Restaging MRI of Rectal Adenocarcinoma after Neoadjuvant Chemoradiotherapy: Imaging Findings and Potential Pitfalls

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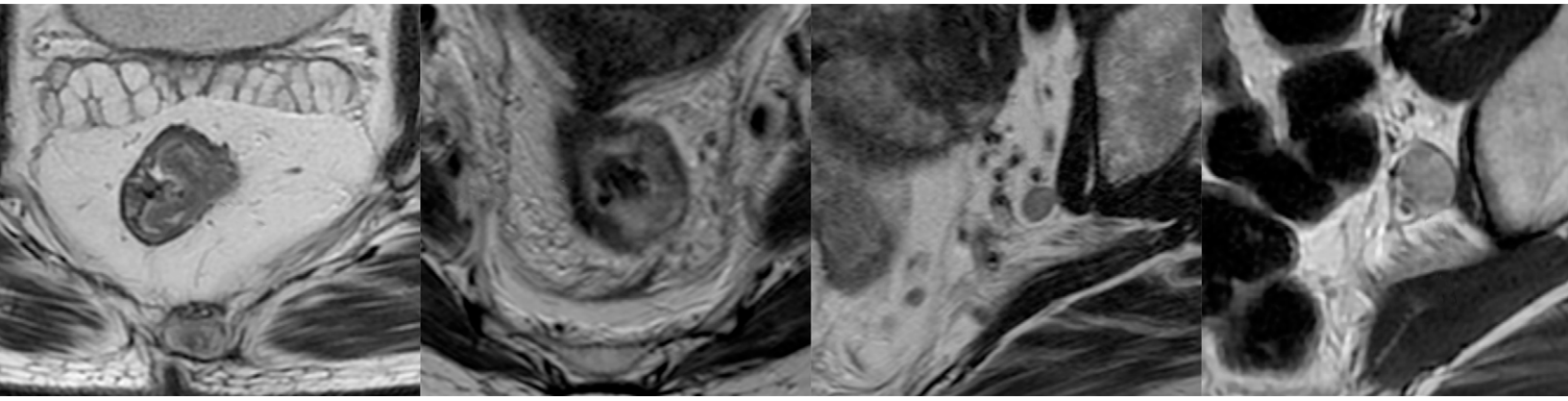
Rectal adenocarcinoma constitutes about one-third of all colorectal adenocarcinoma cases. Rectal MRI has become mandatory for evaluation of patients newly diagnosed with rectal cancer because it can help accurately stage the disease, impact the choice to give neoadjuvant therapy or proceed with up-front surgery, and even direct surgical dissection planes. Better understanding of neoadjuvant chemoradiotherapy effects on rectal tumors and recognition that up to 30% of patients can have a pathologic complete response have opened the door for the nonsurgical "watch-and-wait" management approach for rectal adenocarcinoma. Candidates for this organ-preserving approach should have no evidence of malignancy on all three components of response assessment after neoadjuvant therapy (ie, digital rectal examination, endoscopy, and rectal MRI). Hence, rectal MRI again has a major role in directing patient management and possibly sparing patients from unnecessary surgical morbidity. In this article, the authors discuss the indications for neoadjuvant therapy in management of patients with rectal adenocarcinoma, describe expected imaging appearances of rectal adenocarcinoma after completion of neoadjuvant therapy, and outline the MRI tumor regression grading system. Since pelvic sidewall lymph node dissection is associated with a high risk of permanent genitourinary dysfunction, it is performed for only selected patients who have radiologic evidence of sidewall lymph node involvement. Therefore, the authors review the relevant lymphatic compartments of the pelvis and describe lymph node criteria for determining locoregional nodal spread. Finally, the authors discuss limitations of rectal MRI, describe several potential interpretation pitfalls after neoadjuvant therapy, and emphasize how these pitfalls may be avoided.



Introduction

Colorectal cancer is the fourth most common malignancy in the United States, with an incidence of 150 000 new cases in 2021 and with rectal cancers constituting approximately one-third of these cases (1). Compared with adenocarcinomas involving other parts of the colon, rectal adenocarcinoma has unique anatomic considerations owing to its proximity to other pelvic structures and the anal sphincter, different lymphatic drainage pathways, and potential for postoperative voiding and/or sexual dysfunction secondary to injury of the adjacent nerves. This unique anatomic position is associated with significantly higher rates of local recurrence compared with those of adenocarcinomas occurring elsewhere in the colon. Hence, management algorithms for rectal adenocarcinoma are different from those for its counterparts involving other sites of the colon, with neoadjuvant radiation therapy being offered only to patients with rectal adenocarcinoma (2,3). Owing to its pelvic location, the rectum is relatively less prone to respiratory artifacts, and with administration of spasmolytic agents, motion of adjacent bowels and rectal

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Abbreviations: ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, FOV = field of view, mrTRG = MRI tumor regression grading, TD = tumor deposit

TEACHING POINTS

- Edematous changes can frequently occur at the site of the treated tumor, with a resultant potential pitfall at restaging MRI. Diffusion-weighed images should be interpreted only in conjunction with ADC maps to avoid misinterpretation of edema as residual tumor.
- After neoadjuvant therapy, the high T2 signal intensity of mucinous tumors typically persists, and it may or may not harbor residual malignant cells (cellular mucin vs acellular mucin). There is no reliable imaging modality to distinguish cellular from acellular mucin, and these patients are offered surgery.
- The "split scar sign" at postchemoradiotherapy MRI has high specificity (97%) but moderate sensitivity (52%–64%) for a complete response. It is defined as a fibrotic scar with low signal intensity on T2-weighted images involving the submucosa, with an underlying layer of intermediate T2 signal intensity at the muscularis propria and a third outermost hypointense layer corresponding to perirectal fibrosis.
- A clear understanding of the anatomic boundaries of pelvic lymph node compartments is necessary for accurate localization of metastatic lymph nodes and application of size criteria.
- Involvement of superficial inguinal lymph nodes is considered locoregional nodal disease spread only if the tumor extends below the dentate line; otherwise, it is considered distant metastatic disease.

peristalsis can be minimalized, allowing the acquisition of high-resolution rectal MR images (4,5). Therefore, radiologists have a unique opportunity to contribute detailed information for initial staging of rectal cancer and assessment of response to neoadjuvant therapy.

The purpose of this article is to describe the expected imaging appearances of rectal adenocarcinoma after neoadjuvant chemoradiotherapy and the potential pitfalls at restaging MRI.

Management of Nonmetastatic Locally Advanced Rectal Adenocarcinoma

Neoadjuvant chemoradiotherapy has replaced up-front surgery for treatment of locally advanced rectal adenocarcinoma (T3 or T4) because it provides significantly better local recurrence-free survival and a better side effect profile (6–8). In addition, neoadjuvant chemoradiotherapy may downstage and decrease the size of the rectal tumor, changing the management plan from abdominoperineal resection to sphincter-preserving surgery.

Neoadjuvant chemoradiotherapy is currently recommended for locally advanced (T3 or T4) rectal adenocarcinoma regardless of lymph node status and for early (T1 or T2) rectal adenocarcinoma with locoregional lymph node involvement. Patients with low T1 and T2 adenocarcinomas that involve the anal sphincter may also benefit from neoadjuvant chemoradiotherapy regardless of their nodal status in an attempt to achieve clinical complete response and avoid surgery (2).

Between 8% and 30% of patients with rectal adenocarcinoma who receive neoadjuvant chemoradiotherapy followed by surgical resection have no residual malignancy at pathologic evaluation of the resected specimen (ie, *complete pathologic response*) (7,9–15). Therefore, a watch-and-wait management approach without surgery was investigated for patients with no evidence of residual adenocarcinoma after completion of neoadjuvant chemoradiotherapy. A watch-and-wait approach can be offered to patients with a *clinical complete response,* defined as an absent residual tumor at all three posttreatment evaluations (digital rectal examination, endoscopy, and rectal MRI) (16).

Patients with a clinical complete response who undergo the watch-and-wait approach have no significant difference in overall survival and disease-free survival compared with patients with a clinical complete response who undergo total mesorectal excision (11,17–19). In addition, patients who undergo a watch-and-wait approach have significantly better bowel function, have lower rates of incontinence, and avoid permanent stoma (11,17–20). Tumor regrowth occurs in 2.8%–34% of patients undergoing a watch-and-wait strategy, and most recurrences occur in the first 2 years after completion of neoadjuvant therapy. About 97% of cases with local recurrence have tumor regrowth within the bowel wall, and salvage therapy is still feasible in 88%–100% of these patients (11,16–18,21,22).

Reevaluation after completion of neoadjuvant treatment varies according to the local guidelines, institutional policies, and type of neoadjuvant therapy regimen (23). At the authors' institution, patients are generally evaluated with digital rectal examination, rectal MRI, and endoscopy 12 weeks after completion of neoadjuvant chemoradiotherapy. Endoscopic US is not routinely performed, and it is used only when good-quality MRI is not attainable. If no evidence of residual cancer is identified, a watch-and-wait approach may be offered after discussing the potential risks and benefits with the patient.

Patients undergoing a watch-and-wait strategy are followed up with periodic digital rectal examinations, endoscopy, and rectal protocol MRI every 3 months during the 1st year, every 4 months for the 2nd year, and every 6 months from the 3rd year of chemoradiotherapy completion. Serum carcinoembryonic antigen level is obtained at all follow-up visits. Patients who develop new symptoms (eg, rectal bleeding or bowel obstruction) in between scheduled surveillance appointments are investigated according to their presenting symptoms.

Rectal Protocol MRI Performance and Technique

To ensure optimal image quality, patients should evacuate their rectal contents before the acquisition, which may be facilitated by a self-administered enema (24,25). Spasmolytic agents (eg, butylscopolamine or glucagon) may be administered to reduce motion artifacts related to peristalsis of the rectum and/or adjacent bowel. Dedicated rectal MRI can be performed by using an external coil on 1.5-T or 3.0-T systems.

The Society of Abdominal Radiology Rectal Cancer Disease-Focused Panel and the European Society of Gastrointestinal and Abdominal Radiology have set minimum requirements for rectal MRI sequences, which include large field of view (FOV) axial T2-weighted images and diffusion-weighted images, small FOV coronal and sagittal T2-weighted images through the pelvis, and small FOV axial oblique and coronal

Table 1: Typical Parameters for Rectal Protocol MRI at 1.5 T and 3.0 T

Sequence	FOV (mm)	Section Thickness (mm)	Intersection Gap (mm)	Matrix	NEX	*b* Values (sec/mm²)	1.5 T TR/TE (msec)	1.5 T ETL	3.0 T TR/TE (msec)	3.0 T ETL
Sagittal T2-weighted large FOV	200	4	0.4	320 × 256	1	...	>3000/140	24	>3000/140	24
Axial T2-weighted large FOV	320	5	1	320 × 256	1	...	5000/120	20	5000/140	26
Axial large FOV DWI	380	5	1	96 × 128	1/8	100/800	>3000/70	Single shot	>3000/70	Single shot
Axial oblique T2-weighted small FOV	200	3	0.3	320 × 256	2	...	>3000/130	20	>3000/110	20
Axial oblique small FOV	200	3	0.3	80 × 80	2/16	100/800	>3000/70	Focus	>3000/70	Focus
Coronal oblique T2-weighted small-FOV	200	4	0.4	320 × 256	1	...	>3000/140	24	>3000/122	20
Pre- or postcontrast large-FOV spoiled GRE*	320	5	0	320 × 224	0.7	...	~4/1.7	1	~4/1.7	1

Note.—These values may vary slightly according to the system or vendor, patient's body habitus, patient toleration, and disease extent.
ETL = echo train length, GRE = gradient-recalled echo, NEX = number of excitations, TE = echo time, TR = repetition time.
* A flip angle of 12° is used for spoiled GRE. Pre- and postcontrast images are optional.

oblique T2-weighted images along the long axis of the tumor. Small FOV images should have a section thickness of 2–4 mm (5,26). Small FOV diffusion-weighted imaging (DWI) is associated with significantly better accuracy for response assessment after neoadjuvant therapy (27). Hence, the authors additionally obtain axial oblique small FOV diffusion-weighted images at the tumor bed.

High–*b*-value DWI (>1500 sec/mm²) can help increase the sensitivity for and conspicuity of residual and recurrent cancer (28). Hence, calculated (synthetic) diffusion-weighted images are automatically generated from all small and large FOV DWI sequences at rectal MRI at the authors' institution. Contrast-enhanced images and T1-weighted images are not mandatory for the rectal MRI protocol (5,26). Typical parameters for dedicated rectal MRI at the authors' institution are outlined in Table 1.

MRI for Primary Tumor Restaging after Neoadjuvant Therapy

The purpose of staging MRI after neoadjuvant chemoradiotherapy is to help assess cancer response to therapy, identify any new sites of disease, reevaluate the extent of disease, and plan the future surgical approach.

The imaging spectrum at T2-weighted imaging after neoadjuvant therapy includes a decrease in tumor volume, development of hypointense fibrotic changes at the tumor bed, and complete normalization of the rectal wall layers without evidence of a tumor or fibrosis (scar) (29,30). Persistent intermediate T2 signal intensity (with or without T2-hypointense fibrotic changes) at the tumor bed is indicative of residual tumor (30). The presence of a dense and thick fibrotic scar at the tumor bed is considered a good response (30). Complete resolution of tumor signal intensity with return of normal bowel wall layers and development of a thin T2-hypointense fibrotic scar at the tumor bed are two radiologic features closely associated with a pathologic complete response (30,31).

The addition of DWI to the standard assessment with T2-weighted sequences significantly improves the accuracy, sensitivity, and interreader agreeability for detection of complete responders without a significant impact on specificity (32,33). Assessment with DWI is binary, in which diffusion restriction (high signal intensity at DWI with corresponding low signal intensity on apparent diffusion coefficient [ADC] maps) is suggestive of residual malignancy, and its absence is suggestive of a good response.

Tumor regression grading systems were initially developed by pathologists to categorize the degree of response to neoadjuvant chemoradiotherapy in the resected specimens. Subsequently, MRI tumor regression grading (mrTRG) systems were developed to reflect their pathologic counterparts. However, none has been widely adopted, and they vary according to institutional policies. Brown et al have proposed the most widely used mrTRG system, and it is based on T2-weighted sequences without incorporating DWI, as outlined in Table 2 (34,35). mrTRG has been shown to have better correlation with survival outcomes than T stage after neoadjuvant therapy as determined at MRI (ymrT), and the ongoing TRIGGER trial is investigating the use of mrTRG classification to help direct patient management algorithms (35,36). Examples of

Table 2: Radiologic mrTRG System at T2-weighted MRI

Grade	Radiologic Response	Definition
mrTRG 1	Complete response	Return of normal bowel wall layers without evidence of the treated tumor, or thin curvilinear hypointense scar along the mucosa or submucosa at the tumor site
mrTRG 2	Near complete response	Thick dense hypointense fibrotic scar without obvious intermediate signal intensity at the tumor site, indicating minimal residual disease or no tumor
mrTRG 3	Moderate response	>50% fibrosis or mucin and visible intermediate signal intensity
mrTRG 4	Slight response	Little areas of hypointense fibrosis or mucin, but mostly intermediate T2 residual tumor signal intensity
mrTRG 5	No response	Intermediate T2 signal intensity, same appearances as the original tumor

Note.—Adapted and reprinted, with permission, from reference 34.

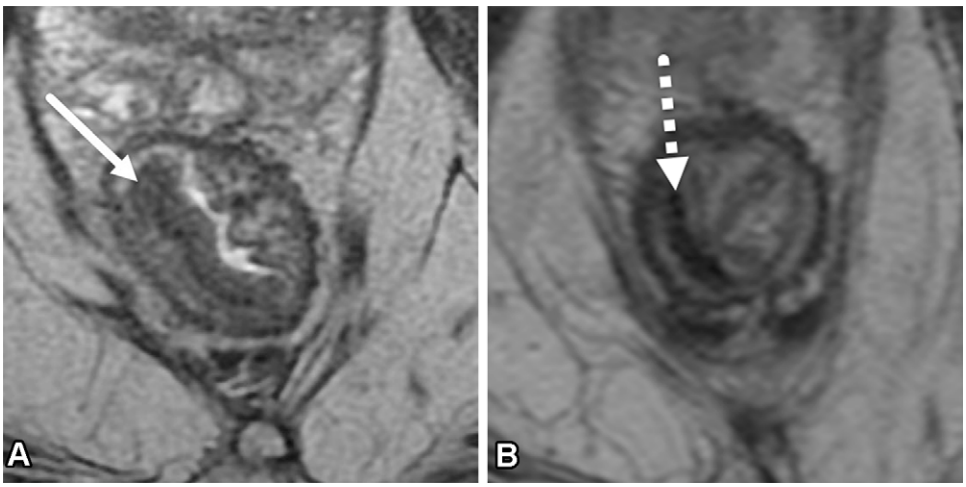


Figure 1. Complete response after neoadjuvant chemotherapy in a 79-year-old man with low rectal adenocarcinoma. **(A)** Pretreatment axial T2-weighted MR image shows a low rectal tumor (arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows a thin hypointense scar at the site of the treated tumor (arrow). No diffusion restriction was present on diffusion-weighted images, and no residual malignancy was identified at endoscopy (not shown). The patient was offered a watch-and-wait strategy and has been without evidence of disease for 31 months.

the spectrum of imaging appearances of rectal adenocarcinoma after neoadjuvant therapy are shown in Figures 1–5.

Qualitative assessment with the strict use of criteria for mrTRG 1 or 2 without diffusion restriction yields high sensitivity of 84% and negative predictive value of 94% for detection of a pathologic complete response but has moderate specificity of 56% (37). Absence of residual malignancy at all posttreatment evaluation modalities (digital rectal examination, endoscopy, DWI, and T2-weighted MRI) can help correctly predict a pathologic complete response in up to 98% of cases (38). In contradistinction, even when residual cancer is identifiable at all three postchemoradiotherapy assessment methods (MRI, endoscopy, and digital rectal examination), about 15% of patients have no residual tumor at resection (38). This overstaging has been attributed to the fact that tumors continue to shrink for up to 3 months after completion of neoadjuvant therapy, the presence of indeterminate mucosal abnormalities at proctoscopy, persistent suspicious lymph nodes, and equivocal abnormalities at restaging MRI (39,40).

Discordant findings between endoscopy and MRI are common. When residual cancer is identified at endoscopy or biopsy despite a radiologic complete response, MRI results can be dismissed, and the patient is no longer a candidate for the watch-and-wait strategy. However, MRI findings suggestive of residual disease with no evidence of malignancy at endoscopy constitute a management dilemma. At follow-up, many of these discordant cases turn out to be false positive at MRI (41). However, in 22% of the cases, abnormal MRI findings can predate endoscopic detection of residual or recurrent malignancy, which may be related to a residual or recurrent tumor growing below the mucosa (41).

Desmoplastic reaction (also known as reactive fibrosis) can be seen at baseline or restaging imaging of rectal adenocarcinoma. At MRI, it appears as thin stranding or spicules at T2-weighted sequences demonstrating low signal intensity and may occur at the base of the tumor or elsewhere in the mesorectum. Desmoplastic reaction should not be confused with tumor extension beyond the muscularis propria, which typically has a nodular appearance (29,30).

Mesorectal fascia involvement is associated with worse survival outcomes, and when it is present, the surgeon may alter the resection plane. A distance of 1 mm or less between the edge of the rectal tumor and the mesorectal fascia is the threshold for defining mesorectal fascia involvement (30). The positive predictive value for identifying mesorectal fascia involvement after neoadjuvant chemoradiotherapy is significantly lower than that for baseline imaging (42% vs 80%; $P \leq .001$) (42). Identification of mesorectal fascia involvement

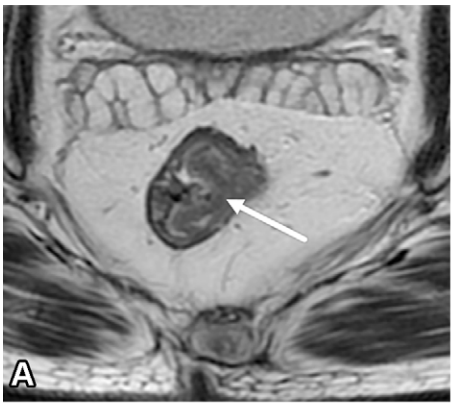
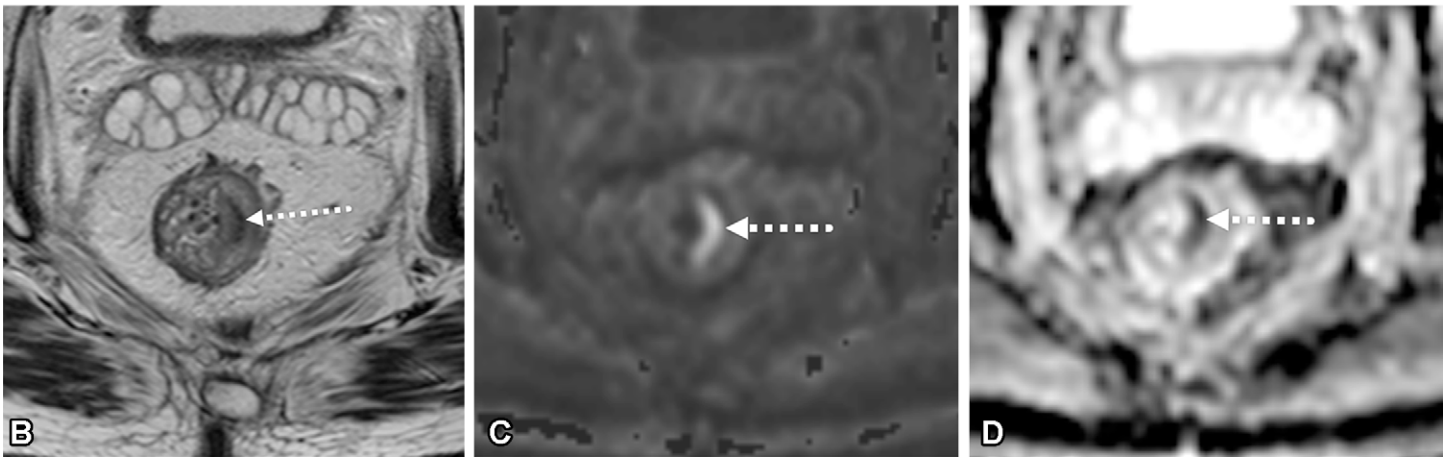


Figure 2. Thin fibrotic scar with diffusion restriction consistent with residual malignancy in a 56-year-old man with mid rectal adenocarcinoma who completed chemoradiotherapy. **(A)** Baseline axial T2-weighted MR image shows a T3 mid rectal tumor (arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows a thin hypointense scar at the site of the treated tumor (arrow). **(C)** Axial diffusion-weighted image shows high signal intensity (arrow). **(D)** Axial ADC map shows corresponding low signal intensity (arrow), in keeping with restricted diffusion. A tumor ulcer was identified at endoscopy, and the patient underwent total mesorectal excision.



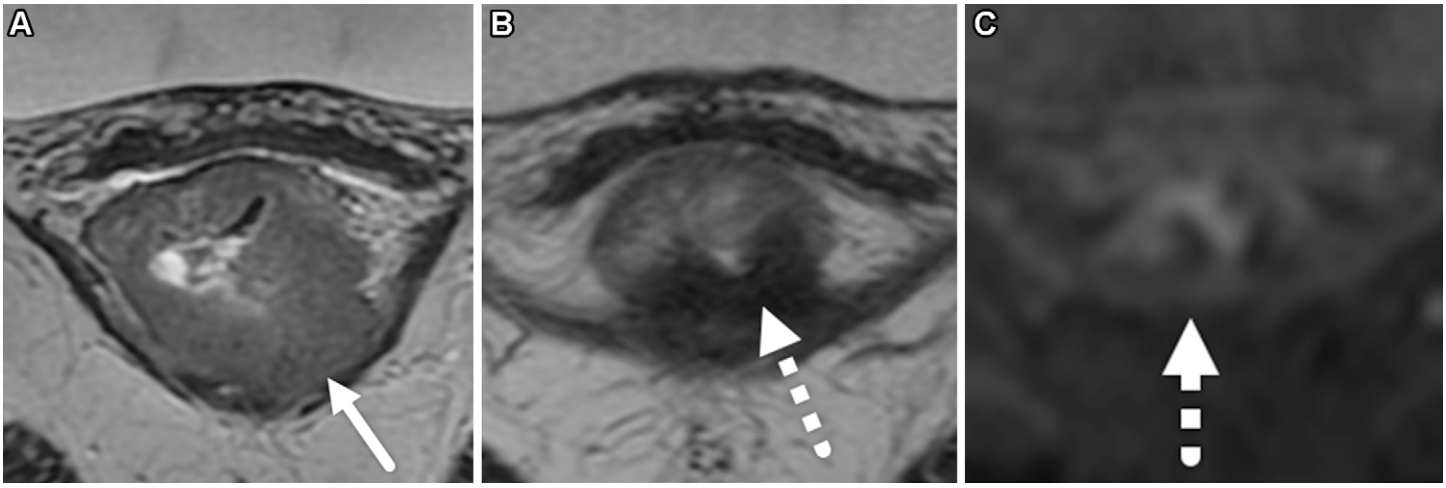
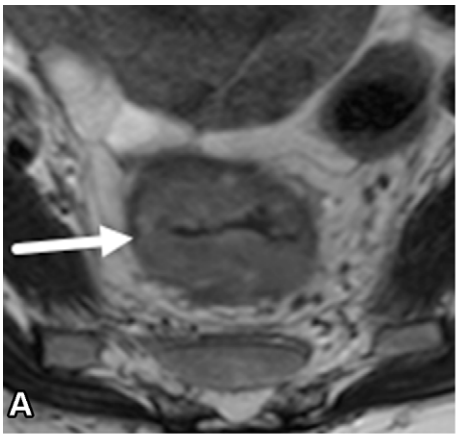


Figure 3. Near complete response with thick or dense scarring after neoadjuvant chemoradiotherapy in a 53-year-old woman with low rectal adenocarcinoma. **(A)** Baseline axial T2-weighted MR image shows an intermediate-signal-intensity, near-circumferential low rectal tumor (arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows a thick hypointense scar at the site of the treated tumor (arrow). **(C)** Axial small FOV diffusion-weighted image after completion of neoadjuvant chemoradiotherapy shows no restricted diffusion in the tumor bed (arrow). No tumor was identified at endoscopy, and the patient has been undergoing a watch-and-wait strategy for 27 months without disease recurrence.

after neoadjuvant therapy is more challenging because it is difficult to exclude residual malignant cells residing within thick fibrotic changes involving the mesorectal fascia (42).

Extramural venous invasion is associated with worse survival outcomes and higher local or distant recurrence rates (30). At baseline MRI, extramural venous invasion appears as an elongated lesion at T2-weighted sequences with intermediate signal intensity, expands the vein lumen, and commonly arises from the primary rectal tumor (30). After neoadjuvant chemoradiotherapy, complete resolution and development of T2-hypointense fibrotic changes within the vein lumen are indicative of a good response and occur in about 56% of patients. The recurrence rate for patients with persistent extramural venous invasion after neoadjuvant therapy is more than double that for patients with a good response (47.1% vs 22.7%) (43).



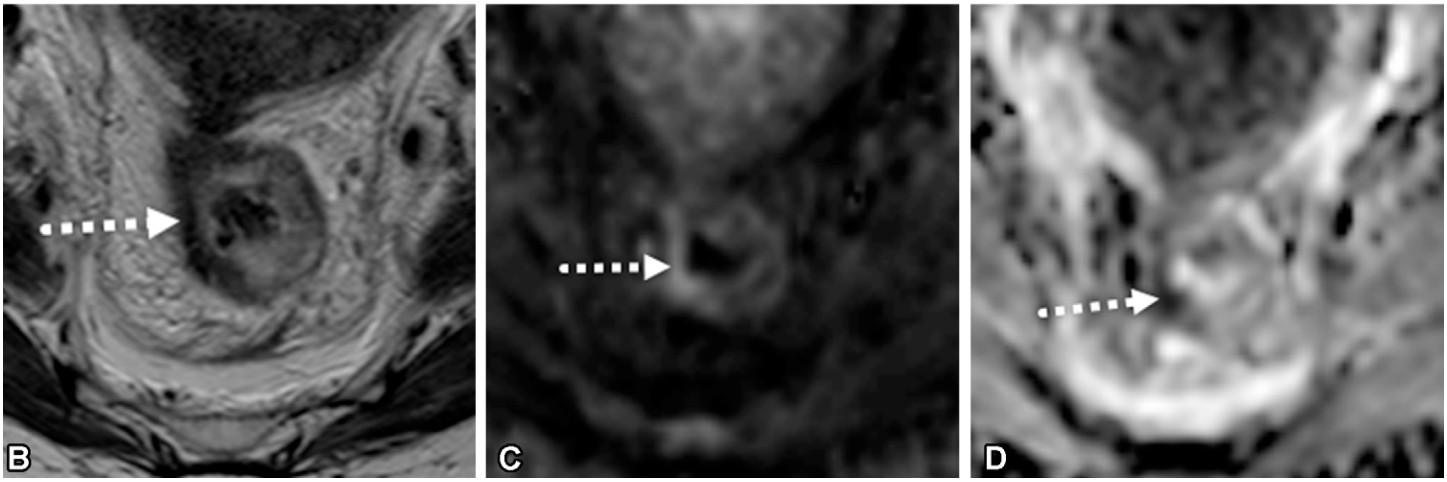
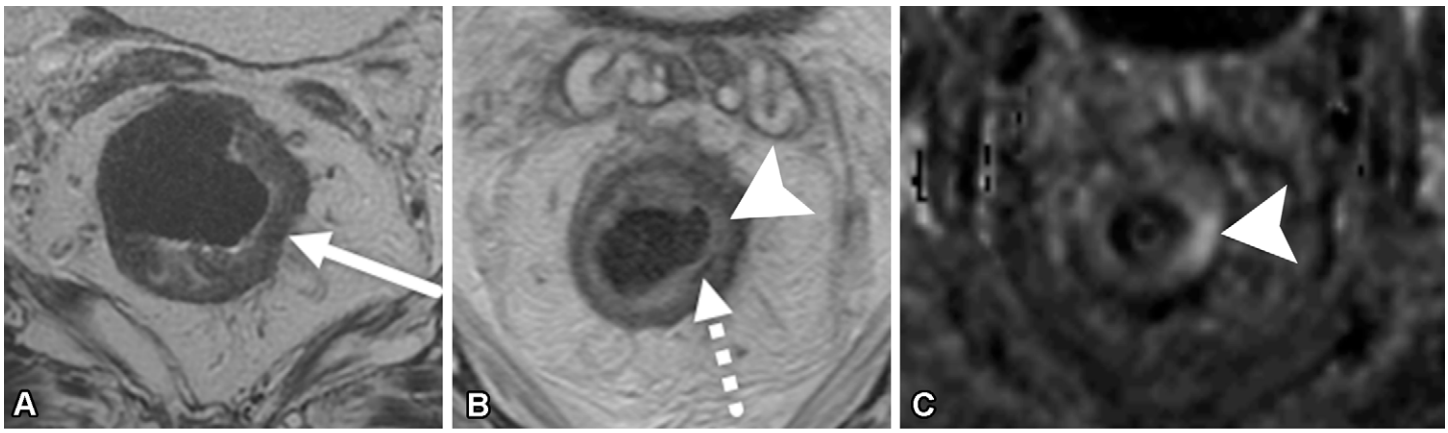


Figure 4. Residual tumor in a diffusion-restricting, thick, dense fibrotic scar after neoadjuvant chemoradiotherapy in a 57-year-old woman with low rectal adenocarcinoma. **(A)** Baseline axial T2-weighted MR image shows an intermediate-signal-intensity, near-circumferential low rectal tumor (arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows a thick hypointense scar at the site of the treated tumor (arrow). **(C, D)** Axial diffusion-weighted image **(C)** shows high signal intensity (arrow in **C**) and axial ADC map **(D)** shows corresponding low signal intensity (arrow in **D**), in keeping with restricted diffusion. The residual malignancy was identified at endoscopy (not shown), and the patient underwent total mesorectal excision.



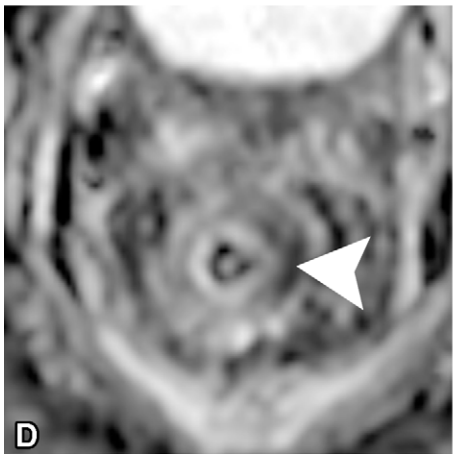


Figure 5. Slight response with a small amount of fibrosis and prominent residual tumor signal intensity after neoadjuvant chemoradiotherapy in a 58-year-old man with T3 rectal adenocarcinoma. **(A)** Baseline axial T2-weighted MR image shows an intermediate-signal-intensity semicircumferential low rectal tumor (arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows a small hypointense fibrotic scar at the site of the treated tumor (arrow), with a larger area of persistent intermediate signal intensity (arrowhead). **(C, D)** Axial diffusion-weighted image **(C)** shows high signal intensity (arrowhead in **C**) and axial ADC map **(D)** shows corresponding low signal intensity (arrowhead in **D**), in keeping with restricted diffusion at the nonfibrotic portion of the tumor. The residual malignancy was identified at endoscopy (not shown), and the patient underwent total mesorectal excision.

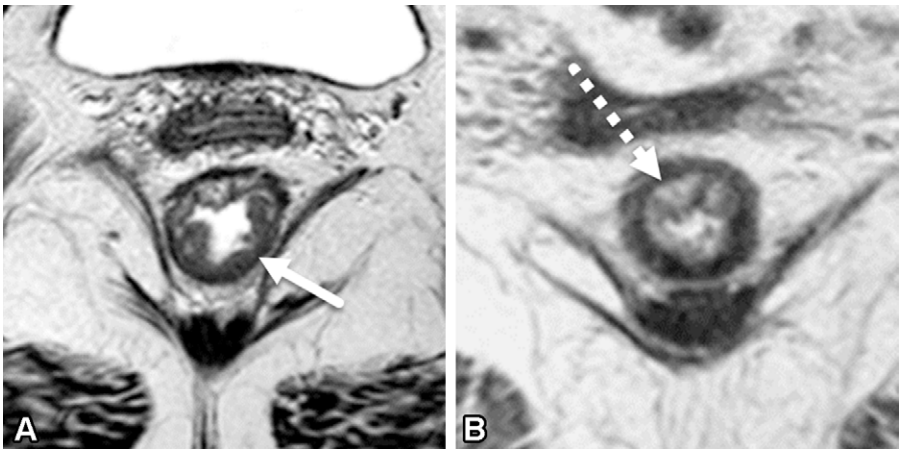


Figure 6. Submucosal edema mimicking residual tumor in the uninvolved rectal wall in a 50-year-old woman with rectal adenocarcinoma. **(A)** Baseline axial T2-weighted MR image shows a semicircumferential rectal tumor extending between the 2-o'clock and 9-o'clock positions (arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows high signal intensity at the uninvolved rectal wall (arrow). Response assessment should not be based on the appearance of the uninvolved parts of the rectum.

Tumor deposits (TDs) are defined in the current eighth edition of the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual* as "discrete tumor nodules within the lymph drainage area of the primary carcinoma without identifiable lymph node tissue or identifiable vascular or neural structure" and are associated with worse survival outcomes compared with lymphadenopathy (44,45). At baseline T2-weighted imaging, TDs have been described as nodules with heterogeneous or intermediate signal intensity, which are discontinuous from the primary rectal tumor and frequently manifest along the superior hemorrhoidal vessels. Unlike lymph nodes, TDs can invade and interrupt adjacent veins, and when viewed on coronal or sagittal images, they can have a comet-tail appearance, tapering into or along the veins (30,45). After neoadjuvant chemoradiotherapy, patients with persistent TDs have significantly worse disease-free survival compared with those in whom TDs resolve (hazard ratio, 3.91 [95% confidence interval: 2.18, 7.03]; $P < .001$) (45).

Evaluation of invasion of adjacent pelvic compartments at MRI after neoadjuvant therapy is highly accurate (87.6%), and negative predictive values for different pelvic compartments range from 90.5% to 100%. On the other hand, positive predictive values are slightly lower and vary from 70.4% to 100%, which may be explained by the limited ability to exclude residual malignancy once residual fibrosis involves adjacent structures (46).

Pitfalls in MRI Restaging of Luminal Rectal Adenocarcinoma

Submucosal Edema

Neoadjuvant chemoradiotherapy can cause submucosal edema of the uninvolved rectal wall that appears as thickening with intermediate-to-high T2 signal intensity and may mimic the intermediate T2 signal intensity of the residual tumor (Fig 6). Comparison with the site of the original tumor at pretreatment MRI is crucial to avoid this pitfall.

T2 Shine-through Effect

The T2 shine-through phenomenon is observed at DWI and indicates facilitated diffusion. This effect occurs in tissues with a long relaxation time (eg, edema). At MRI, the T2 shine-through effect shows high signal intensity at T2-weighted imaging, at DWI, and on ADC maps (as opposed to diffusion restriction, which demonstrates high signal intensity at DWI with low signal intensity on ADC maps). Edematous changes can frequently occur at the site of the treated tumor, with a resultant potential pitfall at restaging MRI (Fig 7). Diffusion-weighted images should be interpreted only in conjunction with ADC maps to avoid misinterpretation of edema as residual tumor.

T2 Dark-through Effect

The T2 dark-through effect (also known as the T2 blackout effect) is used to describe low signal intensity on ADC maps with corresponding low signal intensity at DWI and at T2-weighted sequences (47). Tissues with low T2 relaxation time can show T2 dark-through effect (eg, fibrosis). The T2 hypointense fibrotic scar at the site of treated malignancy can show this phenomenon in the absence of residual malignancy (Fig 8). Evaluation of the ADC map without the corresponding diffusion-weighted images can lead to erroneous interpretation of T2 dark-through effect as restricted diffusion, resulting in a false-positive diagnosis of a residual tumor. A correlation between abnormal findings on ADC maps and findings on diffusion-weighted images is necessary to avoid this pitfall.

Signal Intensity Abnormalities from Intraluminal Contents

Intraluminal contents can mimic imaging appearances of the residual tumor and can show intermediate signal intensity on T2-weighted images with or without restricted diffusion. Layering and air-fluid levels within the distended rectal lumen can help differentiate between intraluminal fluid and residual tumor. However, differentiation between these two can be more challenging when the lumen is collapsed. In this situation, the shape of the abnormal signal may help to differentiate the intraluminal contents, which typically have a star shape (Fig 8), from a residual tumor, which typically has a curvilinear, masslike, and/or *C* or *U* shape (Fig 4).

With the popularization of DWI, a new issue of susceptibility artifacts affecting ADC maps and diffusion-weighted sequences has emerged. Filling the rectal lumen with gel has been proposed in order to displace air and reduce artifacts. However, endorectal gel can compress the tumor against the mesorectal fascia or adjacent organs, potentially causing erroneous overstaging. In addition, it can cause T2 shine-through effect that

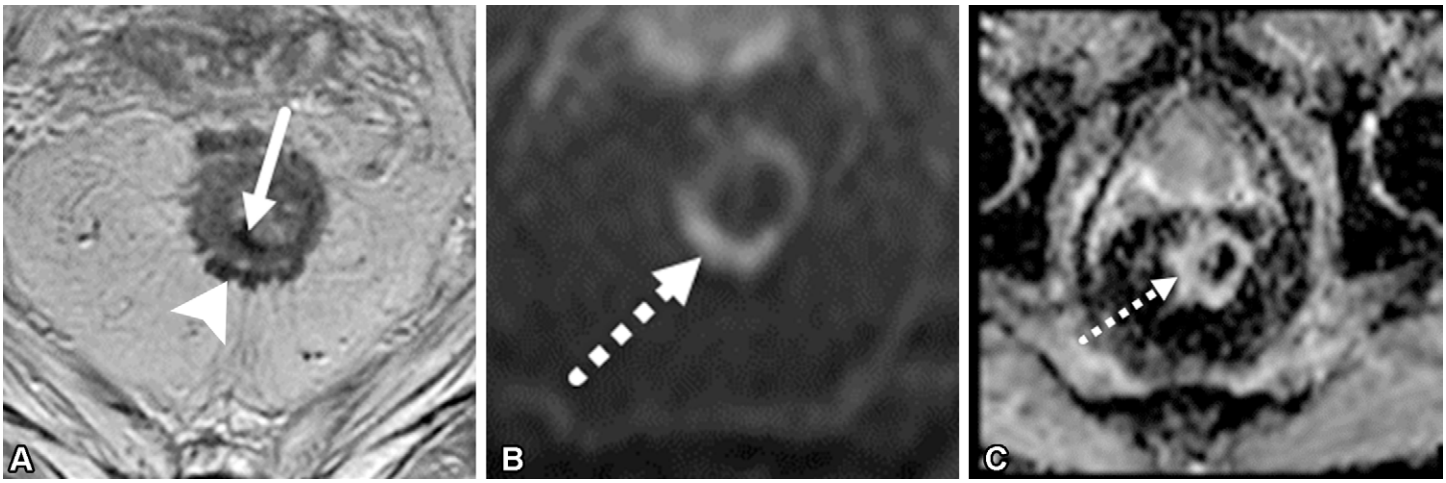


Figure 7. T2 shine-through effect mimicking residual tumor in a 51-year-old man with rectal adenocarcinoma. **(A)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows a thin scar along the mucosal surface at the tumor bed (arrow) and a second scar at the interface of mesorectal fat and muscularis propria (arrowhead), in keeping with the split scar sign, which is highly specific for a complete response and occurs more frequently in tumors extended beyond the muscularis propria layer (T3) at baseline. **(B)** Axial diffusion-weighted image shows high signal intensity at the tumor bed (arrow). **(C)** Axial ADC map shows high signal intensity at the tumor bed (arrow). The presence of high signal intensity on the diffusion-weighted image and ADC map is consistent with T2 shine-through effect (not restricted diffusion) and so the patient has a complete response. The high signal intensity detected at DWI must have corresponding low signal intensity on the ADC map to represent restricted diffusion. The patient has been undergoing watch-and-wait surveillance for 37 months without evidence of recurrent disease.

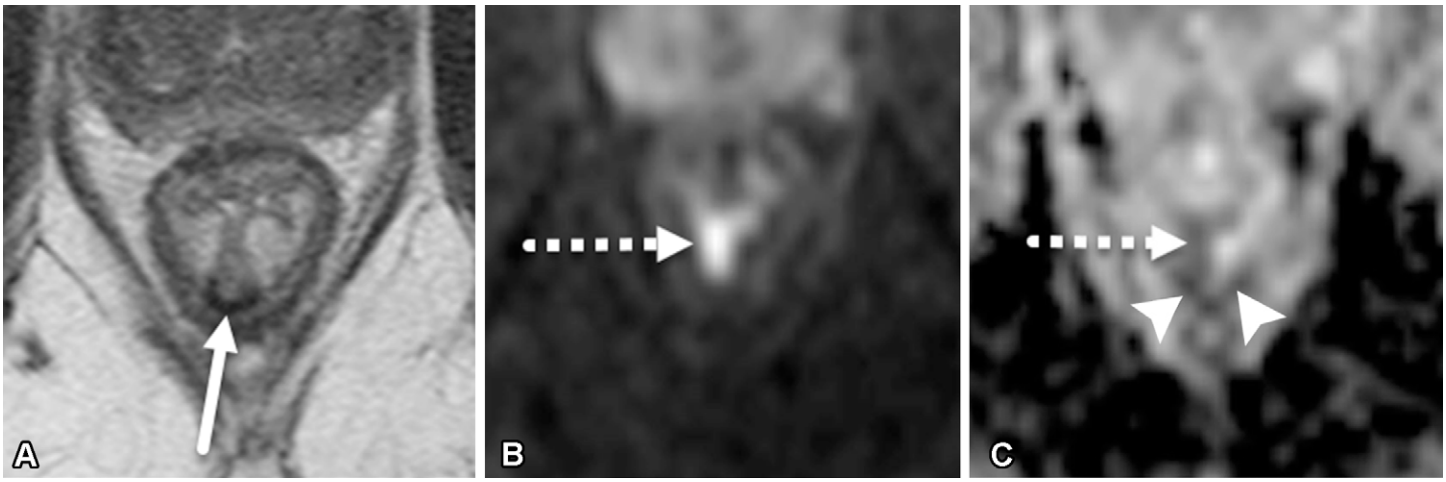


Figure 8. T2 dark-through effect and rectal contents causing restricted diffusion and mimicking residual tumor in a 49-year-old man with rectal adenocarcinoma. **(A)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows a thin hypointense scar at the tumor bed (arrow). **(B)** Axial diffusion-weighted image shows high signal intensity within the rectal lumen at the level of the treated tumor (arrow). Note the absence of any high signal intensity at the scar along the rectal wall. **(C)** Corresponding axial ADC map shows low signal intensity at this site (arrow), consistent with restricted diffusion. Restricted diffusion from residual tumor appears along the rectal wall and often has a *C* or *U* shape. Restricted diffusion of bowel contents often has a branching or starlike shape when the rectal lumen is collapsed, as seen in this case. The *C*-shaped low signal intensity on the ADC map along the scar (arrowheads) has no high-signal-intensity correlation at DWI, in keeping with T2 dark-through effect. Low signal intensity on ADC maps must have a corresponding high signal intensity at DWI to represent restricted diffusion, and so this patient had a complete response. The patient has been undergoing watch-and-wait surveillance for 37 months without evidence of recurrent disease.

may obscure true restricted diffusion of residual malignancy. Hence, the routine use of rectal gel is not recommended (5). Self-administration of a rectal enema a few minutes before the acquisition significantly decreases air-related artifacts and may be used to overcome this issue (24,25).

Diffusion Restriction in the Uninvolved Rectal Wall

Neoadjuvant radiation therapy–related proctitis can cause diffusion restriction that may be erroneously misinterpreted as residual tumor (Fig 9) (48,49). Comparison with baseline images is a crucial step in restaging rectal cancer after neoadjuvant therapy. New signal intensity abnormalities in the uninvolved parts of the rectal wall should be dismissed, and only signal intensity abnormalities occurring at the tumor bed should be considered for tumor response assessment. In most cases, signal intensity abnormalities from inflammation or edema resolve at follow-up MRI.

Susceptibility Artifacts

Commonly used single-shot echo-planar diffusion-weighted sequences are vulnerable to susceptibility artifacts that occur at the interface between air and soft tissues and appear

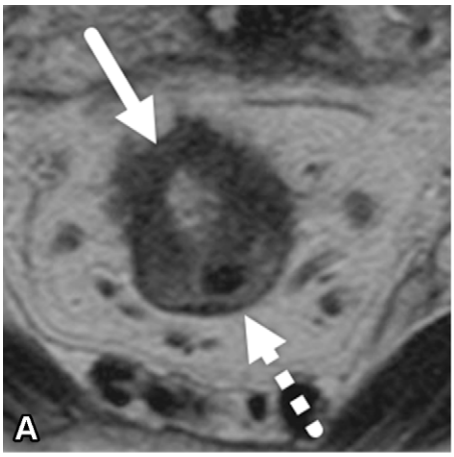
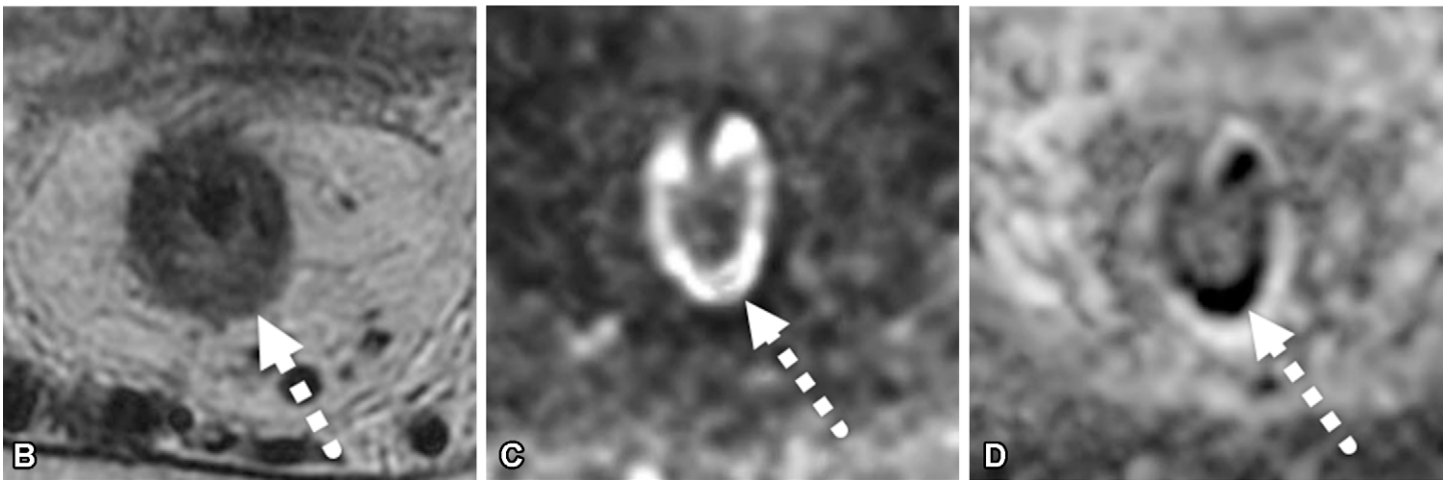


Figure 9. Diffusion restriction in the uninvolved rectal wall mimicking residual tumor in a 61-year-old woman with rectal adenocarcinoma. **(A)** Baseline axial T2-weighted MR image shows a semicircumferential rectal tumor extending between the 8-o'clock and 4-o'clock positions (solid arrow). Note the uninvolved posterior rectal wall (dotted arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows new thickening of the uninvolved posterior rectal wall (arrow). **(C, D)** Axial diffusion-weighted image shows high signal intensity (arrow in **C**) and axial ADC map shows corresponding low signal intensity (arrow in **D**), representing restricted diffusion most prominent at the uninvolved posterior rectal wall (arrow). The response assessment should be based on the appearance of the tumor bed and not on the uninvolved parts of the rectum.



as geometric image distortion with bright and dark areas. In addition, susceptibility artifacts may also result from metallic clips, fiducial markers, hip prostheses, or other metallic pelvic hardware. Severely degraded DWI images can be nondiagnostic.

Evacuation of the bowel before the acquisition can help avoid susceptibility artifacts. Alternatively, administering a microenema shortly before the examination may help significantly reduce susceptibility artifacts (25). Alternative DWI techniques may be used to reduce both air- and metal-related susceptibility artifacts and can be particularly useful in patients with a hip prosthesis or metallic fiducial markers at the site of prior polypectomy (50–53).

Mucin

Mucinous colorectal adenocarcinoma is characterized by abundant extracellular mucin comprising more than 50% of the tumor volume, which is produced by malignant cells (44). On the other hand, signet-ring cell adenocarcinoma contains large globules of intracellular mucin (44). These histologic subtypes are associated with worse survival outcomes, higher rates of metastatic disease, and higher rates of local recurrence compared with their counterparts involving other parts of the colon and compared with nonmucinous rectal adenocarcinomas (54–58). In addition, they are associated with a high level of microsatellite instability, which is a phenotype associated with loss of DNA repair that has been linked to Lynch syndrome and a better response to immunotherapy (2,59).

At baseline MRI, mucinous adenocarcinoma has a typical radiologic appearance, with high signal intensity on T2-weighted images and high signal intensity on both diffusion-weighted images and ADC maps (T2 shine-through effect) (60). After neoadjuvant therapy, high T2 signal intensity of mucinous tumors typically persists, and it may or may not harbor residual malignant cells (cellular mucin vs acellular mucin) (54). There is no reliable imaging modality to distinguish cellular from acellular mucin, and these patients are offered surgery (Fig 10) (54). In one study of patients with mucinous rectal adenocarcinoma, none achieved a radiologic complete response, but about 20% of patients had a pathologic complete response at resection (61).

Nonmucinous adenocarcinomas at baseline may also undergo colloid degeneration in response to neoadjuvant therapy and develop mucin pools at posttreatment MRI (Fig 11). Cellular and acellular mucin pools are also indistinguishable at restaging MRI (62). In one study, only 12.8% of patients with mucin pools after neoadjuvant therapy had no residual malignant cells at evaluation of the resected specimen (63).

Interruption of Scar Tissue

The "split scar sign" at postchemoradiotherapy MRI has high specificity (97%) but moderate sensitivity (52%–64%) for a complete response. It is defined as a fibrotic scar with low signal

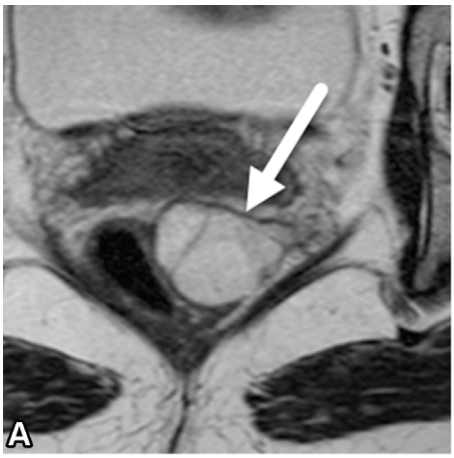
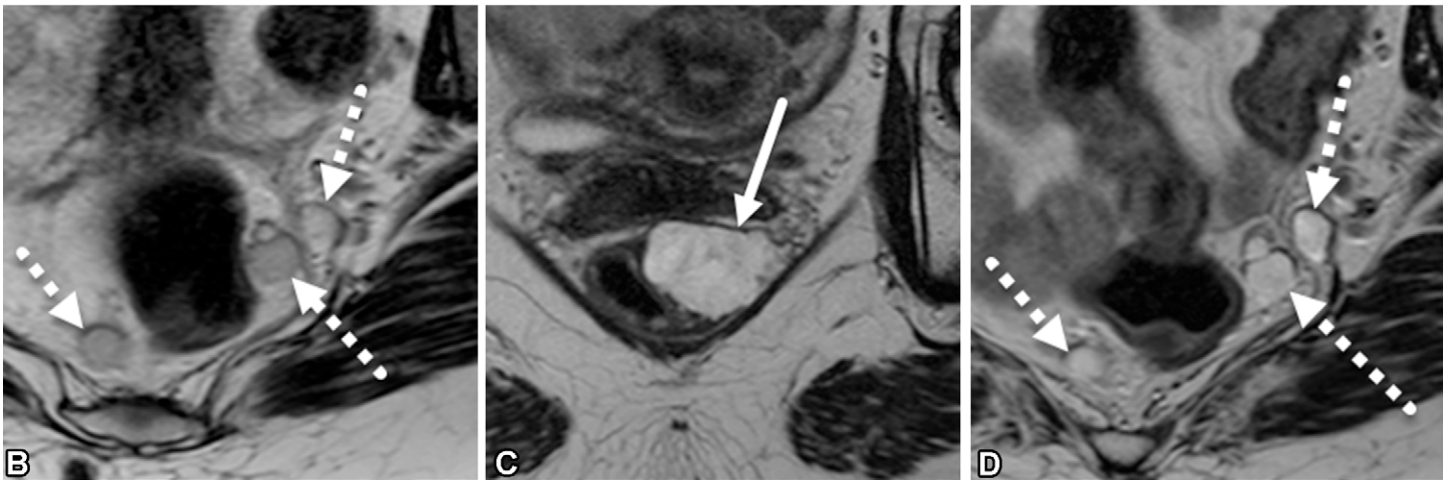


Figure 10. Mucinous lymph nodes in a 55-year-old woman with rectal adenocarcinoma. **(A)** Pretreatment axial T2-weighted MR image shows a high-signal-intensity mucinous rectal adenocarcinoma demonstrating extraluminal exophytic growth (arrow). **(B)** Pretreatment axial T2-weighted MR image shows several high-signal-intensity mesorectal and internal iliac lymph nodes (arrows), consistent with mucin-containing metastatic lymph nodes. **(C)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows persistent high signal intensity in the primary tumor (arrow). **(D)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows persistent high signal intensity in the metastatic lymph nodes (arrows). The mucin may persist after completion of neoadjuvant chemoradiotherapy, and it may possibly harbor malignant cells. Discrimination between cellular and acellular mucin is not feasible with current imaging modalities. The patient underwent total mesorectal excision with left pelvic sidewall lymph node dissection, and the results confirmed the presence of residual malignant cells within the mucinous primary tumor and lymph nodes. Note that the extraluminal exophytic growth pattern of mucinous rectal adenocarcinoma is not uncommon and may mimic the appearance of perianal or perirectal abscess at CT.



intensity on T2-weighted images involving the submucosa, with an underlying layer of intermediate T2 signal intensity at the muscularis propria and a third outermost hypointense layer corresponding to perirectal fibrosis (Fig 7). This appearance occurs more frequently in tumors that breach the muscularis propria layer (≥T3) at baseline (64).

At postneoadjuvant chemoradiotherapy MRI or at follow-up of patients undergoing a watch-and-wait strategy, residual or recurrent tumor can appear as intermediate T2 signal intensity interrupting the hypointense fibrotic scar (Fig 12). Although an intact scar may still be present above and/or below the site of tumor regrowth, interruption of the scar is an early feature indicating tumor recurrence, and it should prompt endoscopic verification while salvage therapy and surgery are still feasible. Intermediate T2 signal intensity dividing the mucosal or serosal scar should not be confused with the split scar sign (Fig S1).

MRI for Lymph Node Restaging after Neoadjuvant Chemoradiotherapy

The rectum has a unique lymphatic drainage that is different from that of other parts of the colon and other pelvic malignancies, and even different parts of the rectum have different lymphatic drainage pathways.

There are two lymphatic drainage pathways of the rectum. The dominant drainage pathway serves the entirety of the rectum and extends superiorly along the superior rectal and inferior mesenteric arteries. The rectum at and below the peritoneal reflection drains laterally toward the lateral pelvic lymph nodes. Hence, locoregional lymph nodes of rectal adenocarcinoma include the mesorectal, superior rectal, internal iliac, and obturator lymph nodes (44).

External iliac lymph node involvement is considered locoregional nodal involvement in other pelvic malignancies (eg, uterine, ovarian, prostate, and bladder), but it is considered distant metastasis in rectal adenocarcinoma (44).

The incidence of lateral pelvic lymph node involvement increases the closer the tumor is to the anal verge (65). In one large study including 1427 patients, tumors involving the upper rectum (at the S1-S2 vertebrae level) never had any pelvic sidewall disease (except in lesions invading adjacent structures); T3 or T4 tumors involving the rectum between the peritoneal reflection and S2 vertebra had pelvic sidewall nodal involvement in only 3.9% of cases (65). In contrast, tumors in which the lower pole was below the peritoneal reflection had lateral pelvic lymph node involvement in 18% of T3 and 28.8% of T4 tumors (65).

The T stage of a tumor is also associated with the risk of pelvic sidewall lymph node involvement. For instance, in tumors lying below the peritoneal reflection, lateral pelvic lymph node involvement occurs in 0.9% of T1 tumors, 5.4% of T2 tumors, 18% of T3 tumors, and 28.8% of T4 tumors (65).

Superficial inguinal lymph node involvement is considered locoregional disease spread only in cases of rectal

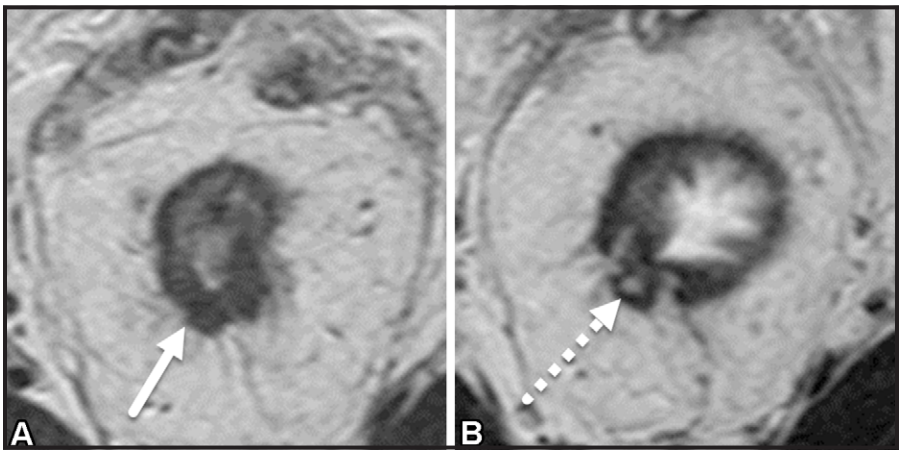


Figure 11. Mucin pool developing at the tumor bed after completion of neoadjuvant chemoradiotherapy in a 61-year-old man with rectal adenocarcinoma. **(A)** Pretreatment axial T2-weighted MR image shows a semicircumferential rectal tumor along the posterior rectal wall (arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows a new high-signal-intensity mucin pool at the tumor bed (arrow). Mucin pools can develop after treatment of previously nonmucinous adenocarcinoma. Although mucinous pools indicate a good response to therapy, they may or may not harbor malignant cells, and discrimination of these two types of mucin pools is not feasible with current imaging modalities. Residual malignant cells were identified at pathologic evaluation of the resected specimen.

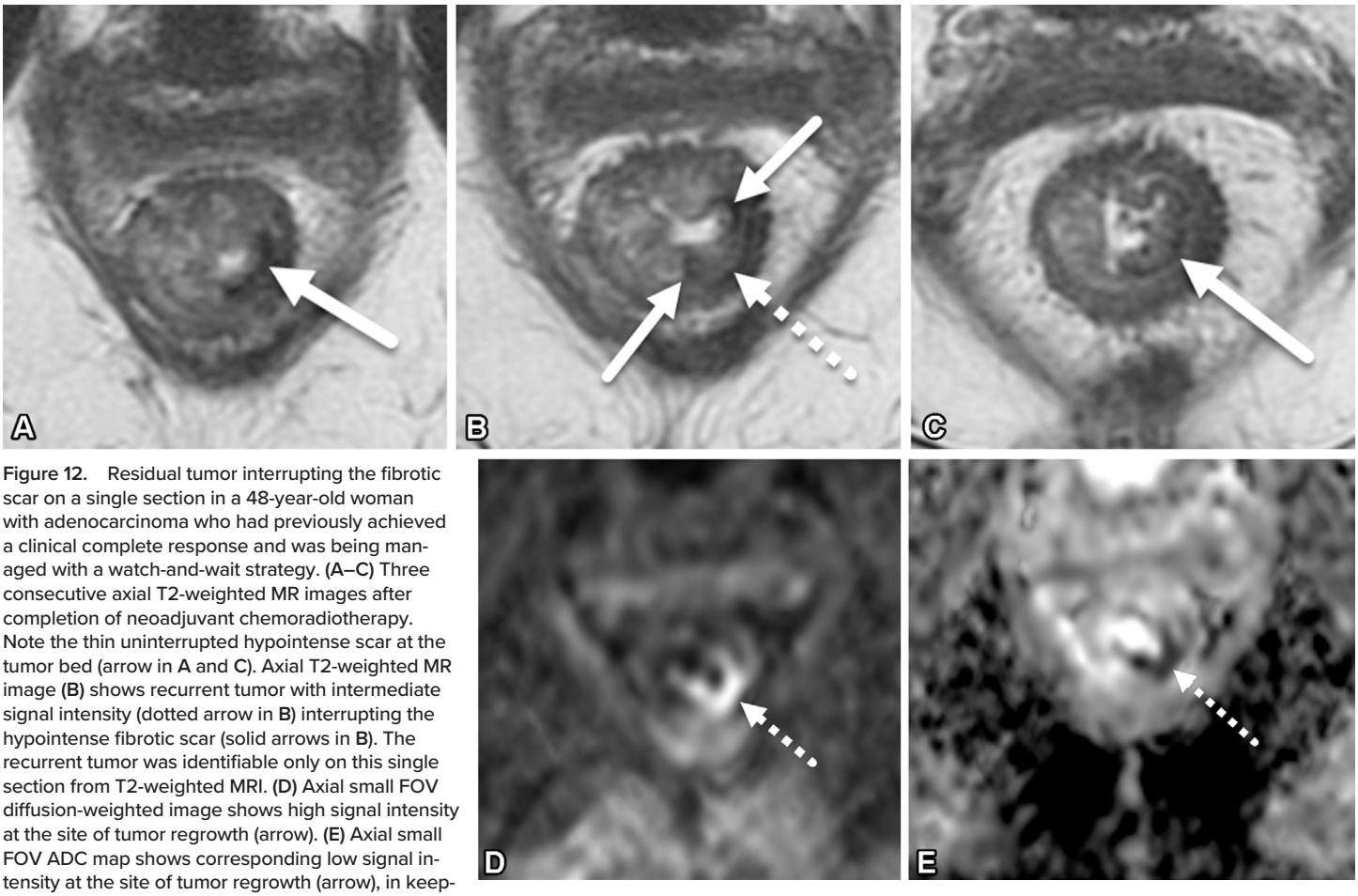


Figure 12. Residual tumor interrupting the fibrotic scar on a single section in a 48-year-old woman with adenocarcinoma who had previously achieved a clinical complete response and was being managed with a watch-and-wait strategy. **(A–C)** Three consecutive axial T2-weighted MR images after completion of neoadjuvant chemoradiotherapy. Note the thin uninterrupted hypointense scar at the tumor bed (arrow in **A** and **C**). Axial T2-weighted MR image **(B)** shows recurrent tumor with intermediate signal intensity (dotted arrow in **B**) interrupting the hypointense fibrotic scar (solid arrows in **B**). The recurrent tumor was identifiable only on this single section from T2-weighted MRI. **(D)** Axial small FOV diffusion-weighted image shows high signal intensity at the site of tumor regrowth (arrow). **(E)** Axial small FOV ADC map shows corresponding low signal intensity at the site of tumor regrowth (arrow), in keeping with restricted diffusion. The fibrotic scar should be scrutinized on thin-section images to identify early recurrence when salvage therapy is still feasible. Radiologists should not have satisfaction of search after identifying a thin fibrotic scar on a few sections.

adenocarcinoma that extend below the dentate line, an anatomic landmark lying approximately at the middle of the anal sphincter (44). Hence, accurate understanding of different lymphatic drainage pathways based on the location of the rectal tumor is crucial for identifying the potential lymphatic spread of rectal adenocarcinoma.

The Lateral Node Consortium Study group provided the only criteria for determining worrisome pelvic sidewall lymph nodes at baseline and after neoadjuvant chemoradiotherapy (66,67). However, a clear understanding of the anatomic boundaries of pelvic lymph node compartments is necessary for accurate localization of metastatic nodes and application of size criteria, as detailed later. The mesorectal lymph node compartment is enclosed within the mesorectal fascia and drains superiorly to the superior rectal and inferior mesenteric lymph nodes (68). All malignancies involving the rectum between the dentate line up to the rectosigmoid junction can spread to the lymph nodes within this compartment.

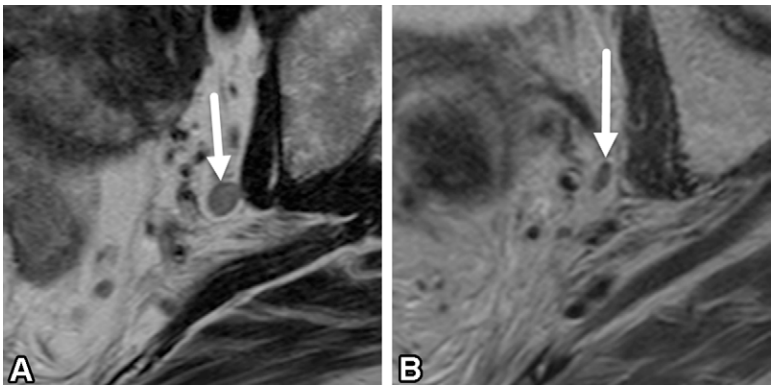


Figure 13. Good response of an obturator lymph node in a 52-year-old woman with rectal adenocarcinoma. **(A)** Pretreatment axial T2-weighted MR image shows a suspicious (>7 mm in short axis) left obturator lymph node (arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows shrinkage of this lymph node (arrow) below the cutoff value for the obturator lymph nodes (<6 mm). Thus, pelvic sidewall lymph node dissection is not indicated in this case.

The accuracy of mesorectal lymph node restaging MRI after chemoradiotherapy is much better than that of baseline staging. At restaging MRI, absence of any detectable mesorectal lymph node at DWI can rule out the presence of nodal involvement at resection (negative predictive value and sensitivity of 100%) (69). When mesorectal lymph nodes are still identifiable at restaging MRI, size criteria are a better predictor of tumor involvement than are morphologic criteria (eg, border irregularity) (70). A cutoff of 5 mm in the short axis is used to differentiate suspicious from reactive mesorectal lymph nodes after neoadjuvant chemoradiotherapy (5). However, there is overlap in size between malignant and reactive mesorectal lymph nodes, with up to 11.2% of nodes that measure less than 5 mm harboring malignant cells at resection (70).

Obturator and internal iliac lymph nodes receive lymphatic drainage from tumors centered at or below the peritoneal reflection (71). Some authors refer to the obturator lymph nodes as the medial group of the external iliac lymphatic vein (72). The *obturator lymphatic chain* is defined as the lymph nodes enclosed within the pararectal fat compartment extending between the obturator internus muscle laterally, the mesorectal fascia and perivesical space medially, the external iliac artery or vein superiorly and anteriorly, the internal iliac vasculature posteriorly, and the levator muscle inferiorly. The internal iliac lymph node compartment extends between the origin of the internal iliac artery superiorly and the point where the internal pudendal artery exits through the infrapiriformis foramen inferiorly, extends medially to the mesorectal fascia, and extends laterally to the lateral aspect of the internal iliac artery or vein (Fig S2) (66,67).

Pelvic sidewall lymph node dissection can cause injury to several nervous structures located within the pararectal or extramesorectal fat planes (superior hypogastric plexus, hypogastric nerve, inferior hypogastric plexus, and sacral nervi erigentes). These nerves provide sympathetic and parasympathetic innervation to the urinary bladder and genital organs. Injury to these structures may result in voiding and/or sexual dysfunction (urinary incontinence, retrograde ejaculation, erectile dysfunction, difficulty achieving orgasm, and lubrication dysfunction) (73,74). Hence, pelvic sidewall lymph node dissection is not routinely performed at surgery for rectal adenocarcinoma, and it is reserved for patients with suspected pelvic sidewall nodal involvement (Figs 13, 14).

The results from the Lateral Node Consortium Study provided size criteria for determining worrisome pelvic sidewall lymph nodes (internal iliac and obturator lymph nodes) at baseline and after neoadjuvant chemoradiotherapy (66,67). Patients with baseline obturator and internal iliac lymph nodes 7 mm or larger in the short axis and who receive neoadjuvant chemoradiotherapy followed by total mesorectal excision (without lateral lymph node dissection) have a 19.5% 5-year incidence of local lateral recurrence (recurrence in the pelvic sidewall), as opposed to 4.9% in patients with lymph nodes smaller than 7 mm and 2.1% in patients with no identifiable obturator or internal iliac lymph nodes. Patients with lymph nodes 7 mm or larger who undergo lateral lymph node dissection (in addition to total mesorectal lymph node excision and neoadjuvant chemoradiotherapy) have a significantly lower 5-year incidence of lateral recurrence (5.7% vs 19.5%) (66). At restaging MRI after neoadjuvant chemoradiotherapy, patients with internal iliac or obturator lymph nodes measuring 4 mm or smaller in the short axis (which were ≥7 mm at baseline) have no lateral local recurrence after 3 years.

The suspicious sidewall lymph nodes (≥7 mm) at baseline, which remained larger than 4 mm in the internal iliac compartment and larger than 6 mm in the obturator compartment after neoadjuvant chemoradiotherapy, were associated with a 5-year lateral local recurrence rate of 52.3% (Fig 15). This rate was significantly lower (8.7%) for patients who underwent lateral lymph node dissection besides total mesorectal excision after completion of neoadjuvant chemoradiotherapy (67). Therefore, internal iliac and obturator lymph nodes 7 mm or greater in the short axis at baseline are considered suspicious according to size criteria. After neoadjuvant chemoradiotherapy, internal iliac and obturator lymph nodes remaining larger than 4 mm and smaller than 6 mm in the short axis, respectively, possibly have residual nodal metastases, and pelvic lymph node dissection is indicated in these patients (66,67).

These pelvic sidewall lymph node size criteria are applicable only for patients with a high pretest probability of nodal involvement (ie, T3 or T4 tumor with a lower pole <8 cm from the anal verge; low and mid rectal tumors) and without known distal metastases (66,67). There are no available size criteria for external iliac lymph nodes that almost exclusively occur in the setting of distant metastases or invasion of other pelvic organs.

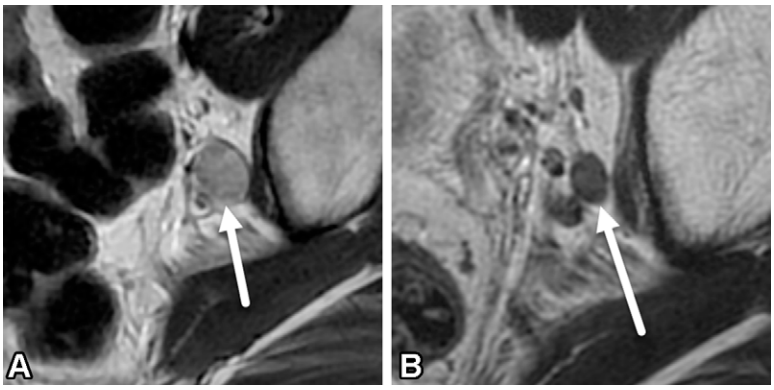


Figure 14. Pelvic sidewall recurrence in a 50-year-old man with rectal adenocarcinoma. **(A)** Pretreatment axial T2-weighted MR image shows a suspicious (>7 mm in short axis) left obturator lymph node (arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows that this lymph node (arrow) is still above the threshold value for the obturator compartment (>6 mm). Therefore, pelvic sidewall lymph node dissection is indicated, and malignant cells were present in this lymph node at pathologic evaluation.

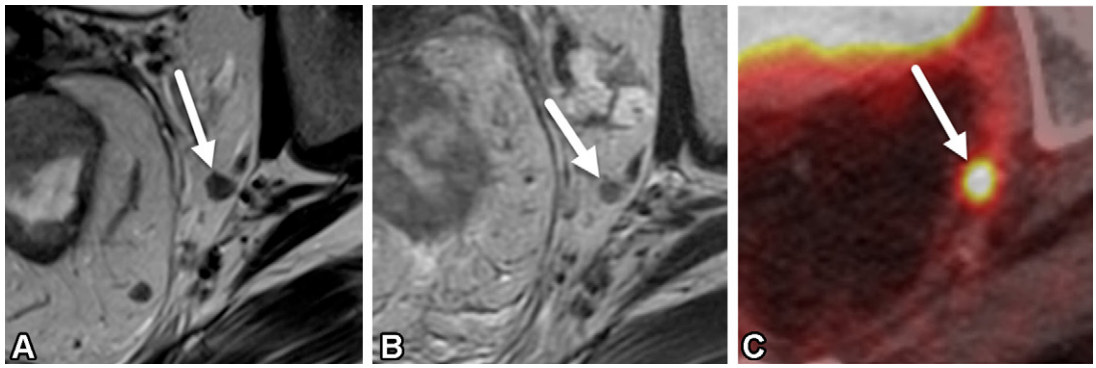


Figure 15. Pelvic sidewall recurrence in a 50-year-old woman with rectal adenocarcinoma. **(A)** Pretreatment axial T2-weighted MR image shows a suspicious (>7 mm in short axis) left internal iliac lymph node (arrow). **(B)** Axial T2-weighted MR image after completion of neoadjuvant chemoradiotherapy shows that this lymph node (arrow) is still above the cutoff value for the internal iliac compartment (>4 mm). The patient did not consent to pelvic sidewall lymph node dissection, to avoid sexual and voiding dysfunction. **(C)** Fused axial PET/CT image obtained 9 months after total mesorectal excision to investigate the increasing serum carcinoembryonic antigen levels shows avid fluorodeoxyglucose uptake at this lymph node (arrow), in keeping with pelvic sidewall recurrence.

Pitfalls in MRI Restaging of Lymph Nodes after Neoadjuvant Chemoradiotherapy

Prominent Lymph Nodes in the Anterior Obturator Compartment

Prominent elongated ovoid lymph nodes often exist in the most anterior part of the obturator lymphatic chain adjacent to the external iliac artery above the point where it passes below the inguinal ligament (Poupart ligament). These lymph nodes are frequently identified in healthy individuals and may be large (Fig 16). However, they should be considered reactive and should not be included in the assessment for locoregional nodal involvement (66,67).

Superficial Inguinal Lymph Nodes

Involvement of superficial inguinal lymph nodes is considered locoregional nodal disease spread only if the tumor extends below the dentate line; otherwise, it is considered distant metastatic disease (Fig 17) (44). No size criteria exist for superficial inguinal lymph node involvement, but when there is concern for involvement (eg, asymmetric enlargement, heterogeneous signal intensity, or irregular borders), these nodes can be easily biopsied under US guidance.

Superior Hemorrhoidal and Inferior Mesenteric Lymph Nodes Mimicking Common Iliac and Retroperitoneal Lymph Nodes

Mesorectal lymph nodes, superior hemorrhoidal lymph nodes, and inferior mesenteric lymph nodes are considered locoregional nodes for rectal adenocarcinoma, and they are routinely resected during total mesorectal excision. Lymph nodes within these compartments can lie in close proximity to the common iliac vasculature or to the retroperitoneal lymphatic chains and may be erroneously categorized as common iliac or retroperitoneal nodes, causing erroneous tumor upstaging (75). The presence of lymph nodes adjacent to the inferior mesenteric vasculature can localize lymph nodes to the correct mesorectal or mesosigmoid compartment and helps avoid this pitfall (75).

When lymph nodes are large enough to abut both the inferior mesenteric vasculature and the common iliac or retroperitoneal vasculature, sagittal reconstructed CT images may be used to identify the posterior layer of the parietal peritoneum and determine whether the suspected node lies posterior to it, indicating a retroperitoneal or common iliac location. Lymph nodes displacing the ureter or gonadal veins anteriorly are extramesorectal (common iliac or retroperitoneal) in location (Fig S3).

Mucinous Lymph Nodes

Metastatic lymph nodes from mucinous rectal adenocarcinoma can contain mucin that has high T2 signal intensity, similar to the primary tumor. After neoadjuvant chemoradiotherapy, lymph nodes can demonstrate persistent high signal intensity secondary to cellular or acellular mucin that may or may not harbor residual malignant cells (Fig 10). Differentiation between cellular and acellular mucin is not possible with current imaging modalities.

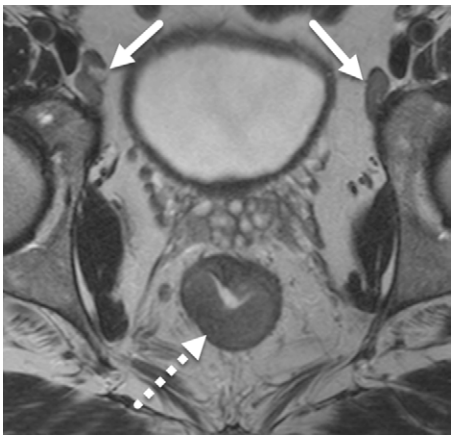


Figure 16. Prominent reactive anterior obturator lymph nodes in a 51-year-old man with low rectal adenocarcinoma (dotted arrow). Pretreatment axial T2-weighted MR image shows prominent bilateral obturator lymph nodes (solid arrows). Although these lymph nodes are above the size criteria (>7 mm in short axis), given their specific location (the most anterior part of the obturator compartment just posteromedial to the external iliac veins as they pass below the inguinal ligament), they should not be taken into consideration when applying size criteria, since they are almost always reactive and frequently identified in healthy individuals.

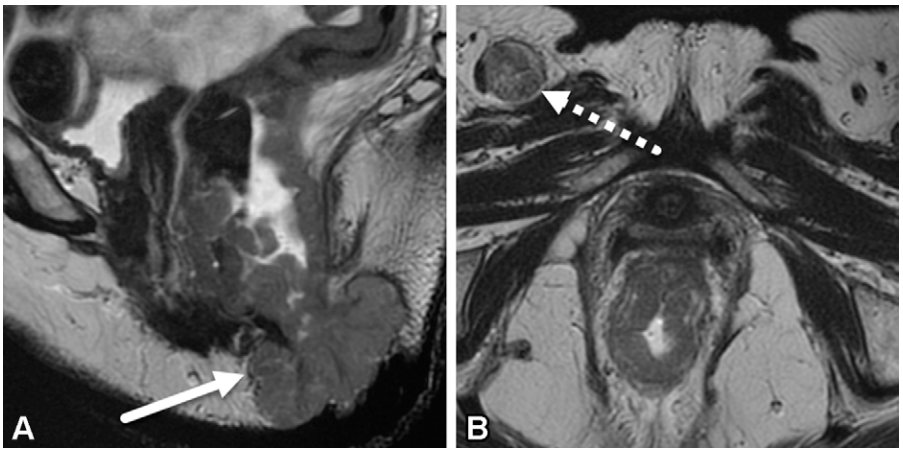


Figure 17. Locoregional inguinal lymph node involvement in a 49-year-old woman with low rectal adenocarcinoma. **(A)** Pretreatment sagittal T2-weighted MR image shows a low to mid rectal adenocarcinoma extending below the dentate line and protruding through the anal canal (arrow). **(B)** Pretreatment axial T2-weighted MR image shows an enlarged right inguinal lymph node (arrow). Involvement of inguinal lymph nodes is considered locoregional disease spread when the tumor extends below the dentate line, but it is considered distant metastasis if the tumor lies above the dentate line. There are no size criteria to determine inguinal lymph node involvement.

Conclusion

Restaging MRI is a reliable tool in response assessment after neoadjuvant chemoradiotherapy for rectal adenocarcinoma. Awareness of potential pitfalls and technical limitations can help avoid erroneous interpretations and increase accuracy. Understanding the rectum's unique lymphatic drainage system and correct application of lymph node size criteria at baseline and at restaging MRI are crucial for identifying metastatic lymph nodes and guiding management.

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