Radiology

REVIEWS AND COMMENTARY • REVIEW

Watch-and-Wait Approach to Rectal Cancer: The Role of Imaging

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The diagnosis and treatment of rectal cancer have evolved dramatically over the past several decades. At the same time, its incidence has increased in younger populations. This review will inform the reader of advances in both diagnosis and treatment. These advances have led to the watch-and-wait approach, otherwise known as nonsurgical management. This review briefly outlines changes in medical and surgical treatment, advances in MRI technology and interpretation, and landmark studies or trials that have led to this exciting juncture. Herein, the authors delve into current state-of-the-art methods to assess response to treatment with MRI and endoscopy. Currently, these methods for avoiding surgery can be used to detect a complete clinical response in as many as 50% of patients with rectal cancer. Finally, the limitations of imaging and endoscopy and future challenges will be discussed.

The evolving landscape of rectal cancer management is fascinating yet challenging. Management of rectal cancer has rapidly evolved since the days of radical abdominoperineal resection, first described by William Ernest Miles in 1908 (1,2). Attempts to perform less radical, more sphincter-saving procedures and to improve local recurrence rates led to the development of anterior resections for upper and middle rectal cancers in the 1940s, low anterior resection for low-lying rectal cancers in the 1970s, and total mesorectal excision in the 1980s (3–10). Thereafter, large randomized controlled trials conducted in the early 2000s, notably the German Rectal Trial and the Swedish Rectal Trial, demonstrated the superiority of neoadjuvant chemoradiotherapy (nCRT) over postoperative chemoradiotherapy and established a combined multimodality sequence of treatments as the standard of care worldwide (11–18) (Fig 1). This regimen was associated with 15%–20% of patients achieving a pathologic complete response. In addition, local recurrence rates plummeted from about 40% to 7%; however, the rate of distant metastases remained high at about 20%–30% (19).

Given the persistently high rates of distant metastases, variations in treatment modality sequencing have been investigated. Prospective trials (eg, RAPIDO, PRODIGE-23, CAO/ARO/AIO-12, STELLAR) have ushered in the current era of total neoadjuvant therapy followed by total mesorectal excision as the standard of care for locally advanced rectal cancer (20–24). Total neoadjuvant therapy shifts postoperative (adjuvant) chemotherapy to before surgery. This shift is designed to more immediately address potential distant micrometastases; it can be given either before (induction) or after (consolidation) chemoradiotherapy. Total neoadjuvant therapy has been noted to improve local response and the likelihood of pathologic complete response (23–26). Strategies to further achieve higher pathologic complete response rates have been accomplished using longer intervals between nCRT and surgery (supported by the TIMING trial) and longer intervals between the end of nCRT and imaging—in recognition of the delayed effects of radiation therapy (27,28).

Up to one-third of patients still develop disease-related treatment failure (eg, distant metastases, treatment-related death, or local-regional failure) (24). Treatment-related morbidity due to surgery and radiation therapy includes bowel, bladder, and sexual dysfunction, and risk of permanent stoma, affecting quality of life (29,30). Thus, treatment de-intensification strategies aiming to exclude one modality have been attempted in clinical trials (eg, chemotherapy with only selective radiation therapy followed by surgery [PROSPECT], nCRT and surgery without adjuvant chemotherapy [Spanish GCR-3], and chemotherapy and nCRT without surgery [Organ Preservation of Rectal Adenocarcinoma, or OPRA]) (31–33). The increasing awareness that patients who undergo surgery may have no tumor in the specimen (ie, a pathologic complete response) has led to possible organ-preserving strategies. Organ preservation after a clinical complete response (cCR) to neoadjuvant therapy seeks to avoid unnecessary surgery that would remove a tumor-free rectum. This approach is referred to as *watch and wait* (W&W), *wait and see*, or *nonsurgical management*.

High-spatial-resolution pelvic MRI is essential to rectal cancer management. It is critical for anatomic delineation of the rectal wall and mesorectal fascia and has become the standard of care for preoperative assessment of prognostic factors in locally advanced rectal cancer, such as bowel wall invasion, extramural spread, extramural vascular invasion, and lymph node and peritoneal involvement. Its routine use has taken a firm hold in the work-up of patients with

Abbreviations

AUC = area under the receiver operating characteristic curve, cCR = clinical complete response, DFS = disease-free survival, DWI = diffusion-weighted imaging, FDG = fluorodeoxyglucose, nCRT = neoadjuvant chemoradiotherapy, W&W = watch and wait

Summary

MRI plays a critical role in assessing clinical complete response for patient selection and monitoring with the watch-and-wait strategy, otherwise known as nonsurgical management, in rectal cancer management.

Essentials

- Watch-and-wait (W&W) strategy, otherwise known as nonsurgical care, is an emerging and attractive option in the care of patients with rectal cancer, aimed at improving quality of life without over- or undertreatment.
- Accurate assessment of clinical complete response (cCR) on MRI scans is critical for optimal patient selection and monitoring under W&W.
- The cCR on MRI scans is signified by presence of dark T2-weighted MRI signal intensity, without any intermediate signal intensity or restricted diffusion within the tumor bed on diffusion-weighted images, and resolution of lymph nodes on MRI scans after neoadjuvant chemoradiotherapy.
- Combined endoscopy and MRI assessment has the best overall performance in the prediction of cCR.
- One of the key challenges in the implementation of W&W is the accurate radiologic and clinical assessment of cCR, which, as such, should be based on a multidisciplinary team decision in an expert center.

locally advanced rectal cancer based on results from the MERCURY study (34–36). Technologic advances in the past 15 years, including higher magnetic field strength, improved surface coils, and functional sequences, such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced sequences, have further improved MRI in rectal cancer assessment (37,38).

Improvement of survival outcomes with an emphasis on better quality of life and avoiding over- or undertreatment informs the current goals of rectal cancer management. This review will provide insight into the pivotal role of MRI in the increasingly practiced W&W approach to treatment. It will also explore the current state-of-the-art methods for staging and response assessment to ensure the success of the W&W approach in standard clinical practice.

Clinical Aspects: A Brief Recap of Key Studies and Trials

The foundation for W&W was laid by Habr-Gama and colleagues in 2004 when they compared surgical with nonsurgical treatment in patients with distal rectal cancer after nCRT (39). In this seminal study, patients assigned to W&W who had cCR after nCRT were compared with patients who had pathologic complete response after surgery. The 5-year overall survival rate was better in the observation group (100% vs 88%, $P = .01$), but there was no evidence of a difference in the disease-free survival (DFS) rate (92% vs 83%, $P = .09$).

In a follow-up study spanning 20 years, Habr-Gama et al reported that most local regrowth was endoluminal, detected with endoscopy, and occurred within the first 12 months of follow-up, with local or pelvic recurrence in 31% of patients (40). Most local regrowth was treated with salvage surgery, leading to overall recurrence-free survival in 94% of patients, sphincter preservation in 85%, and organ preservation in 78%. The study highlighted two important findings. First, most early regrowth is local, amenable to R0 salvage surgery, and probably due to failure to identify residual disease clinically or radiologically. Second, there was a substantial proportion of ypT3-4 disease (35%) in the resected specimens, suggesting residual and deeper foci of viable cancer. Both findings highlight the importance of appropriate clinical and radiologic assessment of cCR in selecting patients for W&W. In the years since the seminal work of Habr-Gama et al, several studies have been published assessing the survival outcomes and benefits of W&W (41–44) (Table 1).

To understand the risks and benefits of organ preservation strategies and to systematically collect retrospective and

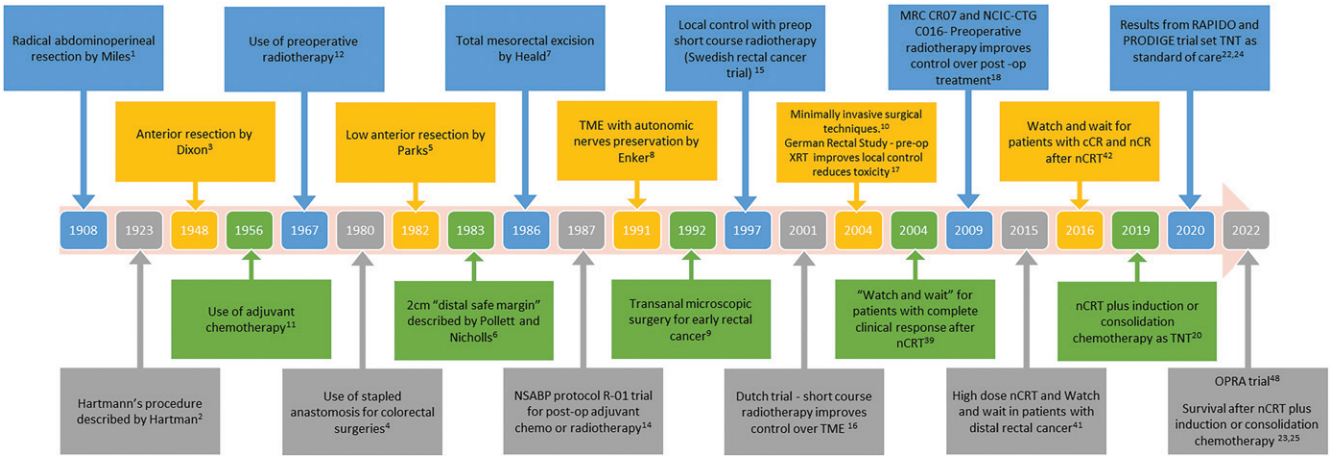


Figure 1: Timeline of development of various surgical techniques and some of the important trials and studies influencing the management of rectal cancer in the past century. cCR = clinical complete response, LARC = locally advanced rectal cancer, nCR = near complete response, nCRT = neoadjuvant chemoradiotherapy, OPRA = Organ Preservation of Rectal Adenocarcinoma, TME = total mesorectal excision, TNT = total neoadjuvant therapy, XRT = radiation therapy.

Table 1: Studies Evaluating the Watch-and-Wait Strategy

Year	Study	Reference	Study Aim	Total No. of Patients	Total No. of Patients with cCR	Median Follow-up (mo)	DFS (%)	OS (%)	LR (%)	DR (%)
2004	Habr-Gama et al	PMID: 15383798	Operative vs nonoperative mx in patients with stage 0 disease after nCRT	265	71	57.3	92*	100*	2.8	4.2
2011	Mass et al	PMID: 22067400	Wait and See policy for cCR after nCRT	192	21	25	89†	100†	4.7	0
2012	Smith et al	PMID: 23154394	NOM with cCR after nCRT	32	32	28	88†	96†	21	8
2013	Habr-Gama et al	PMID: 24022527	W&W following extended nCRT	70	47	53	72‡	90‡	25.5	17.0
2014	Habr-Gama et al	PMID: 24495589	Impact of salvage therapy in W&W	183	90	60	68*	91*	31	14
2015	Appelt et al	PMID: 26156652	W&W following high dose nCRT	51	40	23.9	NR	NR	25.9	7.5
2015	Araujo et al	PMID: 26362228	NOM after nCRT	111	42	47.7	61*	71.6*	19	16.7
2015	Smith et al	PMID: 25787162	Surveillance in cCR after nCRT compared with TME	48	18	68.4	NR	100*	5.6	5.6
2016	Martens et al	PMID: 27509881	W&W following nCRT in cCR or near CR	100	85	41.1	81‡	96.6‡	17.6	5.8
2016	Lai et al	PMID: 26607907	cCR after nCRT, Sx, or W&W	44	18	49.9	NR	100*	11.1	0
2018	van der Valk et al	PMID: 29976470	Long-term outcomes from International Watch and Wait (IWWD) database	1009	880	39.6	94*	85*	25.2	8
2019	Smith et al	PMID: 30629084	W&W after NAT in patients with cCR	113	113	43	75*	73*	21	8
2019	Strode et al	PMID: 30851884	NOM after nCRT	29	29	27.6	NR	NR	6.9	17.2
2019	Spiegel et al	PMID: 30359718	Long-term clinical outcomes in NOM	313	65	67.2	91‡	75.4‡	NR	NR
2020	Coraglio et al	PMID: 33256819	Long-term outcomes of cCR vs pCR	48	26	47	88	86	8.3	3.8
2021	Fernandez et al	PMID: 33316218	Conditional recurrence-free survival in cCR	793	793	55.2	NR	NR	27	11
2022	Garcia-Aguilar et al	PMID: 35483010	Efficacy of W&W in patients with LARC with TNT	324	225	36	76‡	NR	4.8	18.2

Note.—cCR = complete clinical response, DFS = disease-free survival, DR = distant recurrence, LARC = locally advanced rectal cancer, LR = local recurrence, mx = management, NAT = neoadjuvant therapy, nCRT = neoadjuvant chemoradiotherapy, NOM = nonoperative management, NR = not reported, OS = overall survival, pCR = pathologic complete response, Sx = surgery, TME = total mesorectal excision, TNT = total neoadjuvant therapy.

* At 5 years.

† At 2 years.

‡ At 3 years.

prospective data across centers worldwide, an International Watch and Wait Database was initiated in 2014 by the European Registration of Cancer Care and the Champalimaud Foundation (45). Results from this web-based database showed a 5-year overall survival of 85% and a 5-year disease-specific survival of 94% (46). The largest North American cohort of patients in the W&W protocol who developed a cCR after nCRT (n = 113) showed a high rate of rectal preservation (82%) and effective surgical salvage after regrowth (91%) (47). Of note, patients with local regrowth showed higher rates of distant metastasis compared with patients with sustained cCR (36% vs 1%). Similar findings related to regrowth were noted in the International Watch and Wait Database (18% vs 5%) (46).

Recently, results were published from the Organ Preservation of Rectal Adenocarcinoma trial, the first prospective trial integrating W&W and total neoadjuvant therapy (48). In this randomized phase II trial with a median follow-up of 3 years, 152 patients underwent induction chemotherapy followed by long-course chemoradiation, and 155 underwent consolidation chemotherapy after long-course chemoradiation. A three-tiered response schema using physical examination, endoscopy, and MRI was used to determine whether patients underwent total mesorectal excision or W&W (49). Three-year DFS was 76% in both groups. Although the trial did not meet its primary end point of a 10% improvement in DFS compared with historical control subjects (also 76%), it revealed that the 3-year total mesorectal excision–free survival rate (surrogate for organ preservation rate) was 41% in the induction group and 53% in the consolidation group. There were no differences in local recurrence-free survival, distant metastasis–free survival, or overall survival. Patients who underwent total mesorectal excision after restaging and patients who underwent total mesorectal excision after local regrowth had similar DFS rates.

Overall, these data favor safe integration of W&W in a total neoadjuvant therapy strategy wherein half of patients with locally advanced rectal cancer can avoid surgery, and it highlights the important role that MRI plays in decision making.

Imaging Assessment of Response and cCR

MRI

The success of W&W depends on accurate restaging and identification of cCR, as well as appropriate patient selection and monitoring. MRI is the imaging modality of choice for treatment response assessment, surveillance, and detection of local regrowth in patients with rectal cancer. The MERCURY study showed that the MRI-based tumor regression grade and circumferential resection margin assessment on post-nCRT MRI scans provided information regarding DFS, overall survival, and risk for local recurrence (50). There is growing evidence that functional MRI sequences such as DWI allow for qualitative and tumor microenvironment-based quantitative assessment of the posttreatment tumor bed, but further large-scale prospective studies are required (51). To obtain optimal diagnostic-quality images and provide accurate and standardized response evaluation, MRI should be performed and reported according to recommended parameters. The 2016 European Society of Gastrointestinal and Abdominal Radiology and the similar 2017 Society of Abdominal Radiology rectal cancer disease–focused panel consensus recommendations and guidelines are considered the standard of care. These societies recommend guidelines on the acquisition, interpretation, and reporting of MRI scans for baseline clinical staging and posttreatment response evaluation of rectal cancer (52,53). The U.S. National Accreditation Program in Rectal Cancer has adopted these standards as well as the synoptic report from the Society of Abdominal Radiology (54).

MRI protocol.—The principles of MRI scanning in the response assessment setting are similar to those in the staging setting but with greater emphasis on DWI sequences. It is recommended that MRI be performed with an external phased-array surface coil (preferably with between eight and 32 elements) with a minimum magnetic field strength of 1.5 T. There is no recommended preference between 1.5 and 3.0 T. However, significant signal intensity differences have been reported between pre- and post-DWI scans and apparent diffusion coefficient–calculated images between responders and nonresponders, with possibly better visual assessment of treatment response at 3.0 T compared with 1.5 T (55). This must be balanced with the potential for more artifacts on 3.0-T DWI scans. In Europe, where users have more experience, 1.5 T is slightly preferred. An endorectal coil is not recommended. Rectal filling is optional. Spasmolytics and a rectal microenema can improve image quality of DWI scans, especially for high-lying tumors, in the post-total neoadjuvant therapy setting and with 3.0-T scanners (56,57). A study comparing b values of 800 and 1500 sec/mm^2 indicated a preference and suggested greater diagnostic accuracy for cCR using a b value of 1500 sec/mm^2 (58). High-spatial-resolution two-dimensional T2-weighted axial and coronal oblique sequences perpendicular and parallel to the tumor axis with a section thickness of 3 mm or less are essential for accurate response assessment within the primary tumor and for determining the presence or regression of extramural vascular invasion, lymph nodes, or tumor deposits within the mesorectal fascia, as well as for determining the circumferential resection margin. A nonenhanced T1-weighted sequence is recommended by the Society of Abdominal Radiology (52). Additionally, intravenous contrast material is not routinely recommended. MRI protocols for all vendors can be found online at the Society of Abdominal Radiology website (59).

Reporting proforma.—Structured reporting of restaging rectal MRI (available from the Society of Abdominal Radiology website) is essential for the accurate and consistent analysis of primary tumor response and the evaluation of prognostic features and posttreatment changes compared with the baseline MRI findings (60,61). When reporting restaging MRI, the radiologist should be aware of the patient's prior treatment (eg, induction chemotherapy, nCRT, total neoadjuvant therapy, or transanal excision). Restaging MRI, reported in comparison with baseline MRI, must contain information regarding changes in tumor morphology (eg, tumor length, wall thickness, relationship to the anal sphincter complex, mesorectal fascia, and peritoneum). Differences in T2-weighted signal characteristics of the tumor and the presence or absence of mucin should also be reported. MRI-based features of tumor regression after nCRT are better at predicting treatment response than the posttreatment T category (62,63). Describing changes within the mesorectal and pelvic side wall lymph nodes, including node borders and signal intensity features (known as the Dutch Criteria), in addition to site, size, and location, is helpful for a more reliable reassessment of lymph node involvement (35,64).

T2-weighted MRI sequences and MRI-based tumor regression grade.—Multiplanar high-spatial-resolution two-dimensional

T2-weighted MRI sequences are the mainstay for rectal cancer restaging. MRI assessment of treatment response after nCRT or total neoadjuvant therapy is usually performed within 6–8 weeks of completion of therapy. However, longer intervals, such as 8–10 weeks and even 10–12 weeks, are increasingly common in recognition of the delayed effects of radiation (65). At baseline, the untreated rectal adenocarcinoma typically appears as an intermediate T2-weighted signal intensity lesion when compared with the muscularis propria. Mucinous tumors, comprising 10%–15% of all rectal adenocarcinomas, are associated with worse prognosis and have high T2-weighted signal intensity areas (66). On the post-nCRT or total neoadjuvant therapy MRI scan, progressive fibrosis in the primary tumor leads to darkening of T2 signal intensity and a reduction in size.

Assessment of MRI-based T category restaging is extremely limited, and radiologists should not assign this. A meta-analysis demonstrated that the ability of posttreatment MRI to depict residual tumor had a sensitivity of 50% and a specificity of 91% (67). Interestingly, among the included studies that used DWI MRI, the sensitivity improved to 84%, with little reduction in the specificity, which was 85%. Most inaccuracies in restaging T category are due to overstaging, particularly of those small residual superficial T0–T2 lesions with associated fibrosis or peritumoral desmoplastic reactions (68). The Response Evaluation Criteria in Solid Tumors, version 1.1, does not apply to luminal enteric tumors due to differences in degree of luminal distention, circumferential growth pattern, and luminal contents interfering with assessment.

While there are many methods proposed to quantitate response, such as volume and length or maximal thickness reduction, these are not widely applied or validated. A qualitative description of primary tumor fibrosis may be descriptive or semiquantitative to approximate the scale used by pathologists. The MRI-based tumor regression grading system, adapted from the pathologic tumor regression grading system, is used to assess the degree of treatment-induced fibrosis on posttreatment MRI scans (69–71) (Table 2). Patients with MRI-based tumor regression grades of 1–3 are considered good responders with favorable pathologic findings, better overall survival, and better DFS than poor responders with MRI-based tumor regression grades of 4–5 (71,72). More recently, the creators of this system have pointed out some important shortcomings that may explain its lack of widespread use. For example, MRI-based tumor regression grades often do not correctly predict pathologic tumor regression grading (range, 28%–34%), with equal under- and overestimations (73). Sensitivity for the prediction of pathologic complete response is limited at 61%, with a specificity of 89% (74). Interobserver agreement ranges from 60% to 67%, with modest κ interreader agreement values of 0.25 to 0.36 (75). Use of MRI-based tumor regression grades as imaging markers to validate MRI-directed patient care based on imaging response to nCRT is currently being tested in the Magnetic Resonance Tumour Regression Grade as Biomarker for Stratified Management of Rectal Cancer Patients (TRIGGER) trial (76).

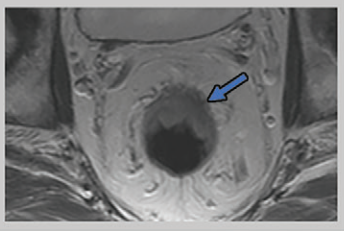
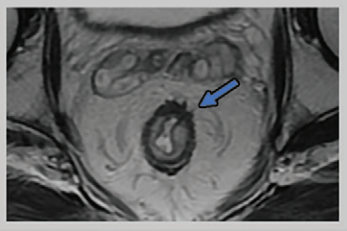
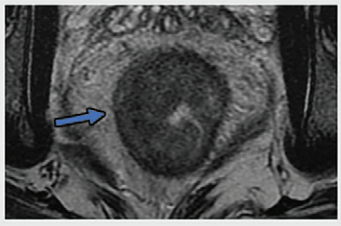
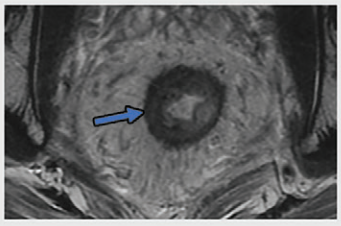
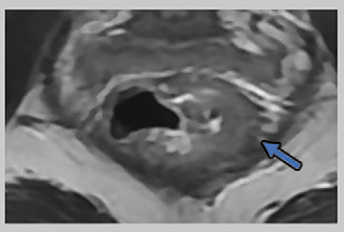
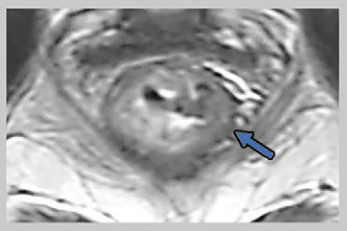
As such, the focus in day-to-day practice is to simplify the qualitative assessment of the degree of T2 darkening and scar formation. Use of a three-tiered system for response assessment showed no loss of accuracy compared with a five-tier system and correlated well with survival outcomes (77). The modified response assessment used in the recent Organ Preservation of Rectal Adenocarcinoma trial is similar to these three-point scales and is used as a measure of MRI-based response assessment within the primary tumor and lymph nodes on T2-weighted and DWI scans, in conjunction with endoscopic findings (Fig 2) (48). Within the primary tumor, complete response refers to either normal-appearing bowel wall without any fibrosis in the tumor bed or presence of only dark T2 signal intensity without any evidence of intermediate T2 signal intensity. Near-complete response refers to mostly dark T2 signal intensity scar with some remaining intermediate signal intensity within the tumor bed. A persistent intermediate signal intensity and the absence of a T2 scar is deemed an incomplete response. This qualitative grading is admittedly subjective and requires experience and validation. Also, it does not apply well to mucinous tumors.

With respect to residual tumor outside the bowel wall, margin assessment is critical for successful curative resection. High-spatial-resolution T2-weighted sequences predict the involvement of the mesorectal fascia, referred to as the circumferential resection margin, when the distance between the lateral-most edge of the tumor is 1 mm or less from the mesorectal fascia (Fig 3) (78). It is important to understand that the circumferential resection margin is determined by the surgeon at surgery. The two terms are equated because the ideal circumferential resection margin is equivalent to the mesorectal fascia, but such surgery is challenging. Thus, it is better to refer to the tumor distance to the mesorectal fascia in radiologic reports. On posttreatment studies, nearly 36% of patients are overstaged for tumor invasion of the mesorectal fascia, probably due to the desmoplastic changes seen in more than 50% of patients (Figs 4, 5). Although MRI has a relatively high sensitivity and negative predictive value (both 100%) in the prediction of mesorectal fascia invasion, it has moderate specificity (range, 32%–59%), positive predictive value (range, 57%–68%), and interreader agreement (κ = 0.38)

Table 2: Five-Point MRI-based Tumor Regression Grading System for Assessing the Treatment-induced Fibrosis on Posttreatment MRI Scans

Grade	Regression
1	Complete radiologic response with no evidence of residual tumor; there is either normalization of the rectal wall at the tumor bed or presence of a thin linear or crescentic scar
2	Good response with residual predominantly low T2-weighted signal intensity dense fibrotic changes, and very minimal, if any, intermediate signal intensity is seen with the tumor bed
3	Moderate response to treatment with up to 50% of fibrosis and 50% of intermediate signal residual tumor present
4	Minimal signal intensity fibrosis within the tumor
5	No low-signal-intensity fibrosis within the tumor

Note.—Adapted from reference 71.

Degree of Response	Baseline T2W	Post TNT T2W	Features
Complete Response			• Dark T2W scar Or • Normalized bowel wall
Near Complete Response			• Mostly dark T2 signal • Some mild remaining intermediate signal
Incomplete Response A			• Persistent intermediate signal intensity • No scar

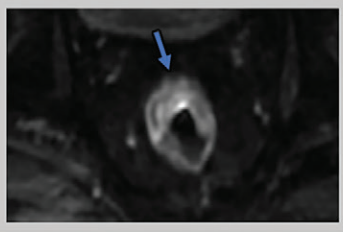
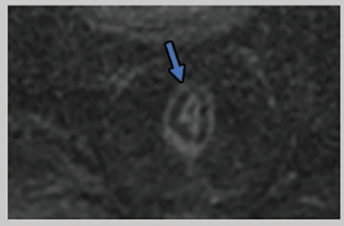
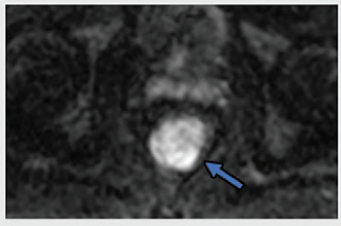
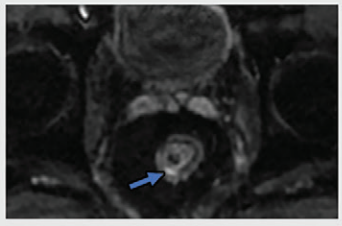
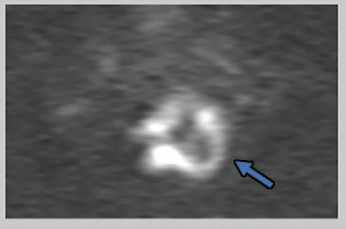
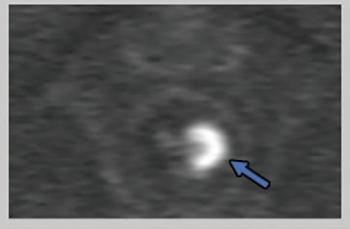
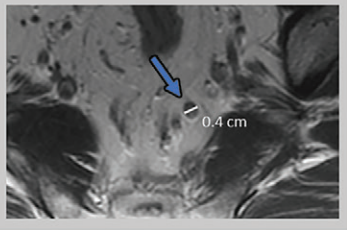
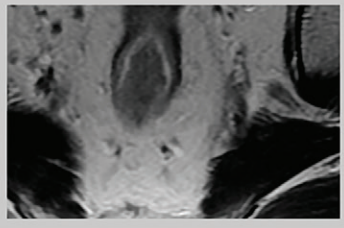
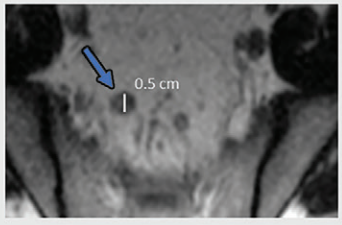
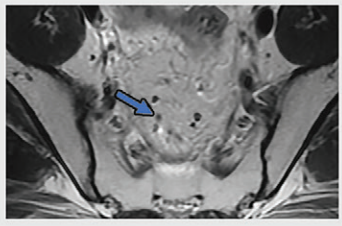
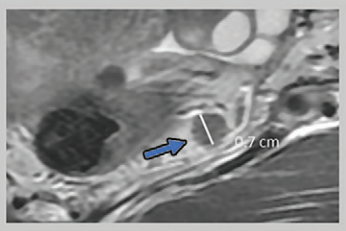
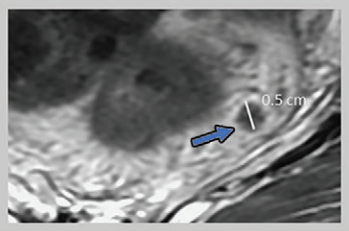
Degree of Response	Baseline DWI	Post TNT DWI	Features
Complete Response			• No restricted diffusion in the tumor bed
Near Complete Response			• Slight residual restricted diffusion in the tumor bed
Incomplete Response B			• Persistent restricted diffusion in the tumor bed

Figure 2: **(A)** Complete, near complete, and incomplete response within the primary tumor (arrows) on axial T2-weighted (T2W) MRI scans at restaging performed after completion of total neoadjuvant therapy. **(B)** Complete, near complete, and incomplete response (arrows) within the primary tumor on axial diffusion-weighted images at restaging performed after completion of total neoadjuvant therapy (TNT) *(Fig 2 continues)*.

Degree of Response	Baseline Nodes	Post TNT Nodes	Features
Complete Response			• No visible lymph nodes Or • Very few, < 0.5 cm
Near Complete Response			• Decreased size of lymph nodes
Incomplete Response C			• Slight or no regression of lymph nodes

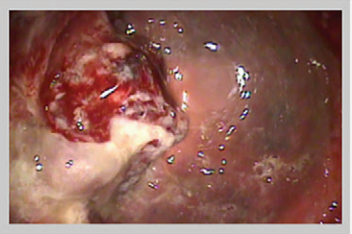
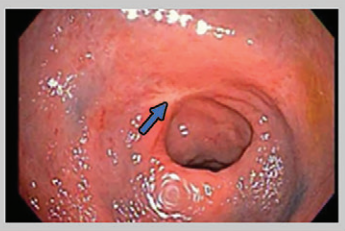
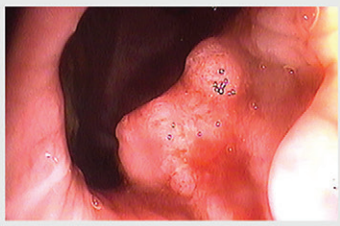
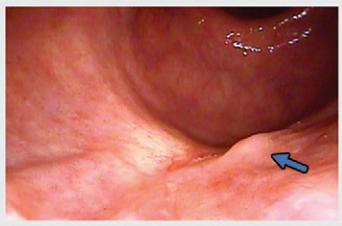
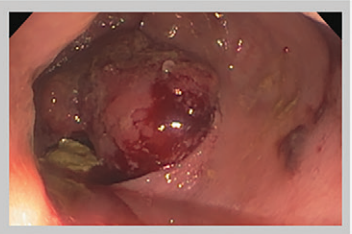
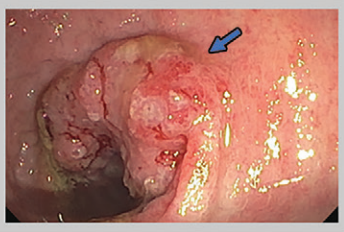
Endoscopy	Baseline	Post TNT	Features
Complete Response			• Flat and white scar • No ulceration • No nodules
Near Complete Response			• Small mucosal nodules/abnormality Or • Superficial ulceration/erythema
Incomplete Response D			• Visible tumor

Figure 2 *(continued)*: (C) Complete, near complete, and incomplete response (arrows) within the lymph nodes on axial T2-weighted MRI scans at restaging performed after completion of total neoadjuvant therapy (TNT). **(D)** Endoscopy images depicting complete, near complete, and incomplete response (arrows) within the primary tumor obtained after completion of TNT.

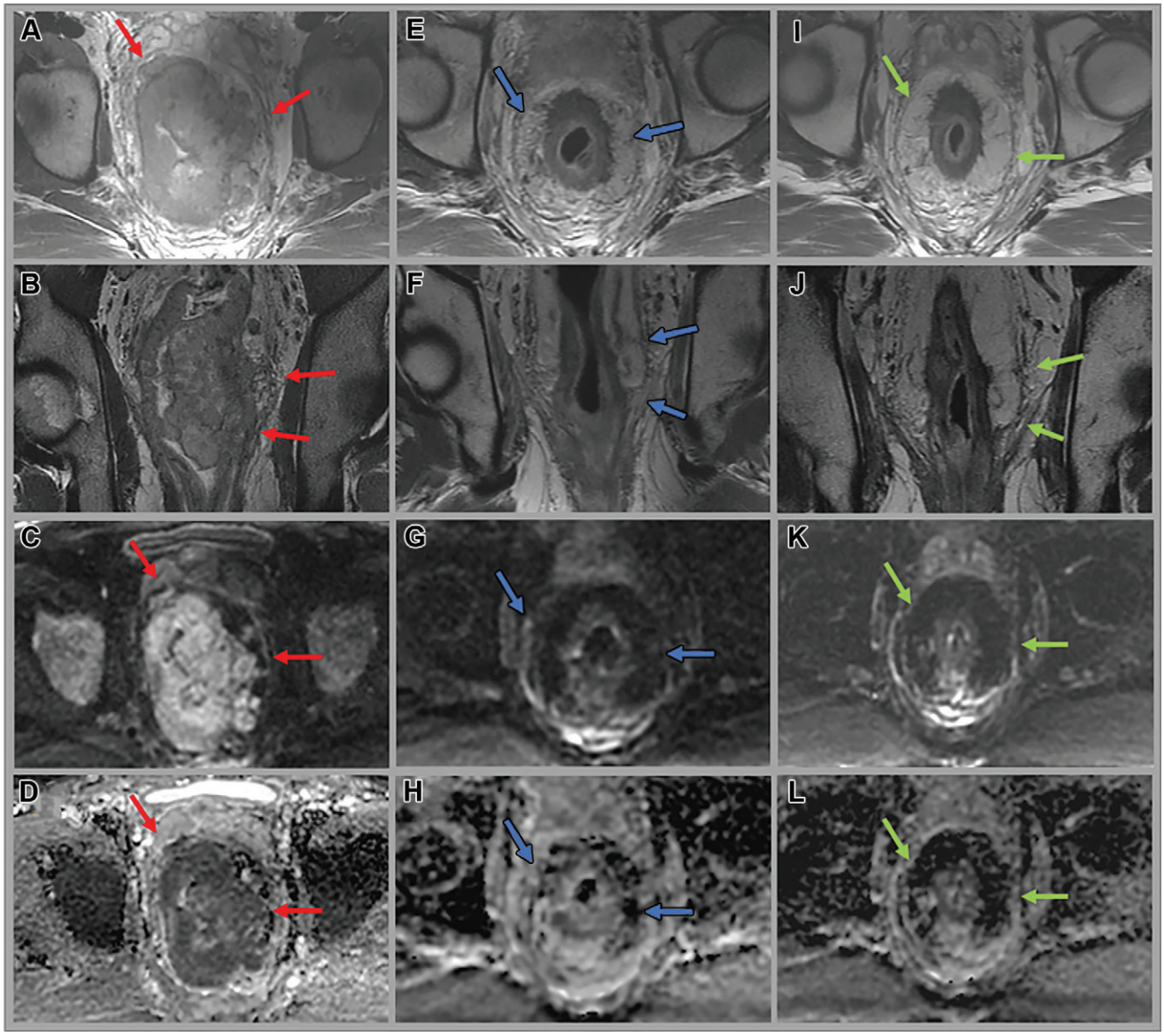


Figure 3: Images in a 53-year-old man with bulky middle to upper rectal adenocarcinoma involving the mesorectal fascia. **(A, E, I)** Axial and **(B, F, J)** coronal oblique T2-weighted MRI scans, **(C, G, K)** axial diffusion-weighted images (*b* value = 800 sec/mm^2), and **(D, H, L)** apparent diffusion coefficient maps through the mid rectum at baseline **(A–D)**, 12 weeks after total neoadjuvant therapy **(E–H)**, and 14 months surveillance after total neoadjuvant therapy while the patient was on a watch-andwait (W&W) strategy **(I–L)**. Baseline images show the primary rectal tumor with multifocal involvement of the mesorectal fascia (red arrows). Post-total neoadjuvant therapy images at 12 weeks show some T2-weighted mixed dark and intermediate signal intensity within the tumor and desmoplastic reactions extending up to the mesorectal fascia (blue arrows). Endoscopy images show intense inflammation (images not shown). Surveillance images at 14 months while the patient was on the W&W strategy show darker T2-weighted dark signal intensity in the scar, no tumor regrowth, clear mesorectal fascia (green arrows), and continued absence of restricted diffusion.

(79). As expected, the accuracy of MRI to assess circumferential resection margin response is relatively low for patients with a higher pretreatment T category than for those with early pretreatment T category disease (79,80).

Assessment of residual tumor spread to vessels and nodes is equally important for safe resection margins. Extramural vascular invasion is seen as serpiginous tumor signal intensity and nodular expansion of the mesorectal vessels, which may or may not be contiguous with the primary tumor mass. Assessment of posttreatment extramural vascular invasion has emerged as an important risk factor associated with reduced overall survival (hazard ratio, 2.3) and reduced DFS (hazard ratio, 5.0) (72) (Fig 6). The significant reduction in DFS in patients with positive posttreatment extramural vascular invasion is independent of yT and yN stage (81). Regression of extramural vascular invasion after nCRT is associated with improved survival outcomes and longer DFS compared with those with persistent extramural vascular invasion (82).

Lymph nodes within the mesorectum are considered suspicious at baseline if they measure at least 0.9 cm in the short-axis dimension, have two or more suspicious morphologic features (eg, round shape, irregular border, heterogenous signal intensity) when they are 0.5–0.8 cm, or have all three suspicious morphologic features when they are smaller than 0.5 cm (24). Assessment

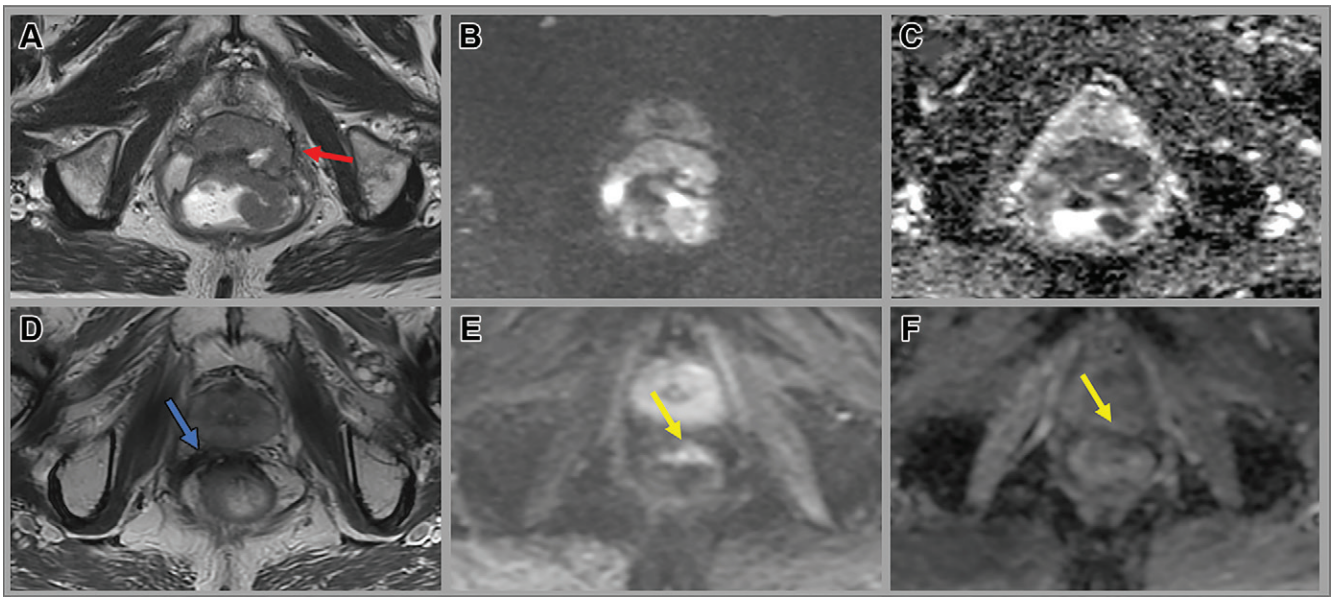


Figure 4: Images in a 65-year-old man with a low rectal tumor with anterior perforation extending to the anterior mesorectal fascia (red arrow). **(A, D)** Axial T2-weighted MRI scans, **(B, E)** axial diffusion-weighted images (*b* value, 800 sec/mm^2), and **(C, F)** apparent diffusion coefficient maps at baseline **(A–C)** and 12 weeks after completion of total neoadjuvant therapy **(D–F)**. Post-total neoadjuvant therapy images show decreased size of the tumor with new scar (blue arrow) and some residual restricted diffusion (yellow arrow), consistent with near-complete response. The patient opted for nonsurgical management and remains free of tumor regrowth at 3.5 years of surveillance.

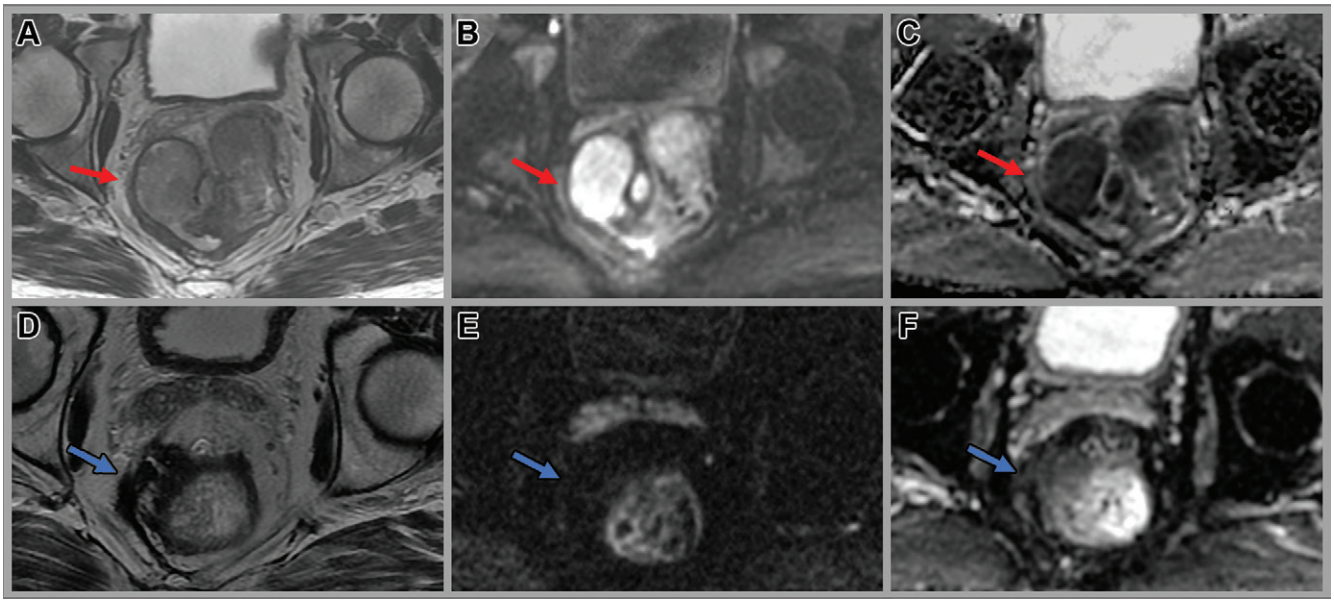


Figure 5: Images in a 58-year-old man with rectal adenocarcinoma. Baseline **(A)** axial T2-weighted MRI scan, **(B)** axial diffusion-weighted image (*b* value, 800 sec/mm^2), and **(C)** apparent diffusion coefficient map show a large rectal mass with an extraluminal component on the right side contacting the mesorectal fascia (red arrow) with restricted diffusion. Axial **(D)** T2-weighted MRI scan, **(E)** axial diffusion-weighted image (*b* value, 800 sec/mm^2), and **(F)** apparent diffusion coefficient image at 4 weeks after completion of total neoadjuvant therapy show a scar in the tumor bed extending to the mesorectal fascia and minimal residual restricted diffusion (blue arrow), consistent with near-complete response. The patient underwent low anterior resection. Final histology revealed a few foci of residual cancer and no involvement of the mesorectal fascia.

of nodal involvement using size criteria on MRI scans obtained after treatment is actually less limited than at baseline for the following reasons: *(a)* many irradiated nodes disappear (30% fewer are harvested at surgery after radiation), leading to fewer interpretation errors; *(b)* 80% of remaining nodes are sterilized; *(c)* one has the ability to compare pre- and posttreatment size and appearance; and *(d)* remaining enlarged nodes are more likely to be malignant (83). Use of a 0.5-cm cutoff, while not ideal, has been promulgated, in part based on studies and in part based on a pragmatic choice after an accumulation of combined experience (Fig 7). For example, in a node-for-node validation study between MRI and pathology findings, only 20 of 178 nodes (11%) 0.5 cm or smaller were malignant (84). In another node-for-node validation study that examined posttreatment decreases

in size of nodes (in parallel with a good responding tumor), nodes 0.5 cm or smaller were benign 86% of the time (85). Of note, in tumors that did not respond well, the 0.5-cm cutoff size had a 33% false-negative rate instead of 14%, confirming the need to assess the primary tumor, as it usually parallels the response in the nodes (Fig 8). Nonetheless, no one size cutoff is perfect; each represents a trade-off between sensitivity and specificity.

The Lateral Lymph Node Consortium has shown different size criteria for nodes in the pelvic sidewall (compared with the mesorectum discussed previously), an area not routinely dissected in the West due to high morbidity regarding bladder and sexual function. In Japan, this procedure has been more routine (86). Ogura et al reported that extramesorectal lymph nodes (specifically internal iliac and obturator lymph nodes) measuring less than 0.7 cm in short-axis diameter at baseline MRI have a higher chance of complete regression than lymph nodes measuring 0.7 cm or more (87). Furthermore, a reduction from 0.7 cm or larger to 0.4 cm or smaller (internal iliac nodes) and to 0.6 cm or smaller (obturator nodes) results in a lower risk of lateral lymph node recurrence at 3 years (87). As with mesorectal nodes, no cutoff size is absolute; however, the consortium reported that posttreatment lymph node size was a better predictor of lateral local recurrence pretreatment lymph node size. For the internal iliac nodes that remain larger than 0.4 cm and the obturator nodes that remain larger than 0.6 cm after all treatment, lateral pelvic lymph node dissection is strongly advised. The external iliac lymph nodes, considered as nonregional lymph nodes according to the American Joint Committee on Cancer, are associated with a twofold increase in distant recurrence but do not result in increased local recurrence rates (87).

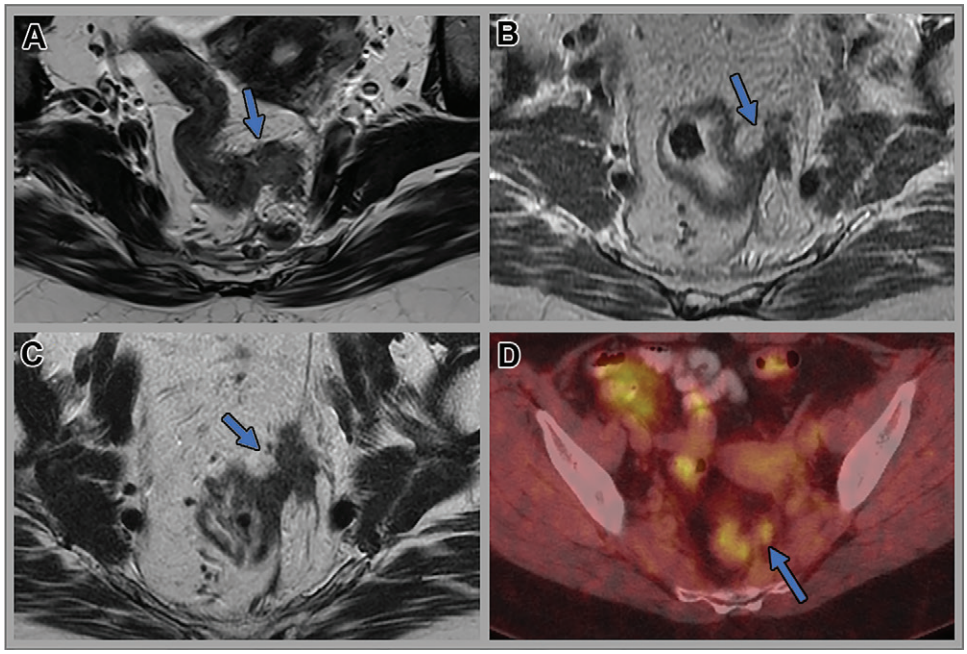


Figure 6: Images in a 53-year-old woman with locally advanced upper rectal tumor. Axial T2-weighted MRI scans **(A)** at baseline, **(B)** 12 weeks after total neoadjuvant therapy, and **(C)** 12 months after total neoadjuvant therapy (surveillance). **(D)** Subsequent fused axial fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) PET/CT image. In **A**, intermediate T2-weighted signal intensity left lateral extramural vascular invasion (arrow) is seen. In **B**, partial regression of extramural vascular invasion (arrow) is shown. No residual tumor was seen at endoscopy. In **C**, tumor regrowth within the extramural vascular invasion site (arrow) is visible. Moderately intense ^{18}F-FDG uptake (maximum standard uptake value, 4.1) is seen within the extramural vascular invasion (arrow) on **D**.

DWI sequence.—DWI, a commonly used functional MRI sequence accomplished by the addition of motion-probing magnetic gradients, is now included in the routine posttreatment rectal MRI protocol and is specifically recommended in the assessment of residual tumor and tumor regrowth (53). Both the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and the Society of Abdominal Radiology recommend its use at restaging MRI, with guidelines of the latter suggesting its use at baseline as well as to help in the detection of small tumors. While the optimal value and number of magnetic gradient pulses (*b* values) to apply are still under investigation, it is common to use DWI with *b* values of 0 and 800 sec/mm^2 or greater to assess tumor in the rectum.

Qualitative visual assessment of DWI scans, the apparent diffusion coefficient map, and T2-weighted images constitute the most common and accepted methods to predict and monitor treatment response. In a pooled analysis of individual patient data from 14 publications, the qualitative analysis of DWI scans had better accuracy in predicting pathologic complete response than quantitative analysis (87% vs 74%–78%) (88). The absence of residual high signal intensity on DWI scans together with complete normalization of rectal wall or scar in tumor bed on T2-weighted images signifies complete response, although uniform linear signal intensity in the wall above the tumor is also acceptable. Near-complete response is suggested by marked regression of the DWI signal intensity on images with *b* values of 800–1000 sec/mm^2. Persistence of areas of high signal intensity without much regression represents incomplete response. Combined T2-weighted and DWI sequences improved the diagnostic performance of MRI in the assessment of complete response, with an accuracy of almost 79% (89). It is challenging to perform DWI well and obtain high-quality images. Air in the rectum causes magnetic susceptibility artifact, especially at higher field strengths, such as 3.0 T. For this reason, the use of a rectal microenema (5 mL of fluid) was found to improve image quality and reduce the severity of gas-induced artifact over DWI performed without the microenema (56,57).

Nonetheless, there are many DWI naysayers in the radiologic community. They suggest that it is too hard to achieve reliable

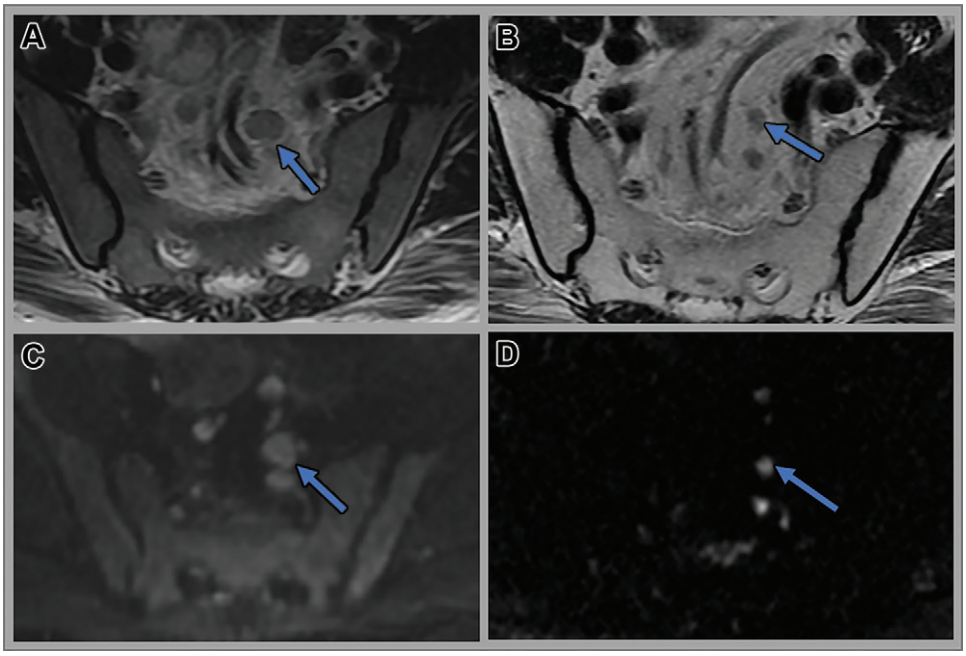


Figure 7: Images in a 58-year-old man with rectal adenocarcinoma. **(A, C)** Axial T2-weighted MRI scans and **(B, D)** axial diffusion-weighted (*b* value, 800 sec/mm^2) images at baseline **(A, B)** and 4 weeks after completion of total neoadjuvant therapy **(C, D)**. Baseline images shows several superior rectal lymph nodes with intermediate signal intensity measuring up to 1.0 cm in short-axis dimension (arrow in **A**). Post-total neoadjuvant therapy image shows decreased size of the lymph nodes with uniform signal intensity measuring up to 0.5 cm in the short-axis dimension (arrow in **B**). Nodes are well seen on diffusion-weighted images, which helps in detection of the nodes (arrows in **B** and **D**). The patient underwent low anterior resection. Final histologic examination showed no evidence of metastasis in the lymph nodes.

sequences with DWI, that DWI is too time consuming, and especially, that T2-weighted sequences are adequate. As mentioned previously, the literature contradicts this stance. A recent meta-analysis indicated a pooled sensitivity and specificity, respectively, of 49% and 86% for T2-weighted sequences alone, 85% and 80% for DWI alone, and 62% and 89% for studies combining both sequences in the assessment of pathologic complete response. This confirms a very real need to use both T2-weighted and DWI sequences complimentarily to best assess complete response (90). Small studies have provided preliminary evidence that the assessment of DWI sequences may assist in posttreatment extramural vascular invasion detection (91) and ypN0 status assessment (92). Also, the addition of DWI sequences to assess tumor regression grades at MRI improves interobserver agreement (72). Lee et al proposed that in patients with locally advanced rectal cancer, a modified MRI-based tumor regression grading system incorporating DWI improved accuracy and interreader agreement and was independently associated with 3-year DFS rate (93). A similar study from a national clinical trial (ClinicalTrials.gov, NCT02921256) analyzed three expert radiologists' readings of tumor regression grades at MRI and DWI. Using a similar modification of the MRI-based tumor regression grade score, essentially fortified by DWI, they found that the addition of DWI to tumor regression grades at MRI showed improved specificity and sensitivity over MRI-based tumor regression grades alone for the diagnosis of pathologic complete response (P = .02) (94). Importantly, in a meta-analysis, studies with experienced MRI observers showed better results (higher sensitivity [P = .01]) compared with studies with less experienced MRI observers for tumor staging (67). Not surprisingly, there is a steep learning curve and many pitfalls. The reader is referred to a helpful expert tutorial that shows the most common interpretation pitfalls in the post-nCRT setting, which includes low signal intensity on the apparent diffusion coefficient map due to fibrosis (T2 dark-through), susceptibility artifacts, and T2 shine-through effects (95). Quantitative use of DWI using the apparent diffusion coefficient is still not validated and remains in the research realm along with many other types of quantitative assessments in MRI for rectal cancer response assessment. These are beyond the scope of this review, but the reader is referred to the excellent review by Joye et al (88).

Other Modalities and Techniques

Fluorine 18 fluorodeoxyglucose (FDG) is currently the most used radiopharmaceutical for oncologic molecular imaging. A systematic review assessing the early response of rectal cancer during neoadjuvant therapy showed that FDG PET/CT had good early predictive value (sensitivity, 79%; specificity, 78%) and higher diagnostic accuracy when there was a minimum percentage decrease of 42% in standard uptake value compared with baseline studies (96). In a prospective study of 68 patients, FDG PET/CT showed an overall accuracy of 92% in the identification of patients with cCR to nCRT, with higher accuracy (96%) when PET/CT was combined with a clinical examination (97). At baseline, PET/CT has lower sensitivity but higher specificity in the detection of regional lymph nodes when compared with MRI (98). Persistence of FDG uptake within the inguinal lymph nodes in patients with distal rectal cancer 12 weeks after the completion of nCRT suggests worse prognosis (99). Initial experiences with combined whole-body PET/MRI have shown a slightly better accuracy for ypT and ypN staging than with MRI alone (100). In an exploratory pilot study, increasing the PET acquisition time from 3 to 15 minutes in the pelvis during PET/MRI improved the detection of FDG-avid lymph nodes, but histopathologic validation was lacking (101). The major drawback for FDG PET/CT or PET/MRI in the clinical setting is the higher background FDG uptake in the rectum, which could be a combination of physiologic uptake and inflammatory changes after radiation therapy. The reduced sensitivity of the regional lymph nodes is in part due to the

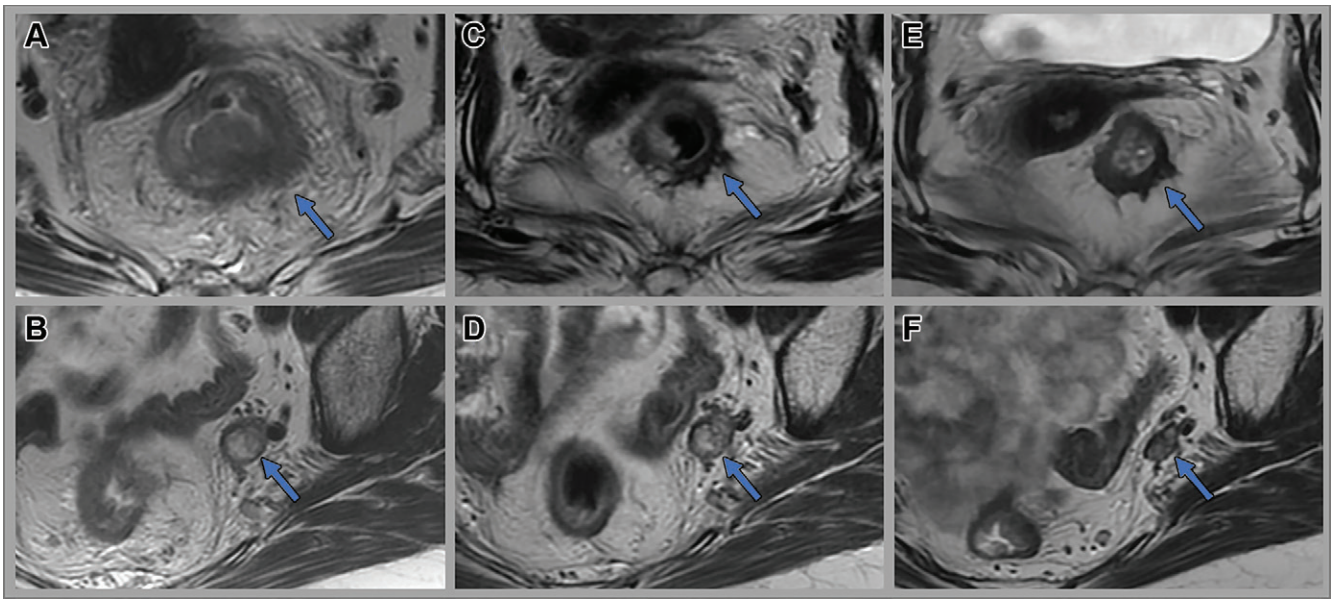


Figure 8: Images in a 56-year-old woman with locally advanced rectal cancer with enlarged 1.3-cm left internal iliac lymph nodes containing heterogenous signal intensity. Axial T2-weighted MR images at **(A, B)** baseline, **(C, D)** 8 weeks after total neoadjuvant therapy, and **(E, F)** 3.5 years after total neoadjuvant therapy (surveillance). Post-total neoadjuvant therapy images show near-complete response within the primary tumor (arrow in **C**) and only slight regression of the pelvic node measuring 1.3 cm (arrow in **D**). Endoscopic biopsy of the tumor bed at this assessment timepoint was negative for malignancy. The patient opted for nonsurgical management and remains free of tumor regrowth at 3.5-year follow-up (arrow in **E**). The left internal iliac lymph node shows regression with decreased size and mixed T2-weighted signal changes measuring 0.8 cm (arrow in **F**).

small size of these nodes and the reduced spatial resolution close to the usually intense primary tumor. For these reasons, FDG PET/CT is currently not recommended in the routine management of locally advanced rectal cancer. Tracers other than FDG have been used in a few studies to assess various metabolic parameters as imaging markers for response to neoadjuvant treatment, although these studies are few in number with small study samples. Negative post-nCRT fluoride 18 fluorothymidine PET/CT findings revealed more histopathologic responders than did FDG PET/CT findings (102). In a small pilot study using copper 60 diacetyl-bis (N4-methylthiosemicarbazone) PET, a marker for hypoxia, response to neoadjuvant treatment, overall survival, and progression-free survival were significantly worse for hypoxic tumors than for nonhypoxic tumors (103).

In recent years, an increasing number of research studies have focused on radiomics and deep learning techniques in various oncologic settings. In rectal cancer, radiomic features have been analyzed for various clinical outcomes (eg, T and N staging, response to treatment, and survival prediction). In a recent study, an area under the receiver operating characteristic curve (AUC) of 0.93 (95% CI: 0.87, 0.96; diagnosis of pathologic complete response) was demonstrated using a radiomic model created from posttreatment MRI in patients with locally advanced rectal cancer, outperforming qualitative assessment of T2-weighted imaging and DWI ($P < .001$) (104). Another study developed and validated a radiomics nomogram with a logistic regression classifier differentiating good responders from poor responders to nCRT in patients with locally advanced rectal cancer, with an AUC of 0.90 in the validation set ($P = .02$) (105). A radiomics nomogram incorporating radiomics score, histologic grade, and T staging demonstrated a better diagnostic performance than clinical and quantitative models in predicting extramural vascular invasion (106). Finally, a meta-analysis showed that radiomics and deep learning models had a per-patient AUC of 0.81 and 0.92, respectively, in the detection of lymph node metastases compared with the radiologist (AUC = 0.69) (107). Radiomics and machine learning algorithms are currently not implemented in rectal cancer MRI readings. Large-scale prospective validation studies are required to address such challenges as combining MRI studies from many different MRI vendors and sequence types. Recently, circulating tumor DNA combined with MRI has been shown to predict nCRT response and help select patients for the W&W strategy (108).

Challenges

Despite the improvements in techniques and in the understanding of rectal cancer pathophysiology, there remain challenges in imaging assessment of patients with rectal cancer. Strict adherence to the imaging protocol at both baseline and posttreatment timepoints is essential to achieve optimal diagnostic quality images. Assessment can be limited by poor acquisition techniques (eg, inadequate scanner magnet strength, failure to use appropriate surface coils, lack of patient preparation, or motion artifacts). Lack of appropriately positioned high-spatial-resolution small field-of-view sequences through parallel and perpendicular planes of the tumor can lead to inaccurate T staging. Posttreatment submucosal edema or postradiation peri- and mesorectal stranding and fibrosis can mimic tumor. DWI sequences may be affected by geometric distortion, susceptibility artifact from intraluminal gas, and T2 shine-through effects from mural or luminal fluid content. Careful scrutiny of the apparent diffu-

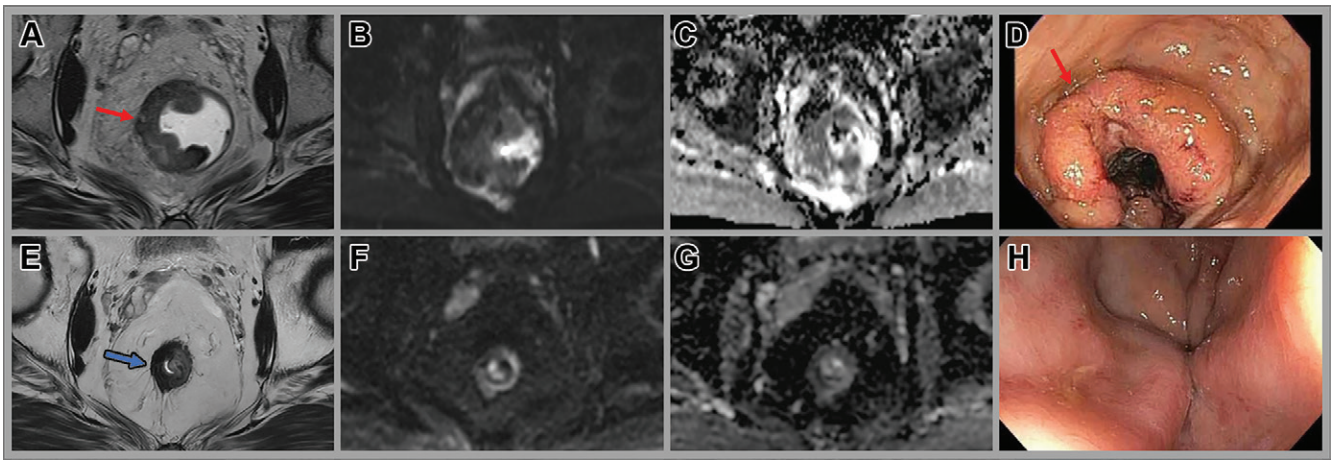


Figure 9: Images in a 46-year-old man with locally advanced rectal cancer. Axial **(A)** T2-weighted MRI scan, **(B)** axial diffusion-weighted image, and **(C)** apparent diffusion coefficient map at baseline show a tumor with intermediate T2-weighted signal intensity (arrow in **A**), concordant with **(D)** the endoscopic findings of a fungating and ulcerating rectal mass (arrow). Note the rectal gel in the lumen masking the high signal intensity on **B**. **(E)** Posttotal neoadjuvant therapy image obtained 8 weeks after completion of therapy shows T2-weighted dark signal intensity in the tumor bed (arrow) and **(F, G)** minimal restricted diffusion. **(H)** No residual tumor was seen at endoscopy, consistent with complete response.

sion coefficient map is also required. Mucinous degeneration of a solid tumor or lymph node in the posttreatment setting is generally considered a sign of treatment response. However, differentiation of cellular mucin from acellular mucin is limited on MRI scans and can lead to challenges during response assessment (109,110). A final and substantial challenge is radiologist experience with W&W imaging surveillance. The volume of studies performed at most centers is quite low, and there is a learning curve in interpretation of MRI results.

Endoscopic or Digital Rectal Examination Assessment of cCR

The landmark study by Maas et al was the first to show that combining endoscopy with MRI allowed for the best overall performance in the assessment of complete tumor response (89). In their 2015 study, the AUC for a combined T2-weighted and DWI sequence was 79% compared with a combined digital rectal endoscopy and endoscopy AUC of 88%. Notably, the combination of all three methods to detect pathologic complete response led to the highest sensitivity and specificity (71% and 97%, respectively), with a posttest probability of 98%. Similar results were seen using clinical and multisequence MRI reading strategies (111). Interestingly, when all three modalities indicated residual tumor, 15% of patients still experienced complete response (89). Patients with complete or near-complete response are offered rectal organ preservation with close follow-up, which includes flexible sigmoidoscopy, digital rectal examination, and rectal MRI (Fig 9). Near-complete responders are reassessed in an additional 4–8 weeks to allow more time for progression to a cCR.

The correlation between endoscopic findings and individual tumor response has not been deeply studied. Felder et al found a strong association with specific endoscopic criteria used in the Memorial Sloan-Kettering Cancer Center Rectal Cancer Regression Schema and tumor grade response (112). These criteria allow for objectivity in assessment and include flat white scar, telangiectasias, absence of ulceration and nodularity, small mucosal nodules or minor mucosal abnormality, superficial ulceration, mild persisting erythema, and visible tumor. The mean diagnostic accuracy for surgeons assigning a cCR after evaluating pre- and posttreatment endoscopy photographs was 89%. The study also showed that surgeons more accurately assigned cCR than nCR, suggesting that the criteria used to assign tumor response may underestimate it. This supports the importance of other modalities to assess clinical response to allow near-complete responders the potential for rectal organ preservation.

Monitoring Tumor Response over Time

International consensus recommendations from a multidisciplinary and interprofessional team identified several key outcome measures for successful implementation of W&W, including determination of cCR, time point of tumor response assessment, and follow-up methods (113). The optimal response assessment timepoint to determine cCR is 12 weeks from the start of treatment in patients undergoing standard short-course radiation therapy or nCRT for early-stage disease, 14 weeks from start of treatment in patients undergoing nCRT followed by brachytherapy, and 24 weeks after start of treatment after total neoadjuvant therapy. In patients with near-complete response at initial assessment, a repeat assessment 4–10 weeks later is recommended. Local regrowth is seen in approximately 25% of patients, with the majority occurring within the 1st year; regrowths are mainly endoluminal and treated with salvage surgery (Fig 10) (46). After completion of treatment, consensus recommends the patient be assessed every 3–4 months with digital rectal examination, endoscopy, and pelvic MRI for the first 2 years and then every 6 months for 3–5 years after treatment. CT of the chest and abdomen should be performed every 6 months for the first 2 years and then annually for 3–5 years.

Summary and Current Status

The watch-and-wait (W&W) approach in rectal cancer treatment represents a safe strategy for selected patients who want to preserve their rectum and undergo surveillance. Not all patients

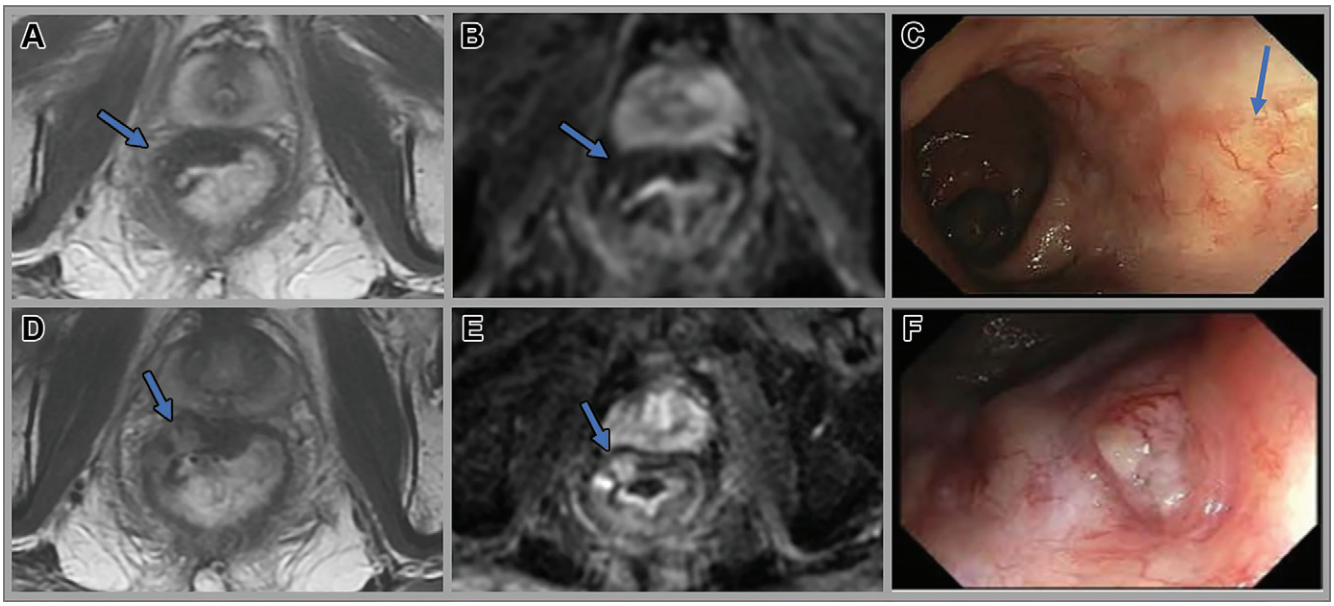


Figure 10: Images in a 68-year-old man with locally advanced rectal cancer. Axial **(A)** T2-weighted MRI scan and **(B)** diffusion-weighted image obtained 12 weeks after total neoadjuvant therapy show a T2-weighted dark scar (arrow). **(C)** Endoscopy 8 months after total neoadjuvant therapy shows radiation-related telangiectatic changes (arrow), with no evidence of tumor. **(D)** Surveillance scans obtained 12 months after total neoadjuvant therapy show higher intermediate signal intensity tumor regrowth (arrow in **D**), with restricted diffusion (arrow in **E**). **(F)** Endoscopy at 12-month follow-up shows a 0.5-cm ulcerated nodule in the tumor bed, consistent with tumor regrowth.

will be eligible, and more data are needed to ensure long-term safety. Prime among the outstanding questions is the potential for worse long-term outcomes due to distant metastases by potentially leaving small amounts of undetectable residual tumor behind in the rectum. Longer follow-up of the Organ Preservation of Rectal Adenocarcinoma trial is required. Many patients have become aware of the W&W approach and often ask if this is available at diagnosis or during treatment. For now, the care of these patients is best approached in a multidisciplinary setting at expert centers where many imaging, clinical, and sociologic factors can be weighed carefully by an experienced multidisciplinary team. While quality control measures for the management of rectal cancer are lacking, it is critical that they be promoted across centers, and efforts to do so have been supported by the National Accreditation Program in Rectal Cancer (114). It is quite clear from the authors' experience that current obstacles to progress include the following: *(a)* widespread inexperience with MRI interpretation; *(b)* variability in surgeon and radiologist interpretation of endoscopy and MRI, respectively; *(c)* lack of agreement on a standard follow-up approach and schedule; and *(d)* the intrinsic limitations of advanced technology to detect minimal residual disease in a scar. However, the advances that have been made have ushered in an exciting era in cancer treatment wherein many more patients may be able to attain a higher quality of life despite aggressive multimodality treatment and even avoid surgery altogether, as has become the case in anal cancer. We anticipate a growing number of resources for both radiologists and surgeons to learn about and attain expertise in the care of patients undergoing W&W. We also anticipate investigation into the use of other noninvasive approaches during surveillance, such as circulating tumor DNA, that have the potential to further improve the efficacy and safety of this approach.

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