iCR), MRI-based response assessment aids in determining the correct surgical strategy and the prognosis. It accurately identifies patients who have progressed on neoadjuvant treatment and, thus, would need a change in the treatment intent.[6–8] While staging MRI has firmly established its role in the management of rectal cancer, regular use of MRI for response assessment is not a routine practice and comes with challenges. This review article describes the different neoadjuvant treatment regimens, patients eligible for these treatments, the MRI imaging protocol for rectal cancer response assessment and its interpretation, and the response assessment criteria and standard terminologies. We also describe a few common problems and solutions while scanning and interpreting response assessment MRI in rectal cancer patients.

DOI https://doi.org/10.1055/s-0045-1802595.
ISSN 2581-9933.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Types of Neoadjuvant Therapy

Neoadjuvant treatment for locally advanced rectal cancer has been classically done using two strategies: (1) short-course radiotherapy (SCRT) with 25 Gy given in five fractions or (2) long-course chemoradiotherapy (LCRT) with 45 to 50 Gy given in 25 to 28 fractions with concurrent low-dose fluoropyrimidine-based chemotherapy, which functions as a radiosensitizer.[9] Although abundant data supports both regimens before surgery, only a few studies have investigated the superiority of one over the other.[10,11] Though there were no statistically significant differences in the R0 resection rates, local recurrence rates, systemic relapse rates, or overall survival (OR) in either of these strategies, there was better local tumor downstaging with LCRT with higher pathological complete response rates.[12]

A further development in neoadjuvant treatment is TNT.[1,9] With TNT, a full-dose chemotherapy is delivered preoperatively, either with SCRT or LCRT. Chemotherapy can be delivered before (induction chemotherapy) or after (consolidation chemotherapy) irradiation. The chemotherapy regimens used in TNT are FOLFIRINOX (folinic acid, fluorouracil, irinotecan hydrochloride, and oxaliplatin), CAPOX (capecitabine and oxaliplatin), or FOLFOX (fluorouracil, leucovorin, and oxaliplatin). TNT appears to offer additional benefits to SCRT or LCRT, both in terms of the higher rates of pathological CR and in reducing the risks of systemic relapse and yet did not affect the 3-year OR rates.[13–16]

Several recent studies have investigated a deescalation of neoadjuvant therapy, whereby neoadjuvant chemotherapy is used as a single-agent modality. The chemotherapeutic regimen used in this strategy is FOLFOX or CAPOX. Proponents for this strategy argue that the low rates of local recurrence seen after TME have reduced the potential benefit of radiotherapy (RT); hence, systemic chemotherapy alone without RT will reduce systemic relapse and reduce RT-related toxicities in patients whose cancers do not require downstaging before TME.[17–22] However, this strategy remains unpopular worldwide and is unsupported by data on long-term survival outcomes. With all these options available for neoadjuvant treatment, there are different approaches among various expert groups about who should receive which type of neoadjuvant treatment. The summary of various neoadjuvant therapies available and the European Society for Medical Oncology guidelines for its use are shown in ►**Table 1**.

Management of Rectal Cancer Following Neoadjuvant Therapy

Following completion of neoadjuvant treatment, the patients are evaluated, and the tumor will be restaged to plan subsequent management. Digital rectal examination (DRE), endoscopy, and pelvic MRI are recommended for evaluation and local tumor restaging.[2] The terminologies and abbreviations recommended for response assessment include cCR for a clinical complete response, nCR, and iCR.[6] Patients are advised surgery or NOM depending on the response to neoadjuvant treatment. TME or beyond TME surgery is a standard management option for patients with iCR, yet completely resectable disease. NOM, also referred to as organ-preserving strategy, watch and wait, or wait and see, is an emerging and attractive option in the care of patients with rectal cancer, aimed at improving quality of life without over- or undertreatment in patients with cCR.[23,24] The success of NOM depends on accurate restaging and identification of cCR, appropriate patient selection using triple assessment (MRI + DRE + endoscopy), and very stringent follow-up protocol. The term "*regrowth*" describes local recurrence in the bowel wall following a period of cCR in a patient on NOM. The local regrowth rate among rectal cancer patients managed with NOM following cCR was 25.2%, with the majority (88%) recurring within the first 2 years and 97% recurring in the bowel wall.[25] Thus, patients on NOM must be on a strict surveillance protocol.

Surveillance Protocol for Patients on Watch and Wait

Surveillance protocol for patients on NOM includes triple assessment every 3 months for the first 2 years and then every 6 months for 3 to 5 years after treatment. Along with MRI, computed tomography (CT) of the chest and abdomen is also recommended every 6 months for the first 2 years and then annually for 3 to 5 years. Regrowth is treated with definitive local treatments such as surgery or a combination of RT with local excision.

►**Fig. 1** shows the management guidelines following neoadjuvant therapy.

Table 1 Neoadjuvant treatment strategies for rectal cancer

Neoadjuvant regimen	Regimen details	ESMO guideline for use
Short-course radiotherapy (SCRT)	25 Gy RT in five fractions	cT3c/d or very low, levators not threatened, MRF clear Or cT3c/d mid rectum, cN1-N2, EMVI+
Long-course chemoradiotherapy (LCRT)	45–50 Gy RT in 25–28 fractions with concurrent low-dose fluoropyrimidine (radiosensitizer)	
Total neoadjuvant therapy (TNT)	Chemotherapy (FOLFIRINOX or CAPOX or FOLFOX) + RT (SCRT or LCRT).	cT3 cancers with MRF +, cT4 cancers, and those with positive lateral lymph nodes
Chemotherapy only	CAPOX or FOLFOX	Not recommended by ESMO

Abbreviations: CAPOX, capecitabine and oxaliplatin; EMVI, extramural vascular invasion; ESMO, European Society for Medical Oncology; FOLFIRINIX, folinic acid, fluorouracil, irinotecan hydrochloride and oxaliplatin; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; MRF, mesorectal fascia; RT, radiotherapy.

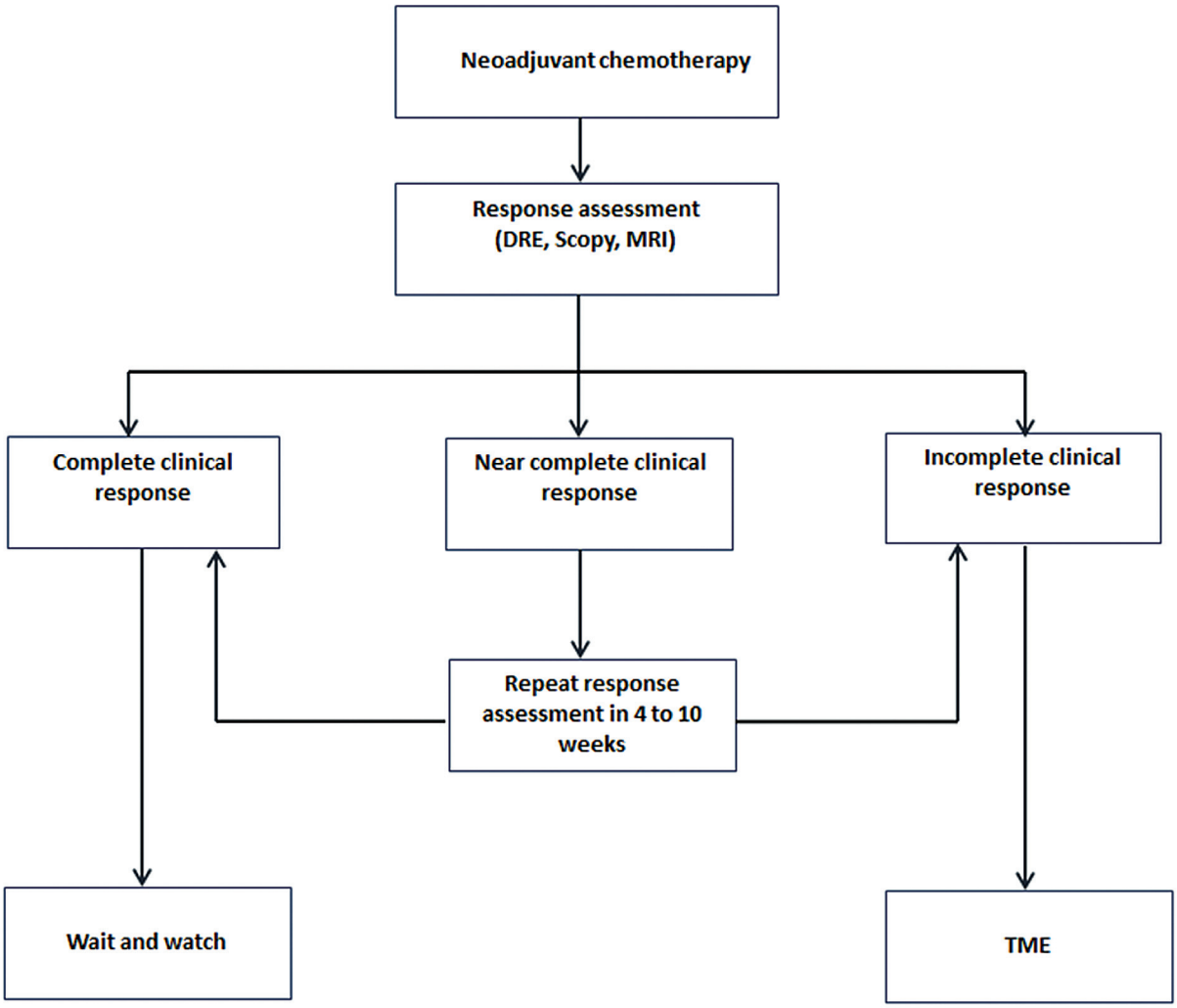

Fig. 1 Management guidelines following neoadjuvant therapy. DRE, digital rectal evaluation; MRI, magnetic resonance imaging; TME, total mesorectal excision.

Timing of Response Assessment MRI after Neoadjuvant Therapy for Rectal Cancer

The timing for restaging MRI is typically 6 to 8 weeks after the completion of NACRT but varies widely based on institutional protocols and guidelines. Rectal cancer, however, continues to respond till 12 to 14 weeks after NACRT.[26,27] The optimal response assessment time point suggested by international consensus recommendations to determine cCR is 12 to 14 weeks for LCRT and 24 weeks after TNT.[23,28] In patients with an nCR at the initial assessment, repeat imaging is recommended in 4 to 10 weeks to look for cCR.

MRI Technique and Image Acquisition

Bowel preparation using microenema to clear rectal contents and routine advice to empty bowel and bladder before rectal cancer MRI is highly recommended to minimize contents.[29] A partially distended or empty bladder is helpful in better appreciating the mesorectal fascia (MRF). The use of spasmolytics is optional and can be helpful for reassessing upper rectal cancers. Administering intravenous contrast is not routinely recommended. The technologist's focus must be guided to the location of rectal cancer on baseline MRI. The imaging protocol is otherwise like the staging MRI. The protocol used is a standard 3-mm section T2-weighted high-resolution (HR) MRI of the pelvis with no interslice gap, with a voxel size of 1 mm^3 or less, acquired in sagittal, oblique axial (perpendicular to the rectum), and oblique coronal (parallel to the rectum) planes. An axial small field of view diffusion-weighted imaging (DWI) is acquired using respiratory-triggered, single-shot echo planar imaging with *b*-values of 0 and 800 to 1,000 mm^2/s in the same plane as oblique axial T2 HR images, and the apparent diffusion coefficient map is automatically generated.[30,31] Detailed MRI parameters for 1.5T and 3T MRI magnets are outlined in ►**Table 2**.

Interpretation of Response Assessment or Restaging MRI in Rectal Cancer

The key to accurate response estimation after neoadjuvant treatment in rectal cancer patients is a systematic approach to the interpretation of response assessment MRI, factoring in the histopathological type of rectal cancer, baseline

Table 2 Technical parameters of restaging MRI in rectal cancer patients

Scan parameter	3T		1.5T	
	T2 HR	DWI	T2 HR	DWI
Repetition time (ms)	3,500	3,750	4,000	3,000
Echo time (ms)	90	75	105	61
Slice thickness (mm)	3	5	3	5
FOV (cm)	20	25	18–20	22
Matrix	368 × 290	128 × 116	325 × 50	128 × 116
Sensitivity encoding factor	2–2.5	1.7	2	1.9
Echo train length	25	1	12	1
No. of signal averages (NEX)	2–6	4–6	2–6	4–6
No. of slices	20–40	20–30	20–40	20–30
Acquisition time (min)	3–4	3–4	4–6	5
B value	–	0,400, 800–1000	–	0,400, 800–1000
Echo planar imaging factor	–	77	–	108
Fat-suppression technique	–	SPAIR	–	SPAIR

Abbreviations: DWI, diffusion-weighted imaging; HR, high-resolution; MRI, magnetic resonance imaging; SPAIR, Spectral Adiabatic Inversion Recovery.

Box 1 MDT checklist for interpreting response assessment MRI after neoadjuvant treatment in rectal cancer patients

1. Where was the rectal cancer at baseline?
2. What is the response to neoadjuvant treatment?
3. Is there disease progression? If so, is there a change in the intent of treatment?
4. What should be the surgical strategy to achieve negative surgical margins? TME versus beyond TME
5. If good response, is the patient eligible for watch and wait?
6. Is there tumor regrowth in a patient on watch and wait?
7. Are there imaging biomarkers which indicate an increased risk for local or distant recurrence?

imaging characteristics of rectal cancer, type of neoadjuvant treatment, and the time elapsed since the completion of neoadjuvant therapy. Taking note of the MRI image quality and attempting to document any artifacts that might limit the interpretation of MRI is also a helpful step. In the following section, we give an multidisciplinary team (MDT) checklist (►**Box 1**) and describe a systematic approach to interpreting response assessment MRI in rectal cancer patients.

Step 1: Review the Baseline MRI to Note the Imaging Characteristics of the Rectal Cancer at Presentation

The location of the tumor, the morphology, and the signal intensity of the rectal cancer on baseline MRI will influence the appearance of the tumor in the response assessment scan. Amidst the posttreatment edema and diffuse wall thickening (►**Fig. 2**), it is often challenging to identify the residual tumor without knowing where to look for it. Taking note of the location (high, mid, or low rectum) and the morphology (annular, semiannular, or polypoidal) of the rectal cancer at baseline will guide our review to the correct anatomical site in the rectum bearing the tumor. The signal intensity of rectal cancer on T2 and DWI at the baseline would dictate the usefulness of these sequences on response assessment MRI (►**Fig. 3**). For example, well and moderately

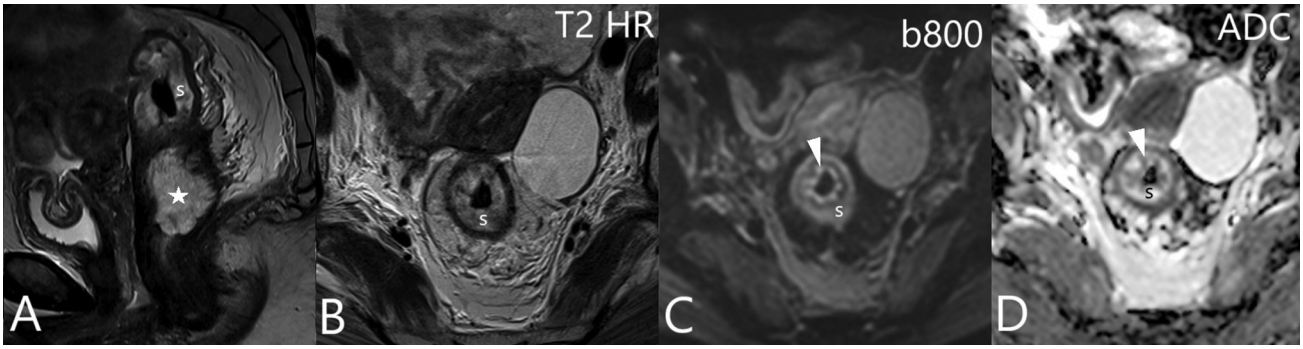

Fig. 2 Magnetic resonance imaging (MRI) following total neoadjuvant therapy (TNT) in a patient with mid-rectal cancer. (**A**) Sagittal and (**B**) axial T2 high-resolution (HR) MRI shows incomplete response with residual T2 hyperintense mid-rectal cancer (*) and extensive submucosal edema (marked "s"). (**C**) High *b*-value diffusion-weighted imaging (DWI) (b800) and (**D**) apparent diffusion coefficient (ADC) map shows the submucosa (s) with facilitated diffusion and mucosa (arrowhead) with restricted diffusion from mucosal necrosis.

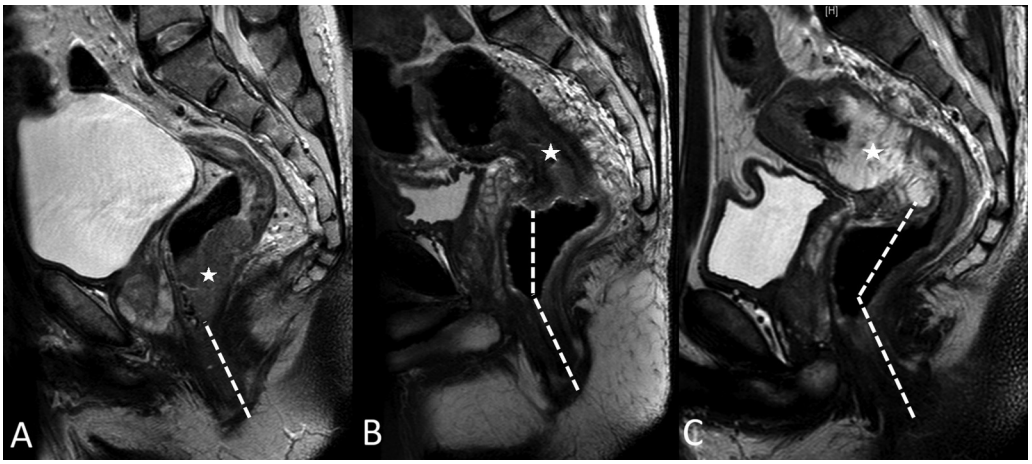

Fig. 3 Sagittal T2 high-resolution (HR) magnetic resonance imaging (MRI) in three different patients demonstrating signal intensity, location (dashed line from the anal verge), and morphology of rectal cancer (*) on baseline MRI. (**A**) Posterior semiannular intermediate signal intensity low rectal cancer (distal margin below 5 cm from the anal verge). (**B**) Annular T2 hypointense mid-rectal cancer (between 5 and 10 cm from the anal verge). (**C**) Annular hyperintense high rectal cancer (above 10 cm from the anal verge or above the peritoneal reflection).

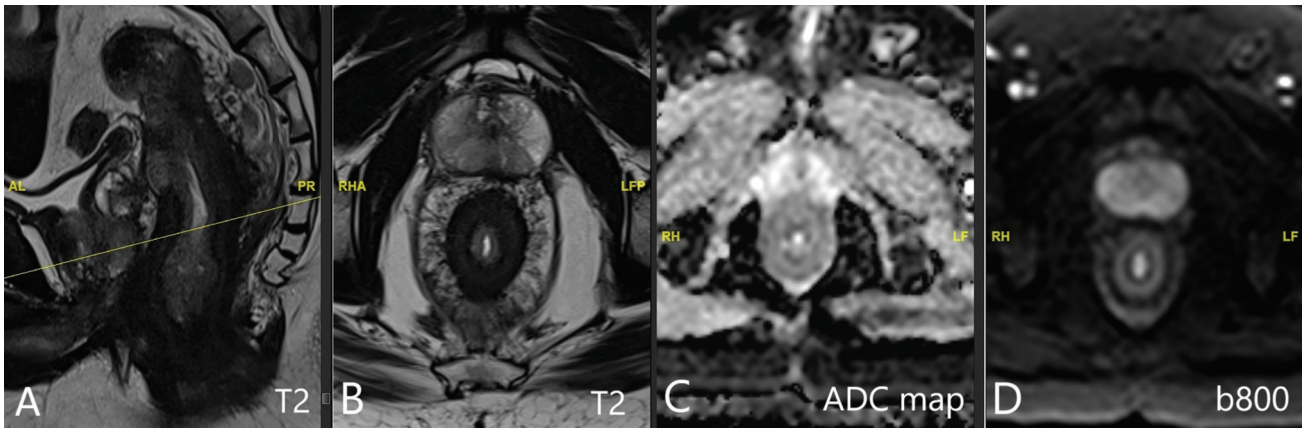

Fig. 4 Baseline magnetic resonance imaging (MRI) of a poorly differentiated rectal adenocarcinoma patient with signet ring cells. T2 high-resolution (HR) (**A**) sagittal and (**B**) axial MRI shows a long segment annular T2 hypointense rectal wall thickening with T2 hypointense stranding within the mesorectal fat and diffuse thickening of the mesorectal fascia. (**C**, **D**) Apparent diffusion coefficient (ADC) map and high *b*-value (b-800) diffusion-weighted imaging (DWI) show no restricted diffusion. Response assessment in these cancers is challenging since residual tumor and posttreatment fibrosis cannot be effectively differentiated on T2-weighted MRI, and these rectal cancers show no diffusion restriction.

differentiated rectal cancers appear T2 intermediate in signal intensity and show diffusion restriction. MRI-based response assessment on T2 and DWI is most accurate in these cancers. Rectal cancers that are T2 hyperintense or mixed in signal intensity are mucinous and show facilitated diffusion on DWI. Detecting cCR in these cancers is impossible unless there is a complete disappearance of the T2 hyperintense tumor and full restoration of rectal wall layers. Signet ring cell cancer and poorly differentiated carcinomas may either appear T2 markedly hypointense or mixed hyperintense and hypointense in signal and may not show diffusion restriction (►**Fig. 4**).[32]

Step 2: Document Response Based on T2 and DWI Appearance of Rectal Cancer in the Current Response Assessment MRI

MR Tumor Regression Grade

The MERCURY study group described the five-point MR tumor regression grade (mrTRG) for response assessment using T2 HR MRI. It was adapted from Dworak's pathological tumor regression grading system.[7] The interpretation of mrTRG on response assessment MRI requires us to compare the current images with the baseline T2 HR images to determine the proportion of the tumor replaced by T2 hypointense fibrosis and the proportion of residual intermediate signal intensity tumor (►**Table 3**).[33]

Complete response or mrTRG1, seen as complete normalization of the rectal wall or thin (1–2 mm) T2 hypointense mucosal scar (►**Fig. 5**), is rare. A more common morphological appearance of complete response is a variable thickness T2 hypointense mucosal and submucosal scar (►**Fig. 6**). Though highly specific, morphological appearances had very low sensitivity for identifying complete responses.[27,30] "Split scar sign" is a recently described morphological appearance for a complete response on T2 HR MRI, which carries a high pooled specificity of 92%, fair sensitivity of 62%, and substantial interobserver agreement ($k = 0.69$).[34–36] In a positive "split scar sign," the rectal wall at the site of the previous tumor

Table 3 Summary of response assessment criteria

Grades	MERCURY study group[7,33]	Pattern-based approach[30,39]	ESGAR/ SAR[6,23,37,39]
	T2 HR MRI	DWI	T2 HR + DWI
mrTRG 1	Normal rectal wall or thin (1–2 mm) mucosal or submucosal scar	No diffusion restriction in the baseline tumor location	Complete response (cCR)
mrTRG 2	Minimal T2 intermediate signal residual tumor and predominant T2 hypointense fibrosis	Few small foci of diffusion hyperintensity in the baseline tumor location	Near-complete response (nCR)
mrTRG 3	More than 50% of baseline tumor thickness is replaced by fibrosis or homogeneously hyperintense mucin reaction. However, a definite intermediate signal residual tumor is seen	C-shaped or nodular diffusion restriction along the mucosal surface in the location of the baseline tumor	Incomplete response (iCR)
mrTRG 4	The bulk of the intermediate signal residual tumor is seen but reduced in size since baseline	Bulk restricted diffusion in the residual tumor	
mrTRG 5	The tumor has been unchanged since baseline	Diffusion restriction in the tumor is the same as baseline	

Abbreviations: DWI, diffusion-weighted imaging; ESGAR, European Society of Gastrointestinal and Abdominal Radiology; HR, high-resolution; MRI, magnetic resonance imaging; mrTRG, magnetic resonance tumor regression grade; SAR, Society of Abdominal Radiology.
Note: Comparison with the baseline staging MRI is mandatory for the radiological interpretation of mrTRG.

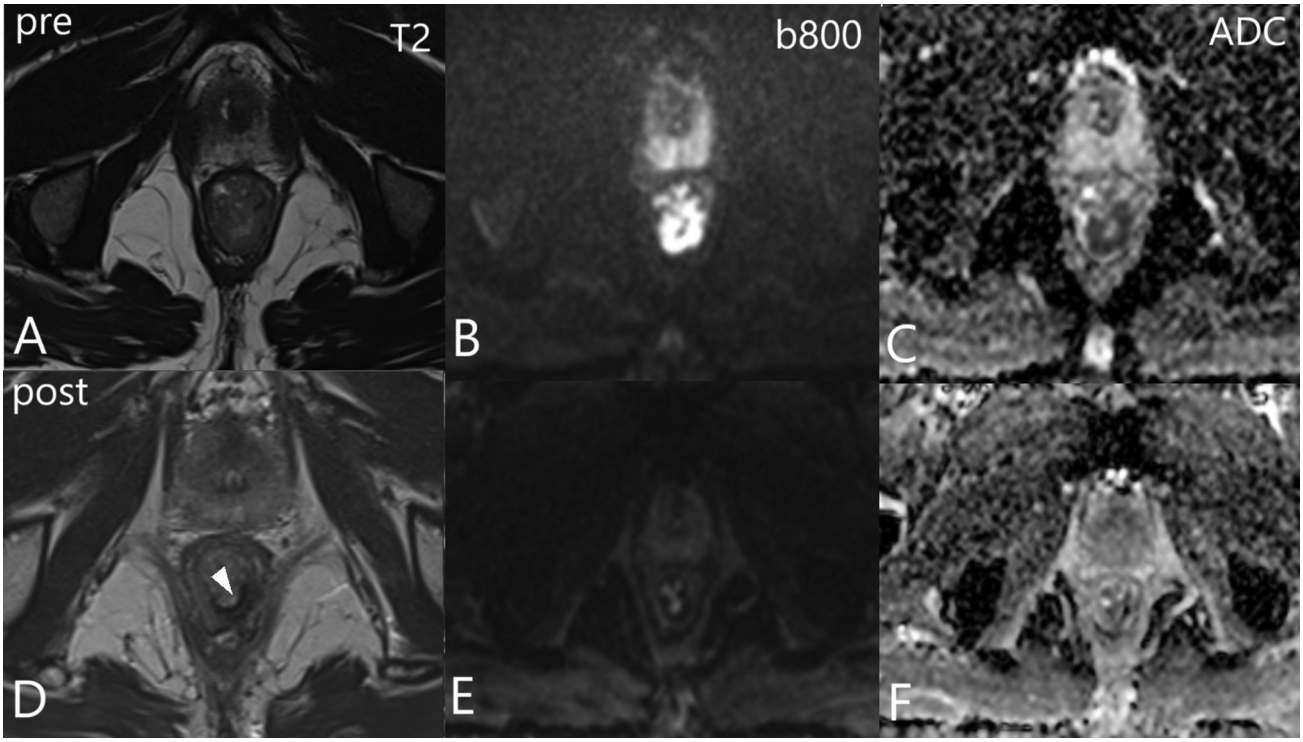

Fig. 5 The baseline and response assessment magnetic resonance imaging (MRI) following long-course chemoradiotherapy (LCRT) of a low rectal cancer with complete response (cCR) or magnetic resonance tumor regression grade (mrTRG) 1. (**A**–**C**) Baseline T2, diffusion-weighted imaging (DWI) (b800), and apparent diffusion coefficient (ADC) map show left posterior semiannular intermediate signal diffusion restricting low rectal cancer. (**D**–**F**) Post-LCRT MRI T2, DWI (b800), and ADC map show a thin curvilinear T2 hypointense scar (arrowhead in **D**) along the mucosal surface of the left posterior wall with no diffusion restriction.

appears in three layers, that is, two thin hypointense layers like a tram track, sandwiched by an intermediate signal layer representing the perirectal and the submucosal fibrosis sandwiching a thickened edematous muscularis propria (►**Fig. 7**).[34]

Modified mrTRG

The most adopted modification of mrTRG is the three-tier system (►**Table 3**), which incorporates T2 HR MRI and DWI and is endorsed by the European Society of Gastrointestinal and Abdominal Radiology and Society of Abdominal

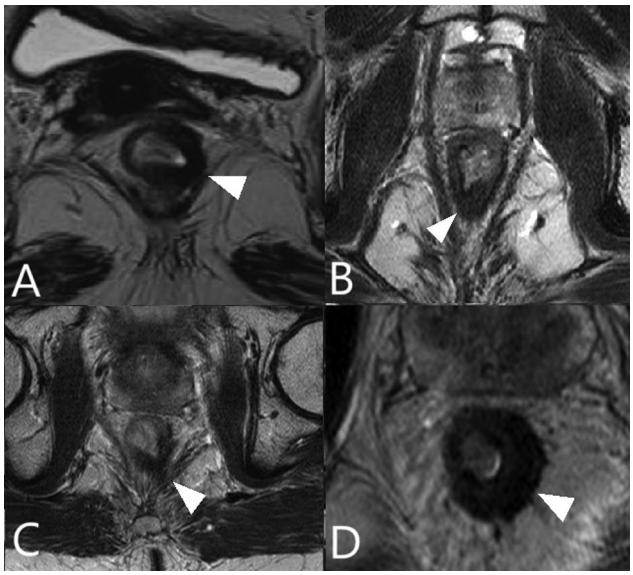

Fig. 6 Morphological appearance of complete response (cCR) on magnetic resonance imaging (MRI). (**A**–**D**) Response assessment MRI following long-course chemoradiotherapy (LCRT) in four different patients with a pathological complete response showing variable thickness T2 hypointense scar (arrowhead). The posttreatment fibrosis extends to the left puborectalis in **A** and **C** (circumferential resection margin [CRM] involved).

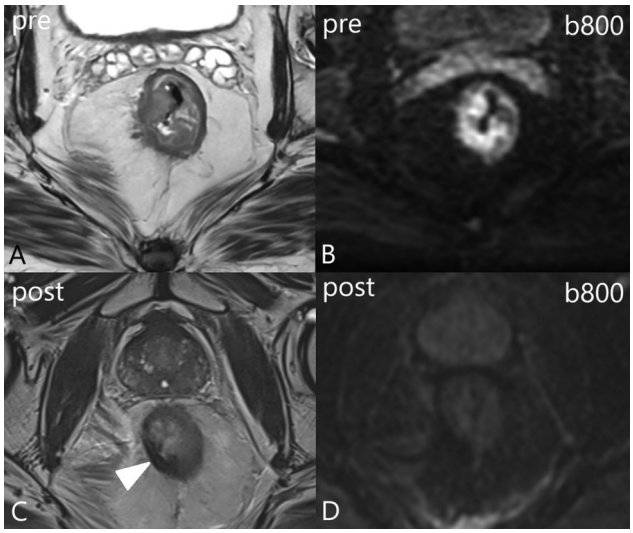

Fig. 7 Split scar sign in magnetic resonance tumor regression grade (mrTRG) 1 or complete response (cCR). Baseline (**A**) axial T2 high-resolution (HR) magnetic resonance imaging (MRI) and (**B**) diffusion-weighted imaging (DWI) (b800) show a right posterior wall, semi-annular, intermediate signal intensity, diffusion restricting cT3b, N0 low rectal cancer. (**C**) Post-long-course chemoradiotherapy (LCRT), axial T2 HR MRI shows tram track-like T2 hypointense signal along the mucosa and muscularis with intervening intermediate signal sub-mucosa (positive split scar sign, arrowhead). (**D**) Post-LCRT, DWI (b800) shows no diffusion restriction.

Radiology.[6,23,37,38] The response patterns on DWI were described based on the morphology of the rectal cancer on baseline T2-weighted MRI (►**Table 3**).[39] The semiannular rectal cancers can have one of these appearances following neoadjuvant therapy: normalization of the rectal wall and thus no diffusion restriction in cCR (►**Figs. 5**–**7**), C-shaped diffusion restriction along the mucosal surface in a partly fibrosed rectal cancer, or semiannular restricted diffusion in frank residual tumor with iCR (►**Fig. 8**). Annular and polyp tumors are less likely to show cCR than semiannular ones. Following neoadjuvant treatment, annular tumors often show multiple small foci of restricted diffusion amidst posttreatment fibrosis and are labeled nCR. Polypoidal growths with iCR show a nodular diffusion restricting focus along the mucosal surface of the rectum at the base of the polyp tumor (►**Fig. 9**). The use of DWI along with T2 HR MRI has been shown to improve the diagnostic accuracy between mrTRG and pTRG, and there was better confidence among readers and interobserver agreement.[30,39] ►**Table 3** summarizes the tumor response criteria and the MRI appearances. Regrowth is seen as an interruption of the split scar sign, scar thickening compared with the previous, and reappearance of tumor signal in the scar (►**Figs. 10** and **11**).

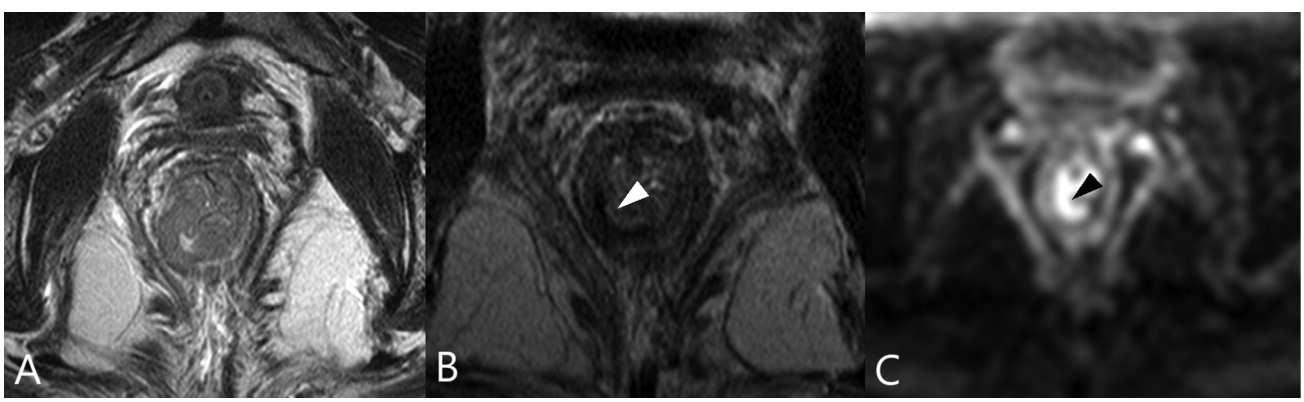

Fig. 8 Magnetic resonance tumor regression grade (mrTRG) 3 or incomplete response (iCR). (**A**) Baseline axial T2 high-resolution (HR) magnetic resonance imaging (MRI) shows an intermediate signal intensity, right posterior semiannular, low rectal cancer. (**B**, **C**) Post-chemoradiotherapy (CRT) T2 HR and diffusion-weighted imaging (DWI) (b800) images show a thick T2 hypointense scar with a C-shaped diffusion restriction along the mucosal surface of the right posterior wall.

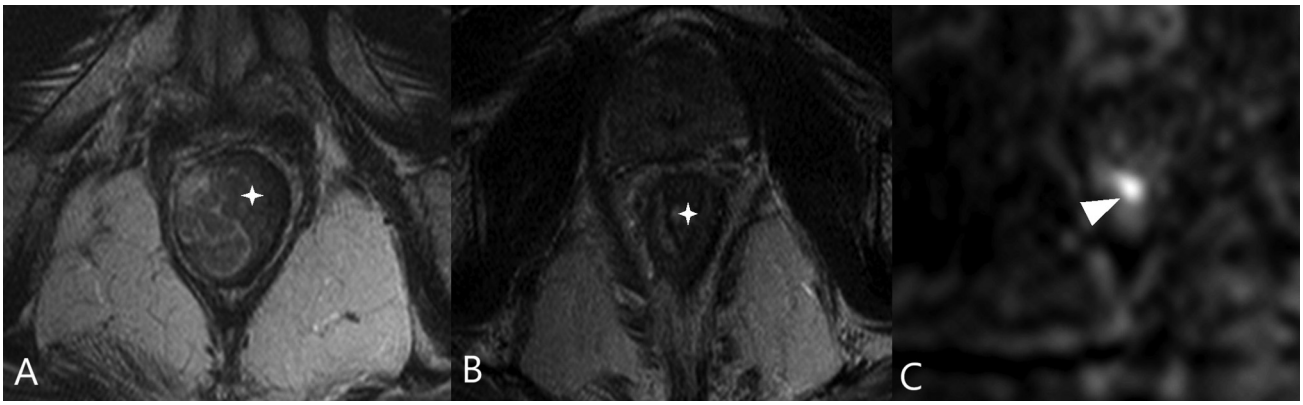

Fig. 9 Magnetic resonance tumor regression grade (mrTRG) 3 or incomplete response (iCR). (**A**) Baseline axial T2 high-resolution (HR) magnetic resonance imaging (MRI) shows an intermediate signal intensity, left anterior sessile polypoidal growth. The base of the polyp is marked with a 4-pointed star. (**B**) Post-chemoradiotherapy (CRT) T2 HR image shows a T2 hypointense nodular wall thickening with an intermediate signal focus at the polyp's base (4-pointed star) along the mucosal surface. (**C**) Corresponding and diffusion-weighted imaging (DWI) (b800) show a focal nodular diffusion hyperintensity.

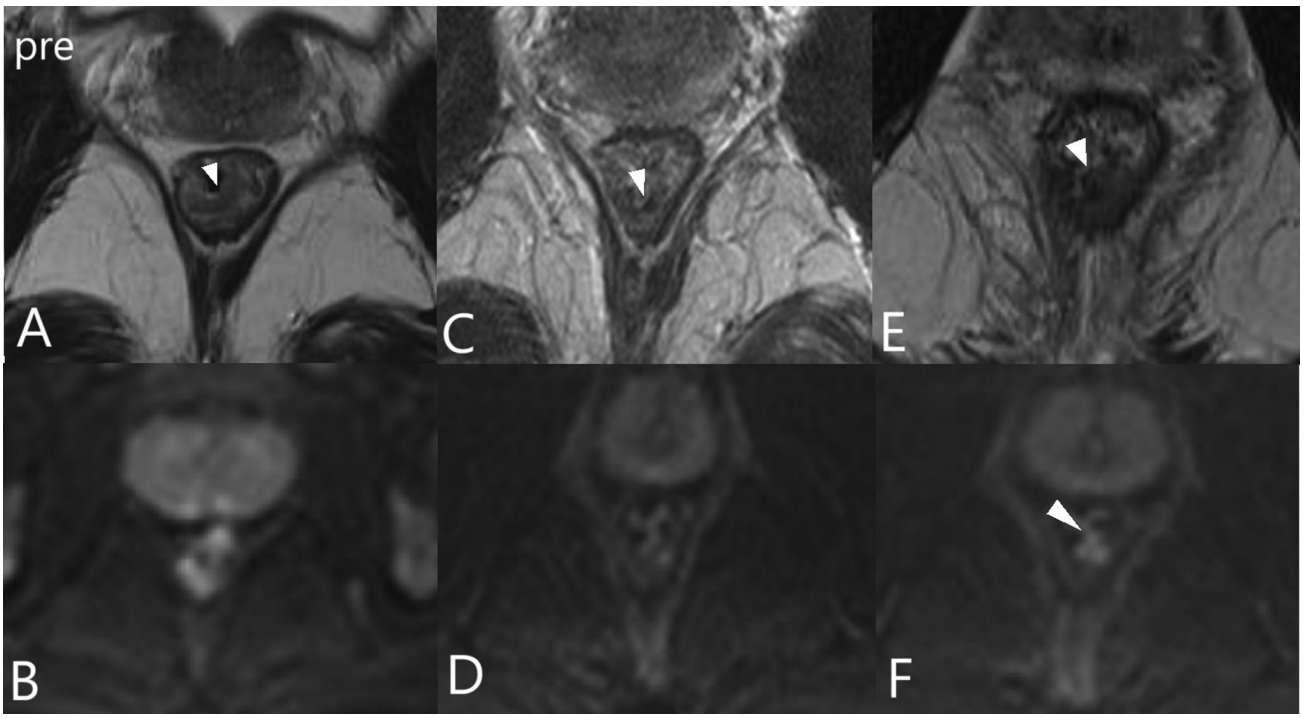

Fig. 10 Regrowth after 9 months of complete response in an early stage (cT1, N0) low-rectal cancer following neoadjuvant long-course chemoradiotherapy (LCRT) with 54 Gy. (**A**, **B**) Baseline T2 high-resolution (HR) and diffusion-weighted imaging (DWI) (b800) show a left posterior semiannular intermediate signal intensity diffusion restricting early rectal cancer confined to the mucosa and submucosa (arrowhead). (**C**, **D**) Response assessment magnetic resonance imaging (MRI) T2 HR and b800 image of DWI at 6 months' follow-up showing a thin T2 scar (arrowhead) and no diffusion restriction. (**E**, **F**) MRI at 9 months of follow-up showed nodular tumor signal intensity thickening of the scar with diffusion restriction (arrowheads). The patient subsequently underwent abdominoperineal excision.

Response Evaluation Criteria in Solid Tumor 1.1

The Response Evaluation Criteria in Solid Tumor (RECIST) 1.1, a commonly used method to quantify response, is not typically applied in rectal cancer due to the challenges in consistently measuring irregularly shaped rectal cancer in a single plane. RESIST focuses on measuring the longest diameter of target lesions. A 30% reduction in the length of rectal cancer is a partial response, a 20% increase in size is a progressive disease, and those in between are a stable disease.[40]

Step 3: Measurements That Must be Mentioned in the MRI Report

The comparison of the length of rectal cancer on restaging MRI with the baseline provides an estimate of response according to RESIST 1.1. The degree of extramural spread gives the subcategories of the ymr-T3 stage. Among those patients with a cCR on MRI, only those with treated rectal cancer amenable to a complete triple assessment with MRI, proctoscopy, and clinical examination, and those highly motivated to undergo stringent monitoring of tumor are

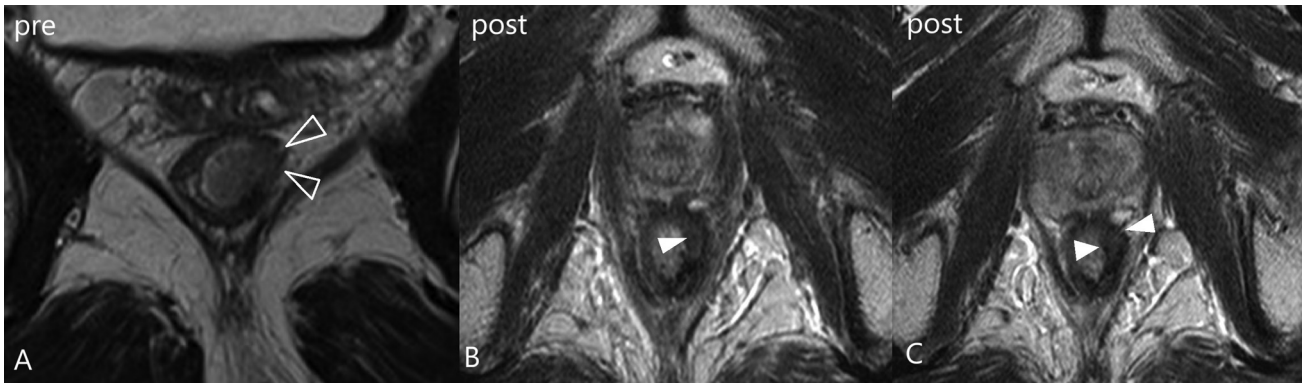

Fig. 11 Regrowth after 6 months of complete response in an early-stage polyp cancer (cT2, N0) following neoadjuvant long-course chemoradiotherapy (LCRT). (**A**) Baseline T2 high-resolution (HR) axial image showing an intermediate signal sessile polyp (arrowheads) in the left anterior wall infiltrating the muscularis. (**B**, **C**) Nodular regrowth at the polyp's base (arrowheads) is seen as tumor signal intensity thickening of the scar.

eligible for watch-and-wait approach or NOM. In effect, only treated low- and mid-rectal cancers with a palpable upper margin are eligible for watch and wait in the author's institution. Thus, documenting the distance of the distal margin from the anal verge and the location of the upper margin of the treated cancer with respect to the peritoneal reflection on MRI aid in establishing the concordance between these three response assessment methods and help in monitoring these patients. The distance between the distal margin of the residual tumor or the scar and the anorectal junction helps decide the type of surgery, that is, abdominoperineal resection versus ultra-low anterior resection versus low anterior resection.

The next measurement that needs special mention in the report is the shortest distance to the MRF, which estimates the surgical circumferential resection margin (CRM). The shortest distance between MRF or puborectalis or anterior pelvic structures such as the prostate or vagina and one of these, that is, residual tumor/posttreatment fibrosis/mucin reaction/residual mesorectal node more than 5 mm in short axis, residual extramural vascular invasion (EMVI), or tumor deposit (TD) is measured to estimate the CRM. CRM is reported as involved when the distance is 1 mm or less. MRF is often involved by either posttreatment fibrosis or mucin reaction on restaging MRI, and surgical histopathology showed tumor cells in 15 and 17% of them, respectively.[39] Restaging MRI following NACRT has low positive predictive value (44–57%) and high negative predictive value (91–100%) for positive pathological CRM with an area under the receiver operating characteristic curve of 0.73 to 0.89.[41] This would mean that the restaging MRI tends to overcall positive CRM compared with pathology. Despite this, the distance to MRF needs to be reported as 0 mm when the radial margin is involved by posttreatment fibrosis or mucin reaction and considered as "involved CRM or MRF" since microscopic tumor cells within these cannot be identified effectively using MRI.[33,42]

Step 4: Are There Poor Prognostic Imaging Biomarkers?

EMVI and TD are important prognostic imaging biomarkers associated with synchronous and metachronous metastasis and confer poor OR and disease-free survival (DFS).[43–45] Other important prognostic quality imaging findings include lateral pelvic disease and mrTRG. The presence or absence of one or more of these imaging biomarkers of prognostic significance on staging MRI increasingly dictates the recommendation of neoadjuvant therapy at the MDT. When there is an excellent response to neoadjuvant treatment, that is, the disappearance of these findings or complete replacement by fibrosis, the prognosis becomes like those without these. On the other hand, persistence confers a worse prognosis.[46–48] Thus, it is critical to compare the baseline and restaging MRI for the presence or absence of these findings and document their morphological changes.

The mr-vTRG score was an attempt to quantify the response in EMVI that considers the degree of tumor signal seen within EMVI noted at baseline replaced by T2 markedly hypointense fibrosis on restaging MRI, mr-vTRG score of 1 being complete fibrosis and 5 being persistent EMVI (►**Box 2**).[49] While it is cumbersome to apply the score, it is a helpful guide to understanding the imaging spectrum of ymr-EMVI and may also be used for ymr-TD. Mesorectal nodes seen on restaging MRI carry no prognostic significance, though persistent mesorectal nodes $>$ 5 mm and all visible T2 hyperintense or mucinous nodes contribute to the ymr-N stage.[7,46,47,50] It is important not to overstage the mesorectal nodes seen on MRI.[50,51]

Lateral pelvic nodes or the pelvic side wall nodes include the obturator, internal iliac, and external iliac nodes. The Lateral Node Study Consortium published a pooled retrospective multicenter analysis of 741 patients and reported a 5-year lateral local recurrence rate of 52.3% among patients

Box 2 mr-vTRG score to assess response in EMVI on response assessment MRI[49]

1: Tumor signal of EMVI replaced by homogeneous T2 markedly hypointense fibrosis.
2: 50–75% fibrosis of tumor signal within EMVI
3: 25–50% fibrosis of tumor signal within EMVI
4: less than 25% fibrosis of tumor signal within EMVI
5: EMVI unchanged since baseline

who had persistent internal iliac nodes > 4 mm after NACRT and 9.5% among those with persistent obturator nodes > 6 mm.[52,53] For staging MRI, a cutoff of ≥ 7 mm was proposed for the obturator and internal iliac nodes to define metastatic nodes. For restaging MRI following NACRT, a cutoff of > 4 mm is recommended for internal iliac nodes and > 6 mm for obturator nodes.[52–55] mrTRG is another significant prognostic biomarker of rectal cancer. Significant differences in DFS and OS were observed between good responders (mrTRG 1–3) and poor responders (mrTRG 4–5).[7,47] ►**Figs. 12**–**14** show examples of iCR (mrTRG 4) and persistent poor prognostic markers.

Step 5: Document the Local Extent of the Rectal Cancer to Decide the Surgical Strategy

The infiltration of adjacent structures is interpreted like the staging MRI. Obliteration of the planes between the rectum bearing the tumor or posttreatment change and the neighboring structures must be reported for surgical planning (►**Fig. 15**). ►**Table 4** shows the types of surgeries done based on the imaging findings in the response assessment MRI.

Step 6: Comment on Nonregional Nodes and Distant Metastases

Response assessment is complete only when the most common sites of metastases, such as nonregion pelvic and retroperitoneal nodes, liver, lungs, and the peritoneum, are reassessed, and disease progression has been excluded. This is especially important in patients who have high-risk features such as signet ring cell cancer or poorly differentiated rectal cancer, persistent EMVI or TD or lateral pelvic node-positive patients on restaging MRI, and those who have progression of local disease on neoadjuvant therapy. Contrast-enhanced CT thorax and abdomen may be considered for these patients. Adding upper abdominal DWI to screen the liver for new metastases as a part of pelvic MRI protocol is a valuable practice during response assessment (►**Fig. 14**).

Step 7: Restage with the 8th Edition of the American Joint Committee on Cancer TNM Staging System

After neoadjuvant treatment, the stage determined on restaging MRI is written with the prefix "y," followed by the imaging modality, for example, ymr-T, N, and M stage. The staging

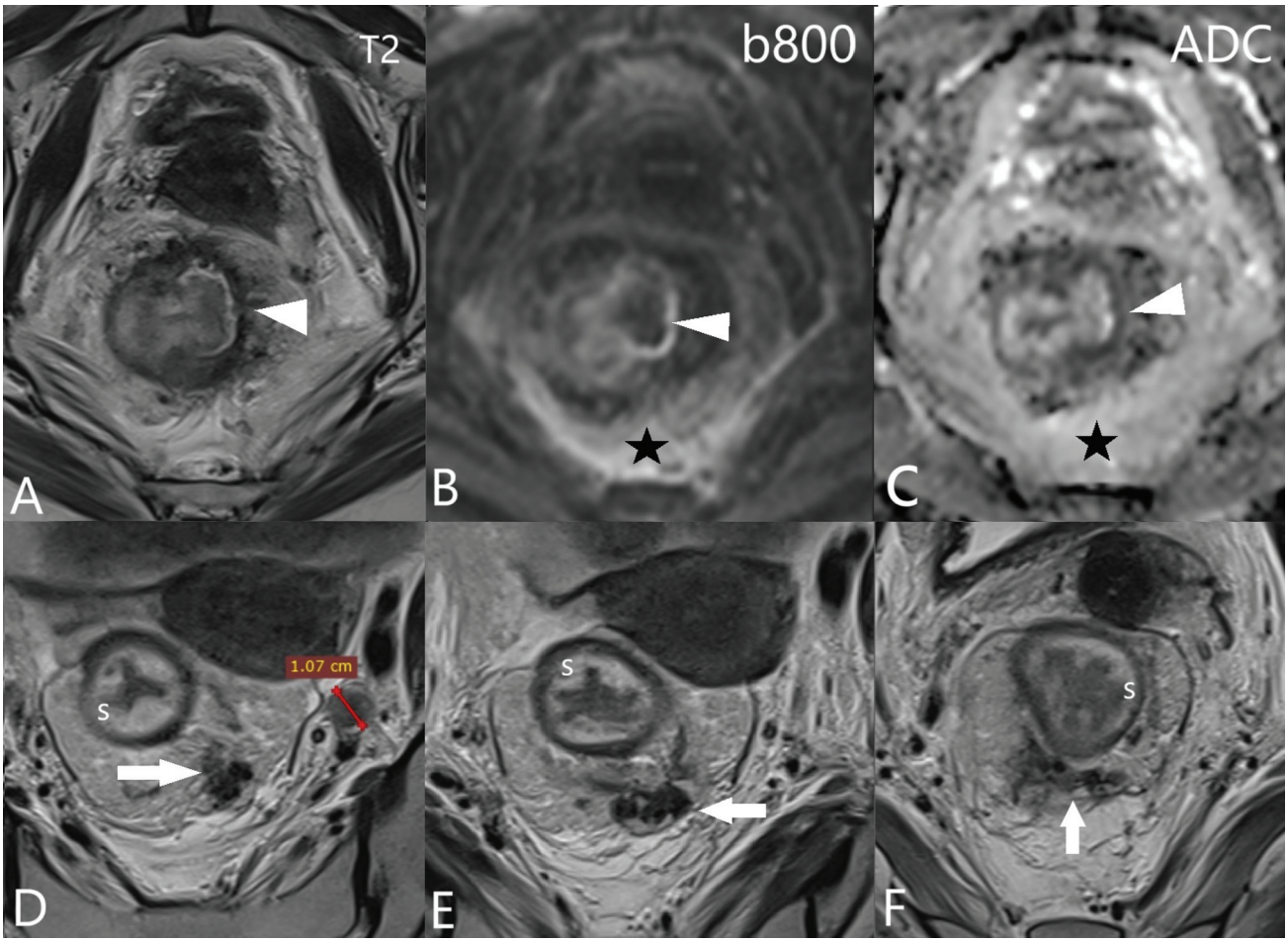

Fig. 12 Magnetic resonance imaging (MRI) following total neoadjuvant therapy (TNT) in a young (23/M) rectal cancer patient. (**A**–**C**) Axial T2 high-resolution (HR), b800 diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) map through the rectal cancer show thick T2 hypointense posttreatment fibrosis in the left lateral wall of the rectum. Curvilinear T2 hyperintensity along the mucosal surface shows diffusion restriction (arrowheads) consistent with an incomplete response (iCR), magnetic resonance tumor regression grade (mrTRG) 4. (**D**–**F**) Higher axial T2 HR images of the same patient show submucosal edema (s), extramural vascular invasion (EMVI) and tumor deposit (TD) (arrows) containing mixed T2 hypointense and tumor signal intensity components (mr-vTRG 4) and a significant left obturator node (measured in **D**).

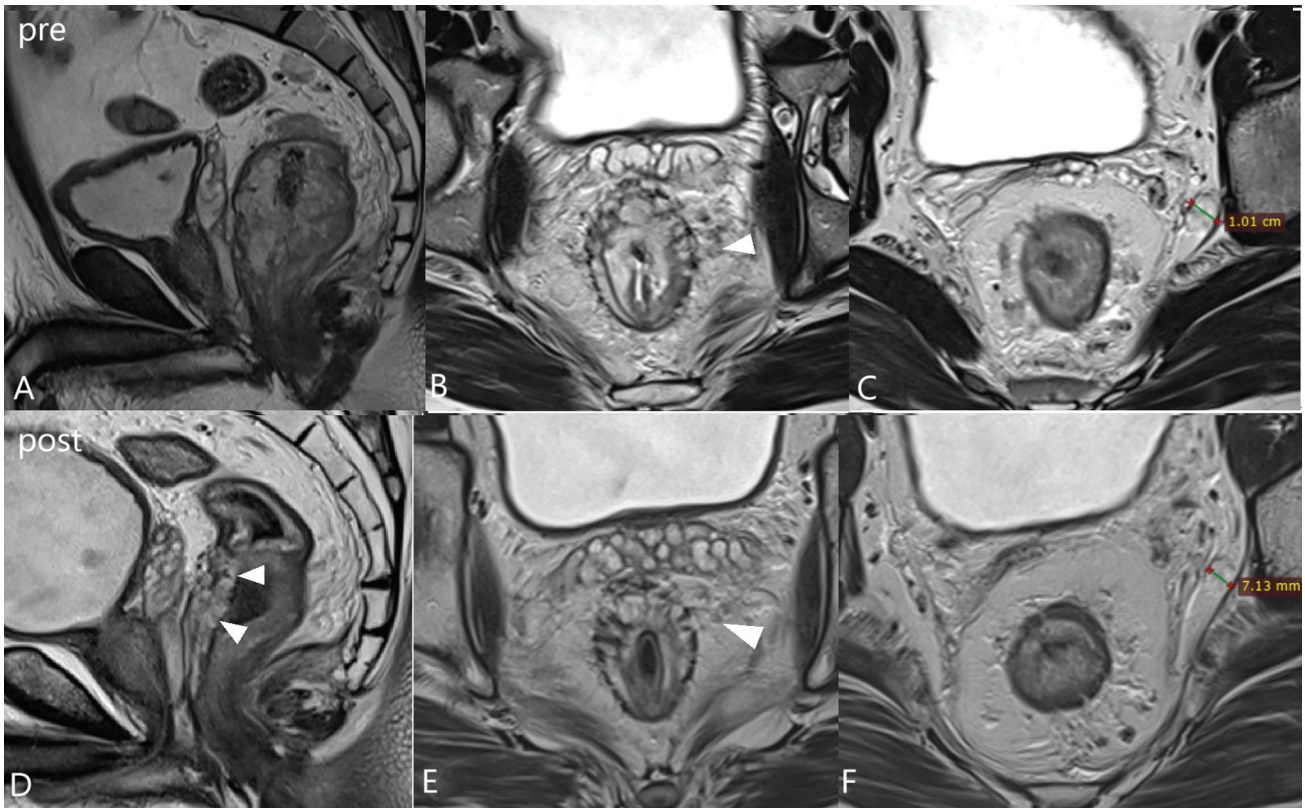

Fig. 13 (**A**–**C**) Baseline T2 high-resolution (HR) sagittal and axial magnetic resonance imaging (MRI) shows a bulky T2 hyperintense mucinous mid-rectal cancer, extramural vascular invasion (EMVI) (arrowhead) seen as T2 hyperintense irregular expansion of the mesorectal vein and significant T2 hyperintense left lateral pelvic node or obturator node (measured in **C**). (**D**–**F**) MRI following total neoadjuvant treatment (TNT) shows persistent EMVI (arrowhead) and a significant (> 6 mm) mucinous left obturator node (measured in **F**).

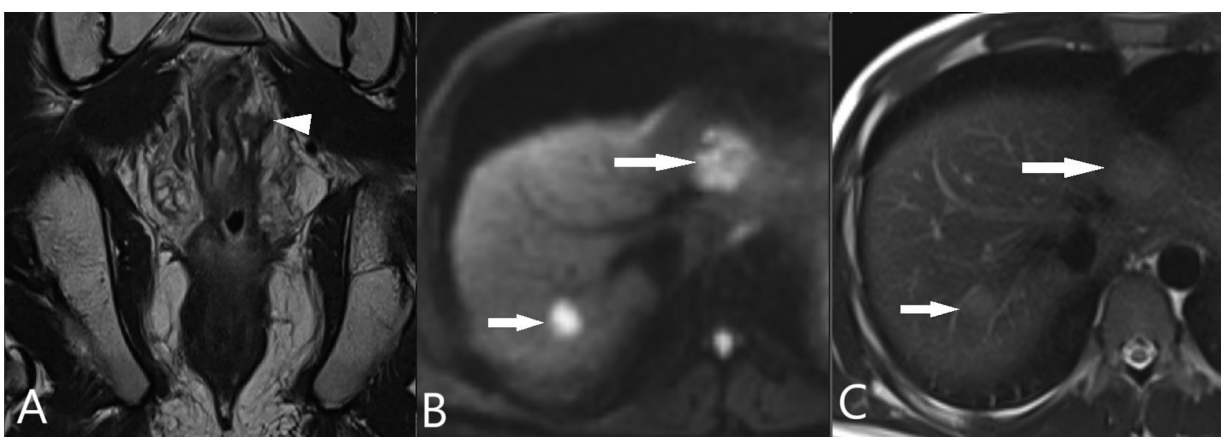

Fig. 14 Progression after total neoadjuvant therapy (TNT) with new liver metastases. (**A**) Coronal T2 high-resolution (HR) magnetic resonance imaging (MRI) shows persistent tumor signal extramural vascular invasion (EMVI) and tumor deposit (TD) (arrowhead). (**B**) Diffusion-weighted imaging (DWI) (b800) shows liver metastases (arrows). (**C**) T2 large field of view (FOV) axial MRI of the liver showing faintly visible mildly hyperintense liver metastases (arrows).

system used is the same as the baseline, but the criteria for lymph nodes are modified, as described above. ►**Box 3** is a structured reporting template for radiologists for restaging MRI or the response assessment MRI in rectal cancer patients.

Common Challenges and Troubleshooting

A detailed review of the pitfalls and challenges in the interpretation of response assessment MRI following neoadjuvant treatment in rectal cancer patients is beyond the scope of the current review. However, we have enumerated a few common challenges and solutions.

Technical

The common challenge in interpreting response assessment MRI concerns suboptimal or incorrect planes of T2-weighted HR images. This is often attributed to a lack of communication with the technologists regarding the location of rectal

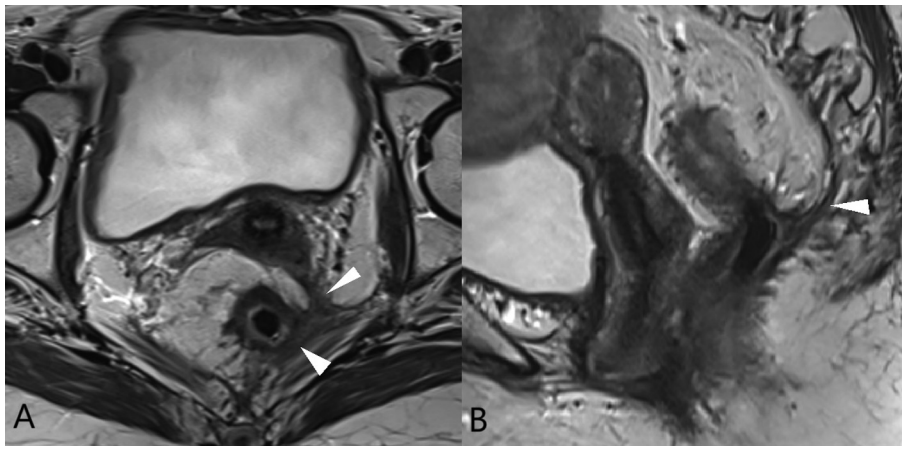

Fig. 15 Response assessment magnetic resonance imaging (MRI) of patients with low-rectal cancer treated with long-course chemoradiotherapy (LCRT). (**A**) Axial and (**B**) sagittal T2 high-resolution (HR) MRI shows annular T2 hypointense posttreatment changes in the rectal wall. Sheets of T2 hypointense soft tissue along the left side of the rectum is seen contiguously thickening the mesorectal fascia (MRF) and loses plane with the left piriformis muscle (arrowheads).

Table 4 Type of surgeries based on post-CRT MRI findings

Type of surgery	MRI findings on post-CRT MRI
Ultra-low anterior resection	Distal margin of treated tumor at least 1 cm line above the anorectal junction and intact anal sphincter integrity
Intersphincteric abdominoperineal excision (APE)	The distal margin of the treated tumor is 1 cm below the anorectal junction and is clear in the intersphincteric plane
Standard APE	Intersphincteric space or external anal sphincter is involved by residual tumor
Extralevator APE	The plane with the puborectalis or levator ani muscle is 1 mm or less or frankly infiltrated
Beyond TME excision	Other pelvic organ infiltration like prostate, seminal vesicles, uterus, cervix, vagina, and pelvic side wall structures
Selective lateral pelvic lymph node dissection	Significant lateral pelvic lymph nodes ($>$ 4 mm internal iliac or $>$ 6 mm obturator nodes).

Abbreviations: CRT, chemoradiotherapy; MRI, magnetic resonance imaging; TME, total mesorectal excision.

cancer on baseline MRI and difficulties in identifying a treated rectal cancer. This can be easily mitigated by insisting that the clinical referrers mention the location of rectal cancer in the MRI request form and by the radiologists reviewing the baseline MRI before protocoling the study. Other challenges affecting DWI quality are susceptibility artifacts from the air in the bowel lumen (►**Fig. 16**), hip prosthesis or fiducial metallic polypectomy markers, and the bowel contents (fluid and feces). Microenema, encouraging patients to empty the bowel and bladder just before the MRI study and administering a small volume (50–60 mL) of rectal gel can help minimize intraluminal air.

Interpretational-Related Challenges

Posttreatment changes in the rectum, such as bowel wall thickening and edema, radiation-related proctitis, mucosal ulcers, and necrotic foci, can be misinterpreted as residual tumor since they may show diffusion restriction. Reviewing baseline MRI for the location of rectal cancer will guide the radiologist to the correct region of interest. Similarly, imaging the patients too early after neoadjuvant treatment can make response assessment challenging due to severe treatment-related edema and result in higher mrTRG.[7,33,54] As mentioned in the previous section, response assessment in signet ring cell and mucinous rectal cancers is challenging. It is impossible to differentiate acellular mucin from a residual tumor in a mucinous rectal cancer (►**Fig. 13**).[30,32,55,56] Mucin reaction can be diagnosed with some confidence only if a T2 intermediate signal rectal cancer at baseline MRI shows a homogeneous T2 hyperintense pool of mucin in and around the posttreatment scar (►**Fig. 17**). However, if the mucin pool has few intermediate signal foci, it is likely to have residual disease (►**Fig. 18**). Reactive anterior group external iliac nodes are common on post-CRT MRI. Despite its borderline size, it appears elongated in shape and is aligned parallel to the pelvic side wall. All T2 hyperintense nodes seen in a setting of mucinous rectal cancers are significant and can be masked in a background of pelvic soft tissue edema and hyperintense mesorectal fat (►**Fig. 13**).

Box 3 Structured reporting format for response assessment MRI in rectal cancer

Clinical details: Document histopathological type of rectal cancer, neoadjuvant treatment received, time since completion of neoadjuvant treatment.
Quality of the scan: Comment on artifacts and suboptimal planes limiting interpretation.
1. *Comparison study:* Document date of baseline MRI and date of prior response assessment MRI for patients on watch and wait.
2. *Document location, morphology and signal intensity on baseline MRI.*
   - T2 signal intensity on baseline MRI: intermediate/ hyperintense/ mixed signal/ hypointense
   - DWI on baseline MRI: restricted diffusion/ facilitated diffusion
   - Location: High/ mid/ low (based on distance from anal verge)
   - Radial extent: annular/ semi-annular
   - Morphology: polypoidal/ ulcero-infiltrating tumor
3. *Document T2 and DWI appearance in the current response assessment MRI*
   - T2: Previous tumor replaced by normal wall/ thin radial scar/ thick radial scar with tumor signal/ residual tumor smaller than baseline/ residual tumor unchanged since baseline.
   - DWI: No restricted diffusion/ few small foci diffusion restriction/ C-shaped or nodular restricted diffusion along the mucosal surface/ frank diffusion restricting residual tumor/ unchanged since previous.
   - Response: Complete response (cCR)/ near Complete response (nCR)/ incomplete response (iCR)/ tumor regrowth
4. *Tumour measurements:*
   - Length: _____cm versus_____ cm in the previous
   - Extramural spread:_____ mm
   - Distance between distal margin of residual tumor or scar to anal verge:___ cm
   - Distance between distal margin of residual tumor or scar to ano-rectal junction:___ cm
   - Shortest distance between mesorectal fascia (MRF) and one of these (residual tumor/ scar tissue/ mesorectal node >5mm, residual EMVI or TD):___ mm
   - Mesorectal fascia: involved/ not involved (involved if 1 mm or less)
5. *Are there poor prognostic imaging biomarkers?*
   - EMVI: present/ absent (mr-vTRG score:___).
   - Tumour deposits: present/ absent
   - Pelvic side wall disease: present/ absent (present if there are persistent internal iliac nodes >4 mm or obturator nodes >6 mm in short axis diameter).
   - mrTRG
6. *Current extent of tumor to decide the surgical strategy:*
   - Highest margin of the treated cancer: below/ at/ above the peritoneal reflection
   - Peritoneal reflection: involved/ not involved
   - Lowest margin of the treated cancer: below/ at/ above the puborectalis
   - Puborectalis/ levator ani: involved/ not involved
   - Anal sphincter complex: status of internal sphincter/ inter-sphincteric space/ external sphincter/ ischio-rectal fossa
   - Adjacent organs: prostate/ seminal vesicles/ uterus/ cervix/ vagina/ bladder
   - Others: muscles like piriformis/ obturator internus/ obturator externus/ extra mesorectal fat/ pelvic side wall/ presacral fascia
   - *Nodes:* Mesorectal, internal iliac, obturator
7. *Metastasis:* inguinal, external iliac, common iliac, para-aortic, liver, lungs, peritoneum, bones, others
8. *Stage on response assessment MRI:* ymr-T__, N__, M_____

Other Imaging Modalities for Response Assessment

Endoscopic Ultrasound

The overall accuracy of endoscopic ultrasound (EUS) for ypT-stage and ypN-stage was quite variable.[57–59] There are conflicting results regarding T- and N-staging when the accuracy of MRI and EUS were compared.[60–62] Nevertheless, EUS was superior for predicting pathologic complete response and anal sphincter infiltration.[60–62] However, this modality is of limited use in proximal and stenotic rectal cancers. Since only the close visual field mesorectal nodes can be evaluated, an MRI of the pelvis will be needed to complete the assessment of treated rectal cancer.

Contrast-Enhanced Thoracoabdominal CT

CT is used to plan the neoadjuvant RT and aids in identifying disease progression on TNT.[63] New metastases seen on RT planning CT in patients treated with TNT represent a biologically aggressive tumor or synchronous distant metastases. In any case, its identification might change the treatment intent and modify the treatment protocol.

Fluorodeoxyglucose F 18 Positron Emission Tomography-CT and MRI

Positron emission tomography (PET) should not be routinely used to determine tumor response.[63] PET/CT had higher accuracy in detecting extrahepatic and hepatic colorectal metastatic disease than CT alone.[64] A recent review has suggested that fluorodeoxyglucose F 18 PET/MRI could be used for rectal cancer restaging due to its better accuracy in T and N staging compared with PET/CT or MRI alone. However, it performed poorly in the detection of lung metastases.[65]

Novel Techniques

Dynamic contrast-enhanced MRI, magnetization transfer ratio, and textural analysis (e.g., radiomics) have been studied to overcome the limitations of MRI in the restaging of

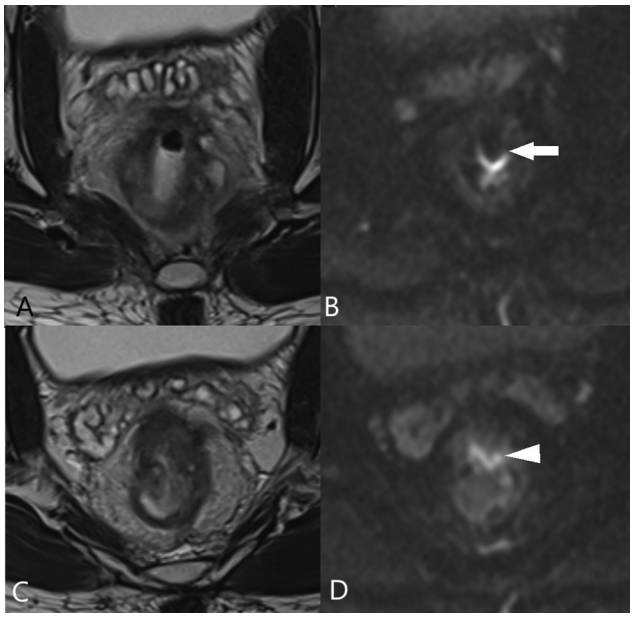

Fig. 16 Susceptibility artifacts in diffusion-weighted imaging (DWI) due to air in the bowel lumen. (**A**, **C**) T2 high-resolution (HR) axial images show intraluminal air close to the bowel wall containing evident residual disease. (**B**, **D**) DWI (B800) shows susceptibility artifacts overlying the tumor-bearing rectal wall (arrow in **B**) and image distortion (arrowhead in **D**).

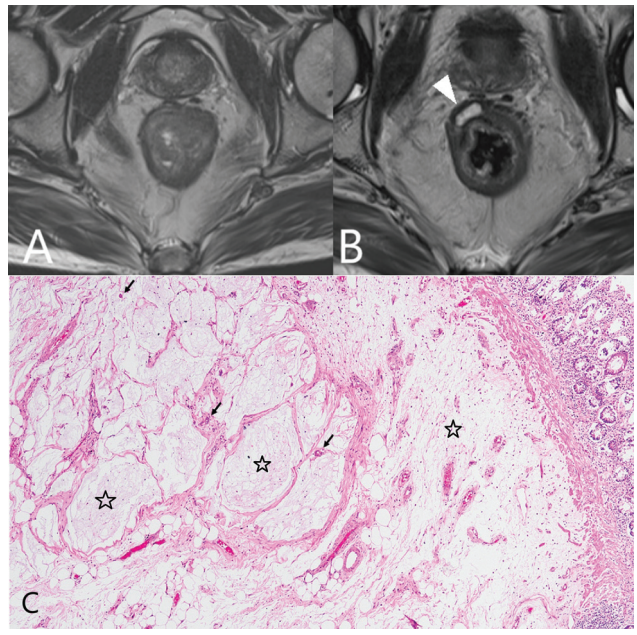

Fig. 18 Mucin pool with tumor cells. (**A**) The baseline axial T2 high-resolution (HR) image shows a right anterior wall semiannular intermediate signal intensity rectal growth. (**B**) Post-long-course chemoradiotherapy (LCRT) axial T2 HR image shows thin T2 hypointense scars along the mucosa and muscularis with a well-defined T2 hyperintensity mucin pool in the submucosa (arrowhead). (**C**) Histopathological evaluation (hematoxylin and eosin [H&E], 100× magnification) showed scanty tumor glands (arrows) and an extracellular mucin pool within the rectal wall (stars), which was reported as a near-complete response and ypT2, N0.

rectal cancer. A few recent studies on radiomics have been used for T and N staging, response to treatment, and survival prediction, with some promising results.[66–69] These tools still need large-scale prospective validation.

Conclusion and Take-Home Message

1. When communicated well to the technologists performing MRI, this single question, "*Where was rectal cancer at baseline*?" would have a significant positive impact on the image quality and the report quality of response assessment MRI. This aspect would require the collective effort of clinical referrers, radiologists, and technologists.
2. Reviewing baseline MRI is critical before interpreting response assessment MRI in rectal cancer patients, and

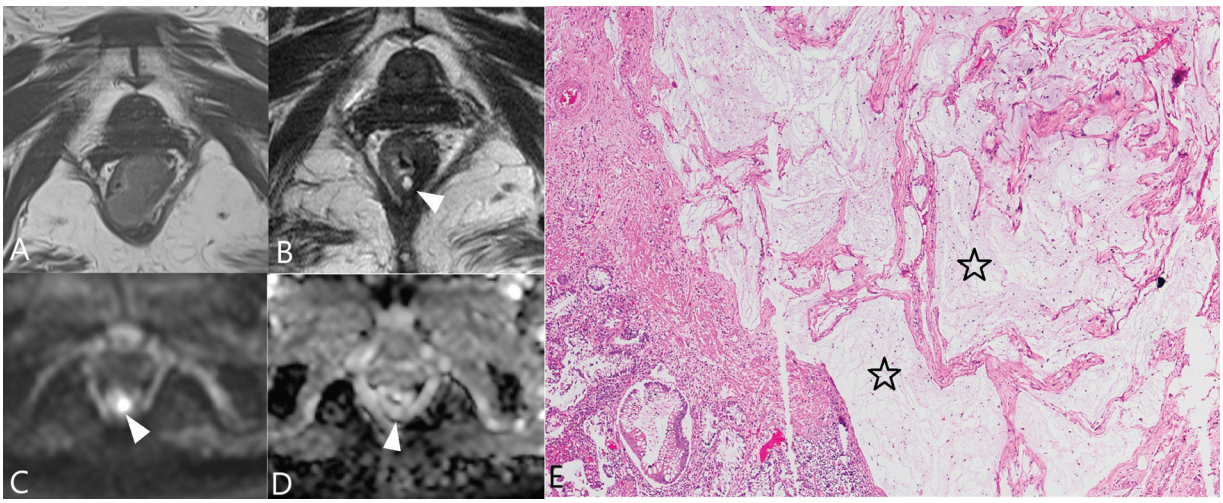

Fig. 17 Acellular mucin reaction. (**A**) Baseline axial T2 high-resolution (HR) magnetic resonance imaging (MRI) shows a sessile polypoidal intermediate signal growth in the left posterior wall of the low rectum. (**B**–**D**) Response assessment MRI (T2 HR, b-800 diffusion-weighted imaging [DWI], and apparent diffusion coefficient [ADC]) after long-course chemoradiotherapy (LCRT) with 54 Gy shows a thick T2 hypointense scar at the tumor site seen at baseline. A well-defined homogeneous T2 hyperintense focus within the posterior wall (arrowhead in **B**) shows facilitated diffusion (arrowheads in **C** and **D**). (**E**) Histopathological evaluation (hematoxylin and eosin [H&E], 100× magnification) showed rectal wall with extracellular mucin pool, no viable tumor cells (stars), and pathological complete response, ypT0, N0.

this must be made available to all radiologists who interpret these studies.

3. Understanding the clinical contribution of response assessment MRI following neoadjuvant treatment in rectal cancer patients and a structured report addressing critical clinical questions will make the radiologist's efforts worthwhile in this area.

Funding
The authors declare that this work did not receive financial support or funding.

Conflict of Interest
None declared.

Acknowledgments
The authors thank the Department of Colorectal Surgery and the Colorectal MDT team, Christian Medical College Vellore. The also thank the sColorectal cancer multidisciplinary team formed by the Departments of Colorectal Surgery (Surgery Unit 2), Radiation Oncology (RT Unit 1), Medical Oncology, dedicated Abdominal Radiology Unit and Gastrointestinal Pathology section of Christian Medical College Vellore, India. The authors thank Dr. Rijo Issac, Department of Pathology and Prof. Rohin Mittal, Head of Colorectal Surgery, for sharing their insights.

Ethical Approval and Consent to Participate
Not applicable.

Authors' Contributions
All authors contributed to the concept/design, a draft of the manuscript, and its editing. All authors read and approved the final manuscript. A.C. is the guarantor for the contents of the manuscript.

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