Shifting Concepts in Rectal Cancer Management

A Review of Contemporary Primary Rectal Cancer Treatment Strategies

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The management of rectal cancer has transformed over the last 3 decades and continues to evolve. Some of these changes parallel progress made with other cancers: refinement of surgical technique to improve organ preservation, selective use of neoadjuvant (and adjuvant) therapy, and emergence of criteria suggesting a role for individually tailored therapy. Other changes are driven by fairly unique issues including functional considerations, rectal anatomic features, and surgical technical issues. Further complexity is due to the variety of staging modalities (each with its own limitations), neoadjuvant treatment alternatives, and competing strategies for sequencing multimodal treatment even for nonmetastatic disease. Importantly, observations of tumor response made in the era of neoadjuvant therapy are reshaping some traditionally held concepts about tumor behavior. Frameworks for prioritizing and integrating complex data can help to formulate treatment plans for patients. **CA Cancer J Clin 2012;62:173-202. ©2012 American Cancer Society.**

Introduction

Why Is a Review of Rectal Cancer Management Important?

The goal of the first part of this review is to introduce the advantages and limitations of rectal cancer staging modalities, surgical procedures, radiation therapy (RT) delivery options, and chemotherapy (CTx) agents. This provides background for understanding the second, more important, section of this article, in which frameworks for integrating data and options into a rational, coherent plan for a patient are outlined. We also discuss what is on the horizon of rectal cancer treatment and why and highlight observations that are challenging more traditional management strategies for rectal cancer. In a 1965 issue of this journal, published during the preendoscopy era, a plea was made for earlier diagnosis.[1] Most patients would have had stage III or stage IV disease at the time of diagnosis (if the American Joint Committee on Cancer staging system had been developed at that time), and while operative mortality had improved, it still ranged from 12% to 25%, and 50% of patients with rectal cancer eventually died of their disease. Historically, radical surgery was the only treatment for rectal cancer. Surgery remains a cornerstone of rectal cancer treatment and, as will be shown, outcomes have improved as a direct result of improved surgical technique. In addition to surgical advances, the number of variables evaluated to determine a treatment strategy has multiplied. A multidisciplinary team is required not only to weigh these variables but also to perform the full spectrum of diagnostic and staging studies and to deliver treatment. In fact, it has been shown that regular multidisciplinary meetings significantly improve rectal cancer outcomes.[2,3] Central to the controversial notion that therapy might be individualized is the growing recognition that some tumors may be biologically more favorable than others and that an indicator of this favorable condition is response to neoadjuvant therapy. The stage of disease at presentation may not be the best predictor of outcome and perhaps should not be the sole determinant of treatment. As treatment alternatives are evaluated, the appropriate choice among them may depend on patient factors, which have not typically been incorporated in published treatment guidelines.

Anatomic Considerations

How can rectal cancer originate in the anal canal? Why is sphincter preservation difficult in rectal cancer surgery? Why have local recurrence (LR) rates after rectal cancer surgery historically been so high? Awareness of a few subtle but critical features of anorectal anatomy lays the foundation for understanding some of these key rectal cancer

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We thank John Marks, MD, and Gerald Marks, MD, for their work defining an unpublished algorithm for treatment planning that incorporates tumor location, staging features, and response to neoadjuvant therapy. Magnetic resonance images and interpretation provided by Paul Knechtges, MD. We also thank Marcos Metzer for providing illustrations.

DISCLOSURES: The authors report no conflicts of interest.

 doi:10.3322/caac.21138. Available online at cacancerjournal.com

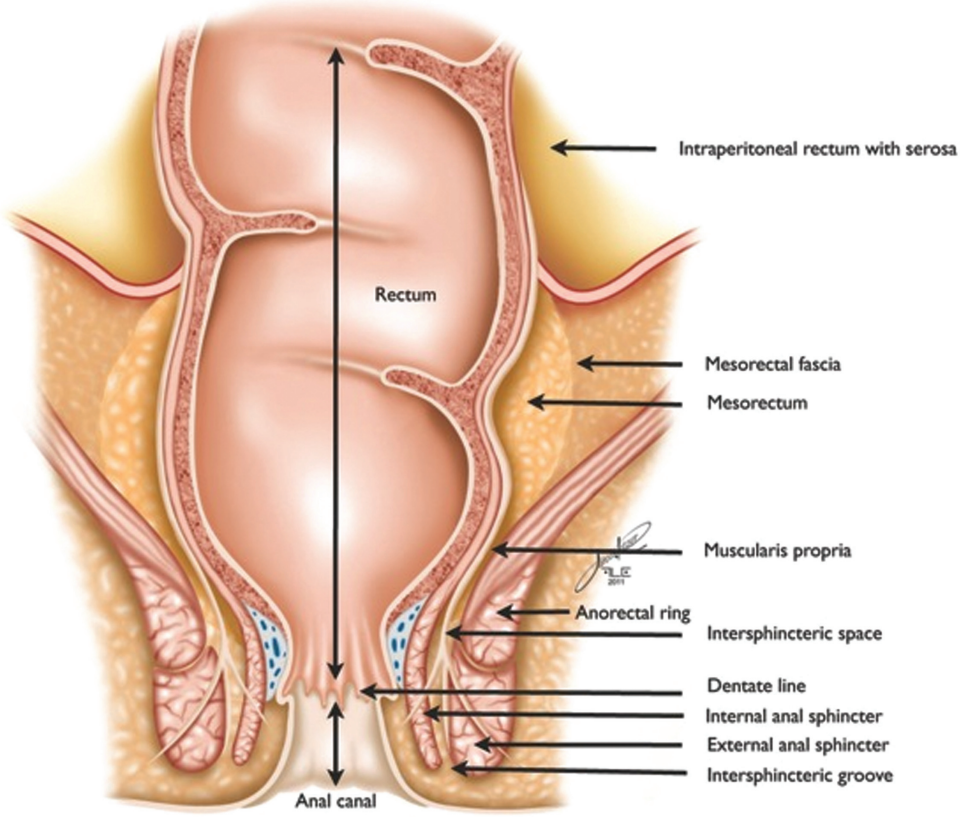

FIGURE 1. Anal and Rectal Anatomy.

management challenges (Fig. 1). There are 2 definitions of the anal canal. The anal sphincter muscular tube defines the functional (or "surgical") anal canal, with the levator ani muscles as the cranial boundary and the anal verge as the caudal limit. The embryological anal canal begins cranially at the dentate line, which is the fusion point of the endodermal and ectodermal contributions to the hindgut, and ends caudally at the anal verge. Rectal mucosa lines the functional anal canal above the dentate line and transition zone and explains how rectal adenocarcinoma can arise within the functional anal canal and make sphincter-preserving surgery technically challenging. The risk of LR has improved with recognition and preservation of the integrity of the mesorectum (rectal mesentery) and the pelvic fascial plane that surrounds it (mesorectal fascia [MRF]). In contrast to the serosa-covered, intraabdominal large bowel, most of the rectum is extraperitoneal. Below the peritoneal reflection, the mesorectum is a circumferential, fatty sheath that contains the perirectal lymph nodes (LNs) and surrounds the muscularis propria. It is sometimes several centimeters thick but it tapers at the lowest level, exposing the distal rectum as a muscular tube in continuity with the internal anal sphincter. Attenuation of the mesorectum may be the key to understanding why treatment failures are more common for tumors in the lowest rectum since tumor penetrating the muscularis propria has no mesorectal fat separating it from the levators, and attainment of a clear radial margin surgically may be impossible. Another anatomic consideration is the geometric constraint of the bony pelvis, which impedes surgical access to the distal rectum and visualization of correct dissection planes. This can be particularly problematic when there is a bulky rectal tumor.

It should be briefly noted that there is a lack of consensus about the exact boundary of the proximal (cranial) rectum and variability identifying the anal verge. A distance of more than 12 cm from the anal verge was adopted to distinguish the rectum from the sigmoid colon in the National Cancer Institute Guidelines 2000 for Colon and Rectal Cancer.[4] The intersphincteric groove is palpable and reproducibly demarcates the anal verge that is the most common reference point for measuring rectal tumor height, but unfortunately it is not appreciated by all examiners, who instead identify the verge much less specifically as the transition from buttock to canal. This combined with the natural variation of anal canal length (2 cm to 5 cm) leads to discrepant measurements of rectal tumor height.

While the anatomic features of the rectum pose particular challenges to extirpation of tumors, the lack of familiarity with this anatomy is probably a bigger contributing factor to low rectal cancer treatment failures.

Initial Clinical Assessment

Beyond securing the diagnosis of rectal adenocarcinoma by tissue biopsy, which can sometimes require an examination under anesthesia and aggressive local biopsy or even excision of the lesion, the clinical assessment takes into account tumor and patient details relevant to staging and treatment. The staging process begins with the digital examination. An experienced examiner will note the size of the tumor and percentage circumference involved, the radial position, tumor morphology, its level, and its fixation (whether it is mobile or it is tethered to surrounding structures or even cemented to them, suggesting a deeper level of invasion).[5] Occasionally, large mesorectal LNs can be palpated. Bimanual palpation of the rectovaginal septum can suggest tumor infiltration. Inguinal adenopathy may represent metastatic disease. The digital rectal examination is essential and necessary for evaluating the resectability of the tumor and the possibility of sphincter preservation. Likewise, the abdominal examination may suggest carcinomatosis by the presence of ascites, implants in the abdominal wall or umbilicus (Sister Mary Joseph nodule), or liver metastases.

Tumor Localization and Characterization

Surgical decisions regarding the feasibility of sphincter preservation, appropriate choice of procedure, and positioning for that procedure require utterly precise localization of the rectal tumor, not just its level in the rectum but also its radial disposition. Anoscopy and flexible sigmoidoscopy are important tools, but rigid proctoscopy is the single most useful tool for the precise localization of tumors, especially those beyond the reach of an examining finger. It is inexpensive and portable, and it provides better orientation to radial tumor position and level in the rectum than flexible endoscopy, bearing in mind the inconsistencies in measuring tumor height discussed in the "Anatomic Considerations" section.[6] Size (percentage circumference and length) and morphology are recorded. Morphologic features may have prognostic value; exophytic (polypoid or sessile) tumors are associated with better survival and decreased LR compared with nonexophytic (ulcerated or flat raised) tumors.[7,8] Flexible sigmoidoscopy can be better suited to this when the lumen is narrowed or when palpation establishes orientation of the tumor. It also enables photo documentation of the tumor in situ before and after treatment (Fig. 2), and it may reveal additional lesions in the distal colorectum not appreciated by rigid proctoscopy.[9] Some tumors partially or completely vanish after neoadjuvant treatment. Tattoos have been used extensively to help identify colon neoplasms for laparoscopic resection, but they have somewhat less usefulness in the rectum. Much of the rectum is extraperitoneal, and the mesorectum is thick enough that

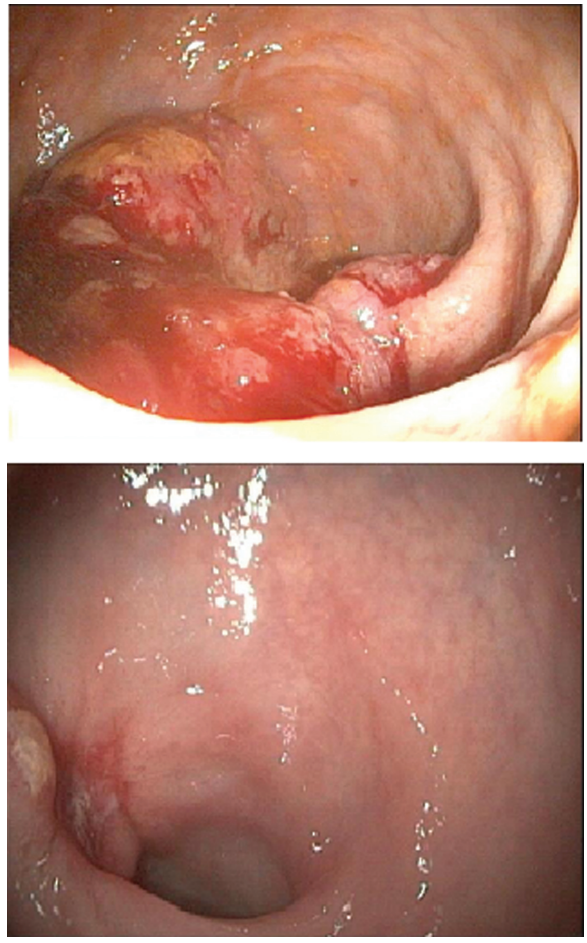

FIGURE 2. Rectal Tumor Endoscopic Assessment. (*Top*) Before neoadjuvant chemoradiation (cT3N0M0) and 6 weeks after the completion of neoadjuvant chemoradiation (ypT0N0M0). (*Bottom*) Six weeks after the completion of neoadjuvant chemoradiation (ypT3N0M0; 1.5 cm residual focus of invasive cancer).

mucosal tattoos are not likely to help guide laparoscopic determination of the rectal transection site. Tattoos at both sites often become diffuse and in the rectum could obscure a small scar or lead to resection at the wrong site if no scar remains.[10,11] A variety of mucosally applied clips have been evaluated in the foregut or used as fiducial markers for imaging as part of RT protocols and may find wider application marking rectal tumors before neoadjuvant therapy.[12-14] For the time being, as long as some form of operative resection is mandatory for all rectal cancers, it is vital that an experienced rectal cancer surgeon evaluate the patient prior to initiating neoadjuvant therapy for just this reason.

Patient Factors

Certainly the patient's overall condition and comorbidities will influence treatment planning. Impending obstruction, sphincter incompetence, and history of prior abdominal surgery or pelvic RT should be noted. Patient outlook, lifestyle, and support system should also be assessed.

TABLE 1. Pretreatment Radiologic Staging Parameters for ERUS and MRI

	RECTAL WALL INVASION	LYMPH NODE INVOLVEMENT	THREATENED CIRCUMFERENTIAL MARGIN (MESORECTAL FASCIA INVOLVEMENT)
ERUS[16]	T1: Break in submucosa.	Round shape, irregular contour, proximity to primary tumor, size > 5 mm.	Mesorectal fascia not imaged with ERUS.
	T2: Penetration through submucosa, thickening of muscularis propria.		
	T3: Extension into perirectal fat.		
	T4: Penetration into adjacent structure.		
MRI	T1: Smooth muscularis propria margin.[17]	Irregular contour and heterogeneous signal intensity are more accurate than size.[18,19] Over 50% of pN-positive lymph nodes are < 5 mm on MRI.[20]	Tumor or suspicious lymph node < 1 mm from mesorectal fascia on MRI.[18] High correlation between pathologic CRM > 1 mm if 5 mm separation of tumor from mesorectal fascia on MRI.[21]
	T2: Tumor penetrates muscularis propria; spiculation in mesorectal fat can be fibrosis, not tumor.[17]		
	T3: Nodular bulge or projection into mesorectum.[18]		
	T4: Abnormal signal extends into adjacent organ (loss of fat plane not sufficient) or into peritoneal space.[18]		

CRM indicates circumferential (radial) resection margin; ERUS, endorectal ultrasound; MRI, magnetic resonance imaging.

Staging of Rectal Cancer

The TNM international cancer staging system incorporates prognostic factors (clinically relevant, tumor-specific features that affect outcome) and predictive factors (features that forecast the likelihood of responding to particular treatments), and forms the basis of stage-directed treatment standards (see Web site link).[15] Even though this is a dynamic process with updates published every few years, there are limitations to the system. Among these is that staging is done at fixed time points and does not formally incorporate response to treatment as a prognostic factor so that features like tumor regression, which appears to be a critical determinant of rectal cancer outcome, are not reflected in the rectal tumor stage. In addition, technical barriers to staging limit the accuracy of the system and force broader generalizations or grouping of tumors than may be useful clinically. Historically, it made sense to merge the staging of rectal and colon cancer when preoperative staging was less refined and the mainstay of treatment was surgical even though worse outcomes stage for stage for rectal cancer were recognized. This makes less sense now that the local staging of rectal cancer (estimation of primary tumor and LN disease) is significantly more evolved than colon cancer staging and requires the evaluation of additional features beyond TNM classification to identify patients at increased risk of local failure and target them for more aggressive therapies. In both cases, as with most gastrointestinal malignancies, the presence of metastatic disease is a major determinant of outcome and underlies the final management decision.

Local Staging: T, N, and Beyond

Imaging studies are central to the local staging of rectal cancer; radiologic staging parameters are summarized in Table 1.[16-21]

Primary Tumor

The extent of tumor penetration through the rectal wall (T status) corresponds with a higher risk of LN involvement and LR. Accordingly, T3 and T4 tumors are more likely to recur locally than T1 or T2 tumors, and they are also more likely to have associated positive LNs, one of the most significant, negative prognostic factors. The accuracy of T category assessment by digital rectal examination performed by colorectal surgeons ranges from 58% to 88%, but there is significant interobserver variability and results are highly dependent on the surgeon's experience.[16] Endorectal ultrasound (ERUS) is less "user-dependent" and more accurately determines T category by direct visualization of layers of the rectal wall and adjacent organs. Overstaging, especially of T2 tumors, is more common than understaging by ultrasound. In a large randomized trial of patients with rectal cancer, almost 20% of tumors initially classified as usT3-usT4 (as classified by ultrasound) actually were pathologic T2 tumors.[22] Ultrasound probe types vary with respect to crystal arrangement and are either static or rotating. The interrogation frequency (in megahertz) also varies from 4.0 to 12.0. In pooled studies, however, these distinctions are not often made.[23] Transanal probes are most common, but endoscopic probes are also used. Recently, 3-dimensional (3-D) ERUS was introduced and may more precisely determine the T category than 2-D modalities.[24] Besides enhancing the accuracy of staging,

ERUS offers the convenience of in-office evaluation, often at the time of the initial consultation. Drawbacks of ERUS are that low-lying, very high, or near-obstructive tumors may sometimes be technically difficult to assess and examinations can be uncomfortable for patients.[25] The endorectal coil required when magnetic resonance imaging (MRI) of rectal tumors was introduced shared these drawbacks but did improve the accuracy of tumor staging, especially for T2 tumors. Since then, significant improvements in high-resolution MRI image acquisition and interpretation have led most institutions to perform rectal MRI without the coil. A recent meta-analysis of local staging by ERUS, MRI, and computed tomography (CTx) highlighted some differences among these modalities with regard to distinguishing T category. The sensitivity of these modalities for detecting muscularis propria invasion (T1 vs T2) was similar, but the specificity of ERUS was better. MRI tended to overstage patients with T1 tumors. Conversely, the specificity of all modalities was similar for assessing perirectal fat invasion (T3 status), but ERUS was more sensitive. CT and MRI appeared to understage T3 tumors compared with ERUS. It could be argued that ERUS, when feasible, more appropriately distinguishes T1 from T2 and T2 from T3 cancers.[25] Positron emission tomography (PET) is a poor determinant of the exact depth of invasion and has little usefulness in establishing the T classification.

Regional LNs

Radiologic assessment of LN involvement is much less reliable than it is for T category. The overall accuracy of N category assessment by ERUS or pelvic MRI ranges from 60% to 80%, and meta-analysis of imaging modalities in LN staging showed no differences in sensitivity or specificity among ERUS, MRI, or CT.[25] Interestingly, the depth of primary tumor invasion correlates not only with the risk of regional LN positivity but also with imaging accuracy of LN staging. A review of patients with early T status staged by ERUS had significantly less accurate LN staging. The risk of understaging LN status in patients with T1 to T2 tumors is that they are offered less radical procedures and have compromised outcomes.[26] Inaccuracies of LN staging even among patients with T3 tumors is underscored by a multicenter study using both ERUS and MRI for pretreatment staging that found LN metastases in radical resection specimens after neoadjuvant chemoradiation therapy (nCRT) in 20% of 180 clinical LN-negative (cLN-negative) patients. This number is especially disturbing because nCRT decreases the rate of LN positivity, so the rate of undetected LN involvement is likely even higher than 20%. In this study, the risk of understaging LNs was not a function of the radiologic staging method used (ERUS vs high-resolution MRI).[27]

Criteria for LN involvement include decreased echogenicity and round rather than oval shape (ERUS), increased signal intensity or inhomogeneity (MRI), and larger size or irregular contour (both).[19,20] Larger size is commonly cited as a marker of LN positivity, but there is little agreement regarding the size cutoff. MRI and ERUS share the risk of understaging small LNs. MRI resolution limits the detection of LNs smaller than 3 mm, which is problematic since as many as 25% of positive LNs measure 3 mm or smaller. There is also a tradeoff between sensitivity and specificity. In a representative study, a cutoff of 3 mm yielded a sensitivity of 78% and a specificity of 59%; a 10-mm cutoff yielded a sensitivity of 3% and a specificity of 100%.[28] At least one report finds irregular contour and inhomogeneous signal intensity to be more accurate predictors of LN involvement regardless of size.[19] Anatomic and tumor features can also interfere with accurate LN staging. For example, ERUS fails to detect upper mesorectal LNs in patients with obstructive lesions. In light of the limitations of clinical LN staging and the escalating risk of LN involvement associated with higher T category, the evaluation of LN metastasis risk should not be based solely on LN imaging findings but should also take T status into account.

Beyond T and N

Although not included in the TNM system, local tumor staging currently involves not only depth of tumor penetration and LN metastases but tumor proximity to the MRF. Involvement of or close proximity to the MRF increases the risk of compromised circumferential (radial) resection margins (CRM+) after radical surgery. This feature has been shown to be an independent predictor of local failure when determined by pathological assessment.[29,30] The MRF can be determined with high accuracy by standard MRI, and tumor (or suspicious LN) proximity to the MRF is ideally measured in mm by the radiologist.[31] The MRF with tumor in close proximity (1 mm on MRI) has an increased risk having a positive CRM and is therefore called a "threatened" MRF.[28] It is not detected by ERUS and despite a recent report demonstrating moderate to substantial interobserver agreement between multidetector row CT and MRI determination of the MRF, improved accuracy is still required, particularly among distal tumors where CT results were poorer.[32,33] In addition, MRI can sometimes detect vascular invasion, which is a recognized prognostic factor and may be a critical predictor of systemic recurrence.[34,35] Besides identifying the threatened MRF, MRI assesses the depth of T3 tumor invasion into perirectal fat, which may be another prognostic factor for stratifying the risk of LR but is not currently included in the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) system (Fig. 3) (Table 2).[21,36] Even though MRI can distinguish

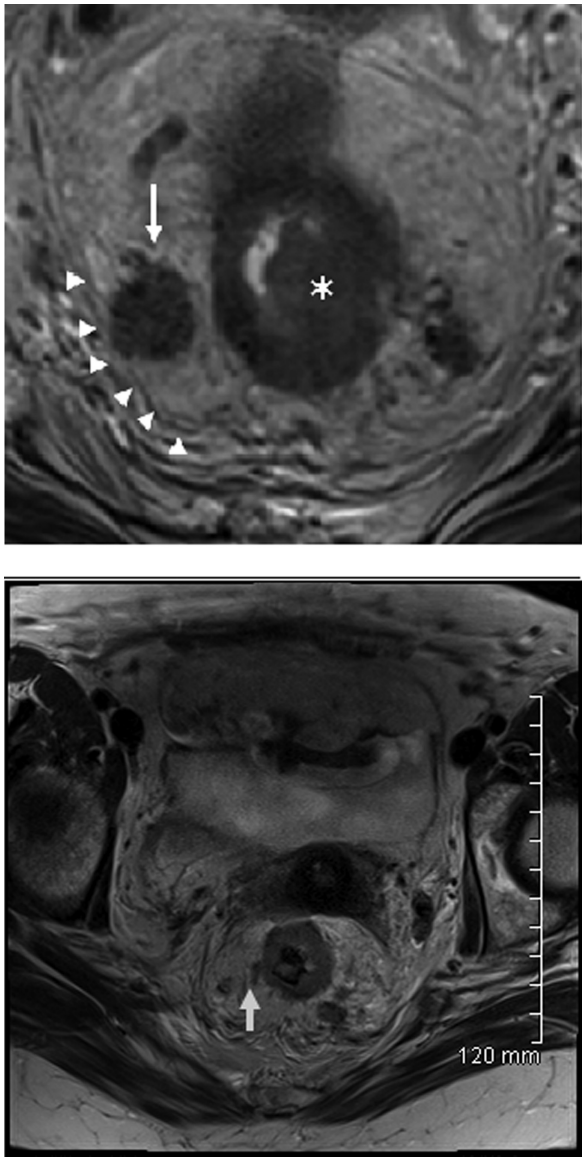

FIGURE 3. High-Resolution Magnetic Resonance Imaging of Rectal Cancer Used For Staging. (*Top*) An axial T2-weighted, non-fat-saturated image demonstrating a rectal tumor identified invading the muscularis propria (*). There is an adjacent enlarged heterogenous lymph node (arrow) in contact with the mesorectal fascia (arrow heads). Incidental note is made of another heterogenous lymph node to the left of the rectum. (*Bottom*) Vascular invasion in the linear area of an abnormal T2 signal extending from the tumor margin (arrow).

levels of tumor penetration in the perirectal fat, it cannot discriminate the depth of T1 tumor penetration into the submucosa (SM1, SM2, or SM3), which also appears to correlate with risk of LR.[28]

Systemic Staging

Usually a CT scan of the chest, abdomen, and pelvis is sufficient for the detection of liver and lung metastases, the 2 most common sites for metastatic disease in patients with rectal cancer. A higher proportion of patients with rectal cancer than those with colon cancer have lung metastases without simultaneous or prior liver metastases, which may substantiate a preference for a chest CT rather than chest x-ray in this group.[25,37] PET-CT imaging can identify previously undetected metastatic disease, but studies have failed to demonstrate a benefit for its routine use in systemic staging in colon and rectal cancer; the findings only change management in 15% of cases.[38,39] Please also see the American College of Radiology Appropriateness Criteria for more information.[37]

Staging Summary

It is rare for a patient with rectal cancer not to undergo radiologic locoregional and systemic staging prior to starting treatment. Currently, MRI (without an endorectal coil) and ERUS are preferred for their accuracy in determining T and N status. ERUS may offer advantages in classifying early tumors (distinguishing T1 from T2 tumors and T2 from T3 tumors). MRI is generally preferred for the staging of more advanced T category tumors (substratification of T3 tumors based on the level of perirectal fat invasion, threatened MRF, and perirectal vascular invasion). However, these distinctions are only important to the extent that they impact final management decisions.[40] For systemic staging, CT scan of the chest, abdomen, and pelvis is usually sufficient.

Surgical Approach to Rectal Cancer

While a door may be opening to the nonoperative management of select rectal tumors, surgical resection is still regarded as the cornerstone of curative therapy. Abdominoperineal resection (APR), which entails the removal of the rectum and the creation of a permanent, end colostomy was the standard of care for nearly 80 years. Modifications (listed in Table 3) were subsequently sought both to address high perioperative mortality and morbidity such as impotence and bladder dysfunction and to reduce high LR rates.

Radical Resection

Radical resection includes sphincter-sparing and non–sphincter-sparing operations. In the early 20th century, it was recognized that the LN-bearing tissue around the rectum and anal canal needed to be removed to help prevent LR, presumably in retained, involved LNs.[41] Nonetheless, emphasis was placed on longitudinal margins, and a 5-cm rule for proximal and distal margins was established with an aim of preventing anastomotic recurrences in retained, microscopically involved mucosa. In 1983, a report of very low rates of intramural spread beyond 1 cm and low anastomotic recurrence rates led to a decrease in the acceptable macroscopic distal margin to 2 cm.[42]

Total Mesorectal Excision

In 1982, R. J. Heald applied a fundamental principle of surgery, namely, respect for naturally occurring tissue planes, to rectal resection by identifying the MRF as the correct

TABLE 2. AJCC/UICC T Categories Versus MERCURY Trial "T Staging" Criteria[a]

	AJCC T CATEGORY CRITERA	MERCURY TRIAL "T STAGING" CRITERIA
Tis	In situ carcinoma.	No corresponding value.
T0	No evidence of viable tumor cells.	No evidence of primary tumor.
T1	Tumor invades submucosa.	Tumor invades submucosa. Low signal in submucosal layer or replacement of submucosal layer by abnormal signal not extending into circular muscle layer.
T2	Tumor invades into but not through muscularis propria.	Tumor invades into but not through muscularis propria. Intermediate signal intensity (higher signal than muscle, lower signal than submucosa) in muscularis propria; outer muscle coat replaced by tumor of intermediate signal intensity that does not extend beyond outer muscle into perirectal fat.
T3	Tumor invades through muscularis propria into mesorectal/subserosal fat.	Tumor invades through muscularis propria into mesorectal/subserosal fat. Broad-based bulge or nodular projection (not fine spiculation) of intermediate signal intensity projecting beyond outer muscular coat.
T3a	No corresponding category.	Tumor extends $<$ 1 mm beyond muscularis propria.
T3b	No corresponding category.	Tumor extends 1 to 5 mm beyond muscularis propria.
T3c	No corresponding category.	Tumor extends $>$ 5 to 15 mm beyond muscularis propria.
T3d	No corresponding category.	Tumor extends $>$ 15 mm beyond muscularis propria.
T4		Tumor invades other organs. Extension of abnormal signal into adjacent organ; extension of tumor signal through peritoneal reflection.
T4a	Tumor involves serosal surface.	No corresponding category.
T4b	Tumor invades adjacent structures/organs.	See T4 above.

AJCC indicates American Joint Committee on Cancer; UICC, International Union Against Cancer.

[a]Mesorectal fascia (MRF) involvement has not specifically been incorporated into magnetic resonance imaging (MRI) "T staging" schema, but a distance of $>$ 6 mm between the tumor or involved lymph node and the MRF on MRI corresponds to a pathologic margin of $\geq$ 2 mm and a distance of $>$ 5 mm on MRI corresponds to a pathologic margin of $\geq$ 1 mm).

Adapted from Sizer BF, Arulampalam T, Austin R, Lacey N, Menzies D, Motson R. MRI in predicting curative resection of rectal cancer: defining a "window of opportunity" for laparoscopic surgery. *BMJ*. 2006;333:808-809[36]; and Beets-Tan RG, Beets GL, Vliegen RF, et al. Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery. *Lancet*. 2001;357:497-504.[21]

plane of dissection, substantially reducing LR rates and improving the functional results of proctectomy.[43] He replaced the practice of blunt dissection with the surgeon's fingers to separate the rectum from surrounding structures with the performance of precise, sharp dissection under direct visualization. Systematic education of surgeons around the world in the technique of Heald's total mesorectal excision (TME) has been shown to improve oncologic outcomes.[44,45] Attention shifted from longitudinal resection margins to the CRM. A positive CRM or even disruption of the fascial encasement of the rectum and its mesentery (MRF) is associated with worse prognosis both in terms of LR and disease-free survival (DFS).[29,30,46-50] A schema for assessing the integrity of the mesorectal dissection has been validated (Fig. 4) (Table 4),[51] but has not yet been widely incorporated in pathology reports.[30]

For tumors in the mid- to low rectum, TME must be taken to the level of the pelvic floor muscles. For tumors in the upper rectum, a portion of the rectum can be left in place, but the circumferential dissection and transection should be complete to a level 5 cm distal to the caudal edge of the tumor or to the pelvic floor muscles. The radical proctectomy that preserves a portion of the rectum is called a low anterior resection (LAR). It is also important to avoid "coning in" on the mesorectum because it increases the risk of pelvic recurrence, presumably by leaving involved LNs in place (Fig. 5A). For more distal tumors, sphincter-preserving approaches include the ultra-LAR with coloanal anastomosis or the intersphincteric resection with a coloanal anastomosis. In each of these cases, TME is still required. Improved instrumentation including lighted pelvic retractors (and now laparoscopic instruments) and stapling devices that allow the surgeon to see the MRF and pelvic nerves and to work in the confined, dark space of the deep pelvis as well as to transect the rectum without spilling rectal contents including tumor cells into the pelvis are contributing factors to the success of these techniques. Saline lavage of the rectum prior to stapling has been shown to decrease the number of exfoliated tumor cells that potentially could seed a metachronous tumor by implanting at the staple line,[52] and tumoricidal irrigants such as povidone-iodine are used by some surgeons.[53]

Non–Sphincter-Sparing Procedures

In experienced hands, APRs are reserved for tumors in the lowest 2 cm to 3 cm of the rectum that remain fixed to surrounding structures (usually the levator muscles or anal sphincter) or when patient factors such as fecal incontinence dictate nonstandard therapy. It has been noted that LR rates are often higher after the more radical APR than after ultra-LARs, even when good-quality TME has been performed.[54] Adherence to the principles of

TABLE 3. Rectal Cancer Operations

	RADICAL RESECTION (TME)[a]		NO RADICAL RESECTION	
Sphincter-preserving	LAR with colorectal anastomosis.	Proctectomy with transection below the peritoneal reflection (mid-rectum or lower) leaving a cuff of rectum; sigmoid colectomy; and colon J-pouch or straight anastomosis.	TEM.	Full-thickness local excision.
	Ultra-LAR with coloanal anastomosis.	Proctectomy with transection at the pelvic floor below the mesorectum at the rectal muscular tube, leaving rectal mucosa within the functional anal canal; sigmoid colectomy; and colon J-pouch or straight anastomosis.	Transanal excision.	Full-thickness local excision.
	ISR or TATA.	Proctectomy with transection of the rectum within the functional anal canal (at or just above dentate line, across the rectal mucosa and superior internal anal sphincter), sigmoid colectomy. Incision can be at the anal verge, in which case the entire internal anal sphincter is removed. Colon J-pouch or straight anastomosis.		
	Total abdominoproctocolectomy with ileal J-pouch anastomosis.	Proctectomy as for ultra-LAR or ISR, total colectomy, ileal J-pouch anal anastomosis.		
Non–sphincter-preserving	APR.	Anal canal removed (either intersphincteric dissection which preserves external anal sphincter, or extralevator or ischioanal dissection, which includes ischiorectal fat and entire sphincter muscle); proctectomy; sigmoidectomy; and permanent end stoma.		
	Total abdominal proctocolectomy.	Same as APR but the entire colon is removed and end ileostomy created.		
Functionally non–sphincter-preserving	LAR with permanent colostomy.	Same as LAR but no anastomosis is created. Anus is left in place and end stoma is created. May remove entire colon.	Permanent diverting colostomy.	No resection, loop or end stoma.

APR indicates abdominoperineal resection; ISR, intersphincteric resection; LAR, low anterior resection; TATA, transabdominal transanal resection TEM, transanal endoscopic microsurgery; TME, total mesorectal excision.

[a]Approach can be open, laparoscopic, hand-assisted laparoscopic, laparoscopic hybrid, or robotic.

TME, which include dissecting along the tapering mesorectum to the muscular rectal tube at the levators, may be disadvantageous when performing an APR (Fig. 5B). An extralevator (cylindrical) dissection avoids this (Fig. 5C). The transabdominal TME is carried to a level just above the levators, before the mesorectum tapers. The perineal dissection then commences by developing a plane outside the external anal sphincter that is carried along the caudal aspect of the levator muscles. Rendezvous with the abdominal dissection is made posteriorly, entering at the sacrococcygeal ligament, often resecting the coccyx, and then completing the rectal mobilization by detaching the levator muscles near their pelvic sidewall insertion. Additional ischiorectal fossa fat can be incorporated in the resection specimen if tumor has grown more widely through the levators.[55] This extended approach achieves a better CRM (Fig. 5C).[56] Perineal wound healing is more problematic when the levator muscles cannot be brought together in a layered closure of the wound, especially following pelvic RT. In these cases, a muscle flap, or even placement of meshes, often improves the probability of healing.[57,58]

Sphincter-Preserving Radical Resections

For the very low rectal tumor located below the lowest rectal valve, it remains a challenge to obtain a defined distal margin. Some tumors actually originate in or extend into the rectal mucosa lining the surgical anal canal (Fig. 1). With tumors that are 2 cm or less above the anorectal ring (the levator ani) or that extend below it, it may be better to perform the rectal transection transanally so that the lowest extent of the tumor can be seen and a transection line chosen that includes a distal margin of normal rectum. An "ultra-LAR" or coloanal anastomosis can be completed transabdominally by dissecting beyond the pelvic floor into the surgical anal canal between the internal and external anal sphincter layers, retracting the lowest portion of the rectum out of the anal canal, and placing a stapler nearly at the level of the levator ani muscles across the muscle tube of rectum (the internal anal sphincter), but this becomes increasingly difficult for tumors 2 cm or less above the anorectal ring. By the transanal approach, an intersphincteric resection with hand-sewn anastomosis (Fig. 5D)[59] can be suitable for highly selected patients who are motivated to

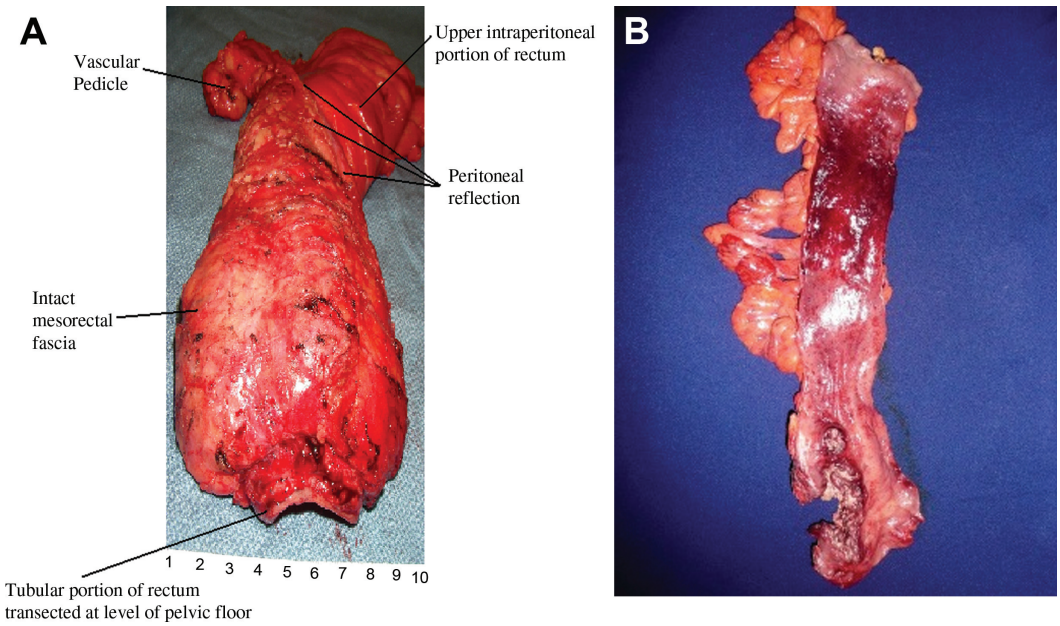

FIGURE 4. Total Mesorectal Excision (TME). (A) Good-quality TME shows vascular pedicle and glistening mesorectal fascia without defects. (B) Poor-quality TME with numerous defects noted not just through the mesorectal fascia but violating the muscularis propria.

accept imperfect function to be spared permanent colostomy. Partial or even total resection of the internal anal sphincter can be performed to obtain an adequate distal margin.[59,60] Mucosectomy (without resection of the internal sphincter) should be restricted to patients with benign tumors and avoided in those with locally advanced rectal cancer as it frequently results in insufficient radial margins (Fig. 5D).

Functional Matters

Most commonly, the descending colon is recruited to function as a neorectum. For reasons that are not yet clearly defined, a set of functional problems, often described as "postproctectomy syndrome," including increased frequency and clustering of bowel movements and impaired continence (likely multifactorial due to sphincter stretch or partial resection, decreased compliance of the neorectal reservoir compared with the native rectum, spasticity as a consequence of autonomic nerve disruption, and loss of the sensitive anal transition zone in intersphincteric resections), are common after radical resections.[61] Reconstruction fashioning a colon J-pouch to increase the neorectal reservoir volume has been shown to improve function in the early postoperative period (6 months to 2 years), but by 2 years after surgery, the advantages in terms of quality of life disappear relative to the "straight" anastomosis.[62-64] Transverse coloplasty makes a smaller reservoir than a J-pouch and is less desirable.[62] A carefully managed bowel care regimen supervised by an experienced rectal cancer surgeon can help patients achieve reasonable function.

Virtually all proctectomy patients are given a diverting colostomy or ileostomy within the first months after surgery, particularly if they have received neoadjuvant RT (nRT). This protective stoma does not prevent anastomotic separation, but it can limit the damage of dehiscence by eliminating fecal spillage that is more likely to lead to pelvic sepsis than mere separation. A multicenter trial that randomized patients to defunctioning stoma versus no stoma found that patients with a stoma had significantly less symptomatic anastomotic leakage (10.3 vs 18.0%; $P < .001$) and were 3 times less likely to need urgent abdominal reoperation. With a median follow-up of 42 months, there was no difference in the long-term stoma rate between the initially diverted and nondiverted groups.[65] A 2010 Cochrane review also found reduced leakage and urgent surgery rates with diverting stoma construction.[66]

TABLE 4. Macroscopic Mesorectal Dissection Grading and Adequacy of Circumferential Resection Margin

NEGATIVE CIRCUMFERENTIAL RESECTION MARGIN (> 1 MM)	MESORECTAL DISSECTION GRADE	FEATURES DEFINING MESORECTAL DISSECTION GRADE
75.9%	Complete.	Intact mesorectum.
		Minor irregularities (< 5 mm deep).
		No coning in toward distal margin.
13.0%	Nearly complete.	Moderate bulk of mesorectum.
		Moderate coning.
		No muscularis propria visible except at levators.
11.1%	Incomplete.	Little bulk to mesorectum with defects down to muscularis propria and/or very irregular surface.

Adapted from Nagtegaal ID, van de Velde CJ, van der Worp E, Kapiteijn E, Quirke P, van Krieken JH. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol*. 2002;20:1729-1734.[51]

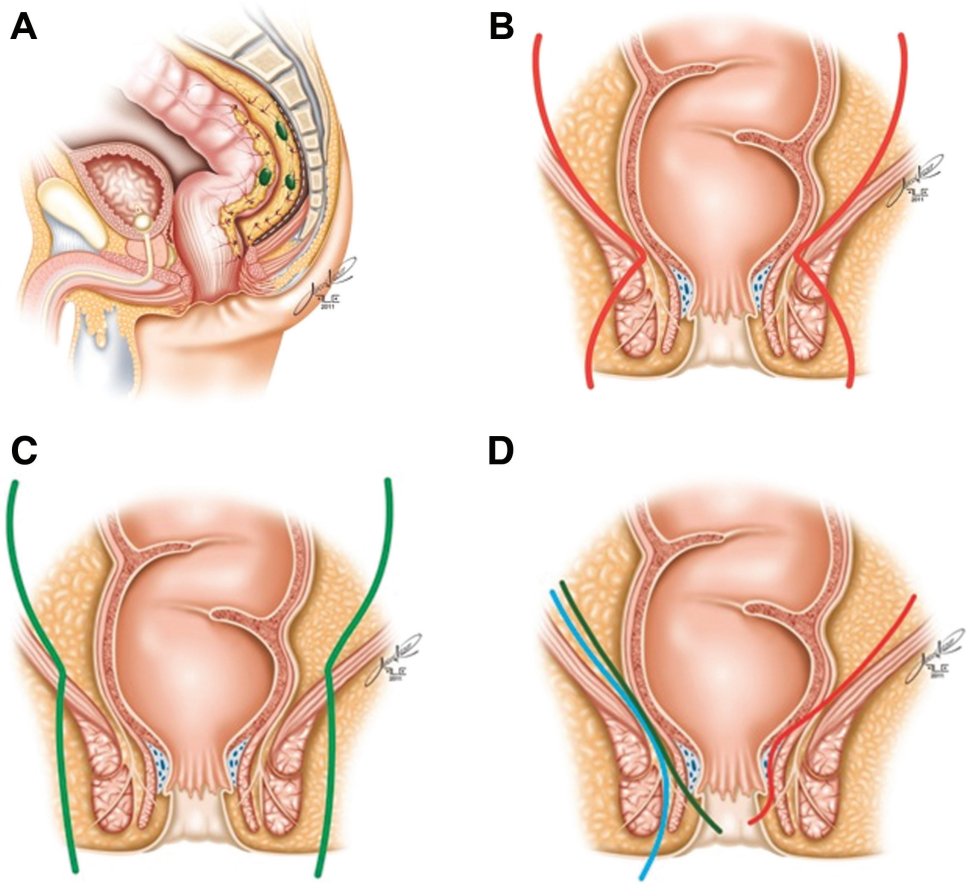

FIGURE 5. Radical Proctectomy. (A) A "coned-in" total mesorectal excision can leave involved lymph nodes in situ that may account for local recurrences. (B) Dissection (shown in red) that leaves a waist at the level of the levators, which is appropriate for a low or ultra-low anterior resection, can leave tumor behind during an abdominoperineal resection (APR) that is typically performed for suspected involvement of the levators. (C) An APR with cylindrical excision (shown in green) that does not taper along the mesorectal fascia as it approaches the pelvic floor and more widely incorporates the levators may result in lower positive circumferential margin rates. (D) Intersphincteric resections maintain gastrointestinal continuity but sacrifice some (or all) of the internal anal sphincter to achieve a full-thickness resection and negative circumferential resection margin in the very low rectum (green indicates standard resection beginning at or just above the dentate line; blue, complete removal of internal anal sphincter [not commonly performed]). Mucosectomy (indicated by the red line) does not achieve a full-thickness resection and is therefore not recommended for rectal cancer.

Minimally Invasive Radical Resections: Laparoscopic and Robotic Techniques

Although laparoscopic colectomy has been proven in prospective, randomized trials to be at least equivalent oncologically to open colectomy for colon cancer with respect to LR and overall survival (OS),[67-70] learning curves are steep and adoption rates are low.[71-74] Laparoscopic proctectomy, whether for cancer or benign disease, is generally regarded as more challenging than laparoscopic colectomy,[75] and few prospective randomized trials have yet been completed. Data from nonrandomized trials assessing oncologic outcomes of laparoscopic versus open proctectomy summarized in a meta-analysis by Anderson et al (1403 laparoscopic and 1755 open procedures)[76] showed no difference with respect to positive radial or distal margin, LR, distant failure, or OS. Although the difference between LN harvest rates was statistically significant (10 vs 11, laparoscopic vs open) this is not likely to be clinically significant.[76] Robotic proctectomy may help overcome some of the technical difficulties of conventional laparoscopy, and preliminary reports suggest comparable results for margin involvement, adequacy of TME, LN harvest, and short-term oncologic outcomes.[77-81] Two prospective, randomized trials are currently accruing to help clarify whether minimally invasive surgical approaches are equivalent to open proctectomy: National Cancer Institute Cancer Trials Support Unit (NCI CTSU) Protocol NCT00726622 (Laparoscopic-Assisted Resection or Open Resection in Treating Patients With Stage IIA, Stage IIIA, or Stage IIIB Rectal Cancer, formerly American College of Surgeons Oncology Group [ACOSOG] Z6051)[82] and The Medical Research Council/National Institute for Health Research ROLARR Trial (RObotic versus LAparoscopic Resection for Rectal Cancer).[83] A recent nonrandomized study performed in South Korea suggested the benefit of robotically assisted TME over the laparoscopic approach in terms of the quality of the mesorectal resection.[84]

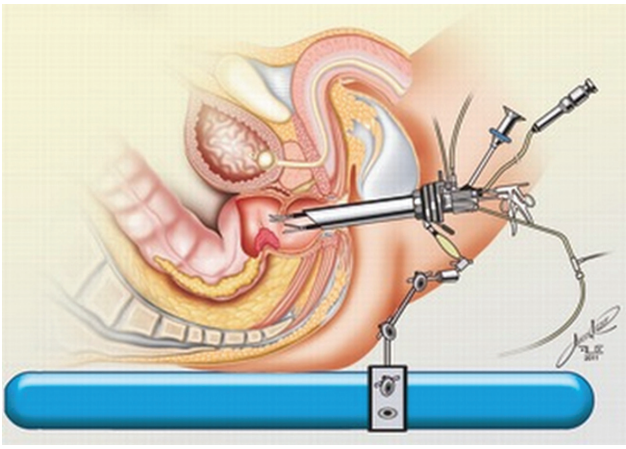

FIGURE 6. Transanal Endoscopic Microsurgery.

Local Excision

Full-thickness local excision (FTLE) is performed transanally with a deep margin outside the muscularis propria into the mesorectal fat and a mucosal margin measuring one cm or greater around the target lesion. Such excisions have traditionally been performed using anal retractors or, less often, an operating rectoscope. Even though a LN or 2 can intentionally or inadvertently be included in the specimen, formal lymphadenectomy is not part of this procedure. Therefore, it should really be restricted to patients with minimal risk of LN metastases. Despite the obvious limitations of FTLE, it carries the advantage of minimal intermediate and late morbidity.[84] An effort should be made to avoid burning bridges for sphincter-preserving radical resection. For example, if local excision performed at the level of the anorectal ring discloses a higher T category tumor than was predicted by preoperative assessment and radical resection is necessary, sphincter preservation may no longer be possible because the local excision scar must be included in the resection.

Transanal Endoscopic Microsurgery

There is growing experience with transanal endoscopic microsurgery (TEM), a system that was introduced in 1984 and uses rectal inflation; magnified, binocular optics; and a 20-cm long rectal rectoscope that provides access through the anus to the upper rectum and even the rectosigmoid.[85] It has also been suggested that the improved optics and enhanced exposure (via insufflation) allow for more precise excision with a higher rate of clear margins, less specimen fragmentation, and lower recurrence rates than conventional transanal excision of polyps and malignancies (Fig. 6).[86,87] Selected application in patients with invasive cancers was supported by the excellent outcomes reported for rectal adenoma excision.[88]

Adjuvant and Neoadjuvant Therapy

In the pre-TME era, LR of rectal cancer was common and often occurred without systemic metastases. RT and CTx, together and separately, were regarded as adjuncts to surgical therapy to improve outcomes. Randomized controlled trials addressed the use of postoperative combined modality treatment for these patients.[89,90] The Gastrointestinal Tumor Study Group conducted a 4-arm trial: no adjuvant therapy, postoperative RT, postoperative CTx, and postoperative CRT. OS and DFS were significantly better among patients undergoing adjuvant CRT (aCRT).[91] The National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01 trial randomized patients with T3/T4 or N+ disease to surgery alone, surgery plus RT, or surgery plus CT and observed that LR rates were significantly lower among patients undergoing adjuvant RT (25% vs 16%).[92] Finally, the NSABP R-02 trial randomized patients to surgery plus CRT or surgery plus CTx and demonstrated a benefit in local disease control favoring those patients undergoing CRT (LR rates: 13% vs 8%).[93] This study clarified that RT could play a role in minimizing recurrence rates in patients with rectal cancer who were at higher risk for it (those with T3/T4 or N+ disease). These studies were performed in the absence of TME. It was anticipated that the benefits observed might be eclipsed by the benefits of optimal radical surgery with proper TME. In addition, functional outcomes and toxicity of postoperative treatment with RT were quite disappointing. Further information about CTx regimens is available in a 2007 review of colorectal cancer adjuvant treatment published in this journal.[51]

By the late 1970s, several theoretical advantages of delivering CRT before surgical resection were postulated,[94] such as:

- "Sterilization" of the mesorectal lymphatic channels, preventing dissemination of viable tumor cells during mesorectal dissection;
- Reduction of tumor bulk to improve resectability and possibly increase sphincter preservation;
- Exclusion of the small bowel from the radiation field by the native rectum (after resection, the small bowel can become tethered in the pelvis by adhesions where it is then subject to repeat radiation exposure);
- Improved response of well-oxygenated (untreated) tumor;
- Superior function of the nonirradiated neorectum.

However, it was not known if these potential advantages were outweighed by the perceived disadvantages of upfront treatment. Clinical staging inaccuracies might lead to overtreatment. Pathologic understaging and subsequent systemic undertreatment might result as a consequence of reduced LN recovery after neoadjuvant therapy. This has been noted with both short- and long-course regimens. With long-course regimens, there is an inverse relationship

TABLE 5. Major Neoadjuvant Therapy Trials

TRIAL	ACCRUAL PERIOD	NO. OF PATIENTS	TME REQUIRED	TREATMENT ARMS
Uppsala[96]	1980-1985	471	No	25 Gy neoadjuvant RT vs 60 Gy adjuvant RT
Stockholm I[97]	1980-1987	849	No	25 Gy neoajuvant RT vs surgery alone
Stockholm II[a,102]	1987-1993	557	No	25 Gy neoajuvant RT vs surgery alone
Swedish Rectal Cancer Trial[b,98]	1987-1990	1168	No	25 Gy neoajuvant RT vs surgery alone
Dutch TME Trial[99]	1995-1999	1861	Yes	25 Gy neoajuvant RT vs surgery alone
German Rectal Cancer Study Group[22]	1995-2002	823	Yes	5040 cGY neoajuvant CRT plus adjuvant CTx vs 5580 cGY adjuvant CRT
Polish Rectal Cancer Trial[100]	1999-2002	312	Yes	25 Gy neoadjuvant RT vs 5040 cGY adjuvant CRT
CRO7[c,101]	1998-2005	1350	No	25 Gy neoadjuvant vs selective 4500 cGy adjuvant CRT

cGy indicates centigrays; CRT, chemoradiation therapy; CTx, chemotherapy; Gy, gray; RT, radiation therapy; TME, total mesorectal excision.

[a]Longer term accrual, minimum 2-year follow-up, excluded patients aged older than 80 years.

[b]Five-year follow-up, excluded patients aged older than 80 years.

[c]Postoperative CRT if circumferential resection margin was involved.

between RT dose and LN recovery. There may be ablation of positive LNs preoperatively in long-course nCRT, but with either regimen, relative radiosensitivity of lymphoid tissue and an increased rate of apoptosis in LNs compared with the tumor have been noted.[95] Perioperative complications might increase because of wound healing or bleeding problems due to irradiation changes in the tissue. Cancer might spread in the recovery interlude between the completion of nCRT and surgical resection. While much work has been done to clarify these issues, some are still relevant and unanswered.

The major trials comparing adjuvant and neoadjuvant therapy vary with respect to RT dosing regimens, the timing of surgery, and concurrent CTx regimens (Table 5).[22,96-101]

RT Regimens

Two preoperative external beam RT (EBRT) regimens dominate clinical trials: short course and long course. Short-course RT, also known as the 5×5 gray (Gy) regimen, offers 5 daily doses of 5 Gy (total of 25 Gy) and is usually followed by radical resection within one week of completing RT.[98] In contrast to short-course RT, long-course regimens deliver daily doses of RT in significantly smaller fractions (about 1.8 Gy-2 Gy) over a longer period of 25 days to 28 days. The total RT dose delivered by this regimen is 45 Gy to 54 Gy and seems to be biologically equivalent to the 25 Gy short-course regimen.[22] After long-course RT, radical surgery is delayed for 6 weeks to 8 weeks. The 2 regimens also differ with respect to concurrent CTx, which is typically offered with long-course but not short-course regimens.

All of the major neoadjuvant treatment randomized trials have shown decreased LR rates with nRT or nCRT versus surgery alone or surgery plus adjuvant RT (Table 5). Four groundbreaking trials were conducted in Sweden just as TME was being adopted, and therefore TME was not required for patient enrollment.[96-98,102] All used a 5×5 (25 Gy) RT scheme without concurrent CTx. In these 4 trials, an OS benefit was only demonstrated when patients aged older than 80 years were excluded. No benefit in terms of distant failure was noted in any of these trials. Once TME alone was shown to decrease LR to the same degree that nRT did in the Swedish trials, the next major contribution was made by the Dutch Total Mesorectal Excision trial, which showed a treatment benefit for nRT (5×5 regimen) even when TME was performed.[99] This trial required that all participating surgeons be proficient in TME; LR rates in the neoadjuvant treatment group were one-half that of the surgery alone group. Next, the German Rectal Cancer Study Group compared long-course CRT given preoperatively versus postoperatively to patients with T3 or T4 tumors.[22] TME was required. Although no survival advantage was demonstrated, the preoperatively treated group had a significant reduction in LR and improved rates of sphincter preservation, with the final surgical plan determined after the completion of neoadjuvant therapy. At this point, both treatment strategies (short-course RT alone and long-course CRT) were found to improve LR rates even after proper TME was performed. Nevertheless, it was unclear if one of these regimens was superior. This question was addressed by the Polish trial that compared long-course CRT with short-course RT.[100] While there was no difference in LR, tumor downstaging was improved in the long-course group but at the cost of increased immediate morbidity.

The data favoring stage-appropriate neoadjuvant therapy to adjuvant therapy are so strong that the need for adjuvant RT can almost be regarded as a failure either of clinical

staging (such as when the cT2 tumor is pT3) or as a means of addressing a technical failure or limitation (eg, the perforated specimen). Nonetheless, RT is associated with acute and chronic morbidity and mortality that vary depending on whether RT is given pre- or postoperatively and whether it is delivered with CTx or not. Mortality rates range from 0% to 18%. Acute toxicities most commonly include nausea, vomiting, diarrhea, radiation enteritis, lethargy/weakness, leukopenia, and skin reactions in 2% to 40% of patients. Late events include bowel obstruction, chronic diarrhea, rectal anastomotic stricture, thromboembolism, sacral/femoral neck fractures, and wound healing problems. Second cancers have been reported. Pelvic floor dysfunction, infertility, early menopause, and sexual dysfunction (erectile dysfunction, ejaculatory dysfunction, dyspareunia, and anorgasmia) have also been reported.[103]

The German Rectal Cancer Study Group found there was less acute and late morbidity with nCRT compared with aCRT.[22] There is conflicting evidence about the late toxicity of short-course RT regimens. Long-term follow-up of the Swedish trial showed significant rates of toxicity, including a higher risk for readmission during the first 6 months, mainly due to gastrointestinal (GI) disorders. After 6 months, specific GI disorders such as small bowel obstruction continued to be more frequent among irradiated patients even though hospital admission rates were no longer higher.[104] This pattern of late readmission and GI complications among irradiated patients was not observed in the Dutch trial, but an increased incidence of fecal incontinence was found.[105]

The Role of CTx in CRT Regimens

The multicenter European Organization for Research and Treatment of Cancer (EORTC) study compared the results of long-course fluorouracil (5-FU)–based CRT with RT alone in a randomized study.[106] This study also randomized patients to receive 5-FU–based adjuvant CTx following surgery. Surprisingly, patients who never received CTx (neither during the neoadjuvant nor in the adjuvant period) had worse LR rates. All other groups had similar LR-free survival. Concurrent CTx during nRT had the added benefit of improved tumor downstaging compared with RT alone.[107] The equivalence of infusional 5-FU and capecitabine (an oral agent converted in tissues to 5-FU) has been established by the NSABP R-04 randomized controlled trial with regard to rates of pathologic complete response (pCR), surgical downstaging, and sphincter preservation.[108]

A review of phase 2 and 3 trials of different CRT regimens for rectal cancer revealed that the addition of a second drug to 5-FU regimens might enhance the rate of pCR. This observation provided the impetus to study CRT regimens using additional drugs to 5-FU exclusively based regimens.

TABLE 6. Radiation Therapy Modalities

MODALITY	EFFECT ON T CLASSIFICATION	EFFECT ON N CLASSIFICATION	TOXICITY
External beam radiation therapy	Yes	Yes	Yes
Endorectal brachytherapy	Yes	2 cm	Minimal
Contact radiation therapy	Yes	No	None
Intraoperative tadiation therapy	Yes	No	Decreased

Unfortunately, the addition of oxaliplatin did not improve tumor response rates compared with standard 5-FU–based CRT regimens.[109] In the ACCORD (Action Clinique Coordonnées en Cancérologie Digestive) 12 trial, patients who received oxaliplatin in addition to capecitabine had significantly increased toxicity and no improvement of pCR rates (19% vs 14%; *P* value not significant).[110] The results of adding cetuximab to 5-FU–based CRT regimens are even more disappointing. Pooled analysis of available studies indicate a pCR rate of less than 10% for combination therapy compared with 15% to 30% for standard 5-FU regimens.[111]

Since combining drugs during nCRT regimens has failed to improve pCR rates, different schedules for the delivery of CTx in the neoadjuvant setting have been investigated. One regimen designed to address the possibility that failure to treat micrometastatic disease contributes to treatment failures administered induction CTx (5-FU and oxaliplatin) to patients with M0 disease followed by standard nCRT. However, the significant toxicity and even mortality associated with this treatment strategy has limited its widespread adoption and data acquisition.[112] Another study designed to evaluate the effect of extending CTx by giving it during the interval between standard long-course nCRT and definitive surgery (sometimes referred to as the "resting" period) has yielded more promising results. Surprisingly high CR rates of up to 65% have been reported compared with historical controls of nearly 30% with more conventional CRT regimens.[113] A neoadjuvant treatment strategy using FOLFOX (leucovorin, 5-FU, and oxaliplatin) and bevacizumab without any RT at all has very recently been reported. Preliminary results show a pCR rate of 27%, which is comparable to standard nCRT regimens.[114]

RT Modalities

Table 6 shows RT modalities (Table 6).

EBRT

EBRT is the primary radiation technique used for adjuvant and neoadjuvant treatment. It delivers RT to the rectal wall harboring the primary tumor as well as to the complete mesorectum to treat tumor deposits in it. It also exposes perianal

skin and the sphincter complex to radiation, which may lead to toxicity and deterioration of anorectal function. More recently, intensity-modulated RT (IMRT) that uses 3-D conformational planning has been considered in an effort to minimize radiation effects on adjacent organs secondary to EBRT.[115,116] IMRT is still in the investigative phase and has not been implemented in routine clinical practice.

Brachytherapy

High-dose endorectal brachytherapy (HDRBT) offers the advantage of direct delivery of higher doses of RT to the mural rectal tumor, minimizing skin and sphincter exposure. The HDRBT effect is limited to a 2-cm radius from the primary tumor, so it provides limited treatment of the mesorectal LNs, vessels, and lymphatic channels. In a single-center experience using HDRBT in combination with TME, patients with locally advanced rectal cancer had reduced LR rates (6%) and pCR rates up to 29%.[12] If the equivalence of this modality to EBRT or IMRT is substantiated in future investigations, perhaps some of the morbidity of full-pelvic RT can be avoided by using HDRBT more often.

Contact RT

Contact RT was initially described by Papillon et al[117] as another method for the direct delivery of RT to the rectal wall using a rigid proctoscope and a specially designed RT machine. Like HDRBT, there is minimal toxicity but also minimal, if any, activity within the mesorectum. This treatment strategy has been suggested for the management of early tumors by RT alone as a form of local therapy or as a neoadjuvant approach followed by resection. There is no associated toxicity but also minimal, if any, activity within the mesorectal LNs.[117,118]

Intraoperative RT

Single-dose RT can be delivered intraoperatively as either electron beam or high dose rate brachytherapy (HDRBT). Radiosensitive adjacent structures can often be shielded or retracted, resulting in more precise localization. The expense of retrofitting an operating room or, alternatively, the inconvenience of transporting a patient mid-operation to the radiation oncology suite has limited the application of this modality. Newer mobile units that do not require rooms outfitted with shielding have made this technique more feasible. Improved LR and OS rates have been reported when intraoperative RT was used after nCRT when either a microscopically positive margin is anticipated (eg, pelvic sidewall or presacral) or for locally recurrent disease.[119]

Stereotactic Body RT

Stereotactic body RT uses stereotactic principles for localization and delivers multiple beams to well-defined targets in few fractions. It has the potential to reduce mechanical error margins and enable the delivery of higher doses of RT. Even though this modality has not yet been used for rectal nRT, LRs have been treated this way with promising results.[120]

Summary

Neoadjuvant therapy alternatives include different combinations of CTx agents and methods of radiation delivery. 5-FU–based CRT regimens seem to be beneficial both in terms of tumor downstaging and local disease control. Nevertheless, short-course RT (without CTx) has resulted in similar LR rates compared with 5-FU–based long-course CRT regimens but with less associated toxicity. In addition, HDRBT appears to be an excellent option in terms of local control. Contact RT may be useful in patients with significant comorbidities and early stage disease.

Posttreatment Assessment

Why Is Posttreatment Assessment Important?

Several important observations were made as experience with nCRT grew. Some tumors that at initial assessment were fixed to surrounding structures (presumably as a consequence of local extension and/or desmoplastic reaction) became mobile. Some tumors appeared to shrink both macroscopically and histologically. Even if a visible scar remained, often there would be no viable tumor in the scar. LN recovery was smaller in radical resection specimens and often included only benign LNs even though suspicious LNs had been identified at initial staging. Although in prospective trials it has been difficult to discern an advantage of nCRT in terms of distant disease or OS, a very different picture emerges when the subgroup of treatment responders is evaluated: there is abundant evidence that response to nCRT is the single best predictor of oncologic outcome.

This raises a rather revolutionary question of whether subsequent treatment should still be based on initial presentation or on restaging after nCRT. There are conceptual and practical hurdles even to designing studies that investigate treatment based on post-CRT assessment. The concept of restaging is not new, but it has generally been used to establish a new baseline after surgery and/or nCRT and before starting the adjuvant therapy regimen planned at the time of initial staging. Restaging has also been used to assess response to adjuvant treatment. Treatment reductions were virtually never planned, occurring only if patients chose to forego more therapy or providers deemed additional treatment to be futile. It is a novel concept that restaging might help to discriminate among biologically distinct tumors or be used to roll back treatment that was planned based on the original presentation.

The technical challenges of restaging, especially if the goal is to modify the treatment plan going forward, are fraught with the same (and sometimes greater) inaccuracies as pretreatment clinical staging, as will be discussed below. Clinical assessment of complete response (cCR) has

over- and underestimated pCR. Standardization of criteria for and timing of this assessment will at least enable a better evaluation of technique.

Characterization of Tumor Response

A Problem of Terminology

We do not yet have the terminology to adequately describe emerging concepts about tumor behavior, particularly the response of tumors to therapy. The terms "downstaging," "tumor regression," and "downsizing" often are used interchangeably, ambiguously, or even incorrectly. T, N, and M are tumor classifications that are grouped based on prognostic features into stages (0, I, II, III, and IV). Strictly speaking, downstaging should describe a change from a higher stage group to a lower one (eg, stage III to stage II). A downshift in T classification such as T2 to T1 does not constitute downstaging in the rectal cancer nomenclature, nor does a downshift from N2a to N1. To distinguish shifts among T, N, or M categories from changes in actual stage groupings, we refer to them as "downshifts" or "downclassifications." Tumor regression as described by the tumor regression grade (TRG) refers to the pathological ratio of residual viable tumor to scar after CTx or RT, which reveals nothing about change in tumor size nor about downstaging/shifting. Unfortunately, "tumor regression" is often used to indicate all forms of tumor response to treatment. We advocate using this term only in the sense of TRG. Conversely, a change in tumor size (downsizing) is not necessarily equivalent to tumor regression. There is imperfect understanding of how tumor bulk is lost or what accounts for apparent recession from the pretreatment margin, some of which may be represented clinically or pathologically by fibrotic scar but some may be due to other processes such as tissue sloughing. Finally, the TNM system does not include a stage grouping for cCR or pCR (yc- or ypT0N0M0). Although several authors have described this as stage 0, in the TNM nomenclature, stage 0 indicates in situ disease (TisN0M0).[121] We propose stage CR for complete responders (yCR or ycT0N0M0 if clinically assessed and ypCR or ypT0N0M0 if pathologically assessed).

When Should Posttreatment Assessment Be Done?

Having provided the rationale for basing at least some of the posttreatment strategies (such as sphincter preservation) on tumor response to CRT, it is important to determine when to perform this assessment and how. Perhaps, despite the histologic differences between anal cancer and rectal cancer, there are parallels with respect to the duration of CRT's tumoricidal effects and timing of treatment assessment. Clinical CR is found in just 20% of anal cancer patients at 30 days after CRT compared with 80% of patients evaluated at 60 days.[122] The optimal interval between CRT and surgery has not been identified. The Lyon R90-01 study is the only randomized trial to evaluate the time interval between the completion of neoadjuvant therapy and surgery (fewer than 2 weeks vs 6 weeks-8 weeks), and this demonstrated improved T and N downshift with a longer interval.[123] In addition, retrospective studies echo the finding that a longer interval to surgery improves pCR rates.[124,125] In a recent review of the Cleveland Clinic experience, there was a steep increase in the pCR rate after 7 weeks from CRT completion; the rate plateaued only after 12 weeks.[124] Therefore, an interval of at least 8 weeks but fewer than 12 weeks after the completion of neoadjuvant therapy seems reasonable for observing maximal downstaging before deciding upon a final management strategy and performing definitive surgery. The observation that the post-nCRT LN positivity rate of 12% declines to less than 5% after an 8-week waiting period also supports the value of a longer wait time.[79,126-130]

A longer interval to surgery may confer another benefit. A review of patients treated with different intervals after neoadjuvant therapy suggested that delayed surgical resection was associated with decreased perioperative morbidity and no oncologic compromise.[131] The short-course RT regimen that typically entails resection within one to 7 days of RT completion when there is minimal if any downsizing or T,N-downshift also appears to benefit from longer intervals between RT completion and surgery in a subset of patients with unresectable T4 rectal cancers. The 87% rate of R0 resection (no residual gross or microscopic tumor) was quite high with an interval of 6 weeks to 8 weeks.[132]

How Should Posttreatment Assessment Be Done?

Examination

Ideally, the same surgeon who performed the pretreatment assessment performs the posttreatment assessment, using the same modalities: digital examination and endoscopy (rigid or flexible proctoscopy). The presence of residual ulceration, stenosis, or intraluminal mass are important findings that can be ascertained by this simple and inexpensive examination. Although no standardized definition of cCR has been determined, it has been suggested that the absence of these abnormalities can be considered a complete clinical response even when mucosal whitening or telangiectasia persist.[133] Unfortunately, endoscopic biopsies of residual lesions are unreliable as are biopsies distal to the tumor to determine the distal resection margin or to help judge suitability for sphincter-preserving surgery.[134]

Laboratory Studies: Carcinoembryonic Antigen

Data suggest that a low carcinoembryonic antigen level compared with the pre-CRT level correlates with response to treatment. It should never be the sole determinant of tumor response but might be used as an additional assessment tool.[135,136]

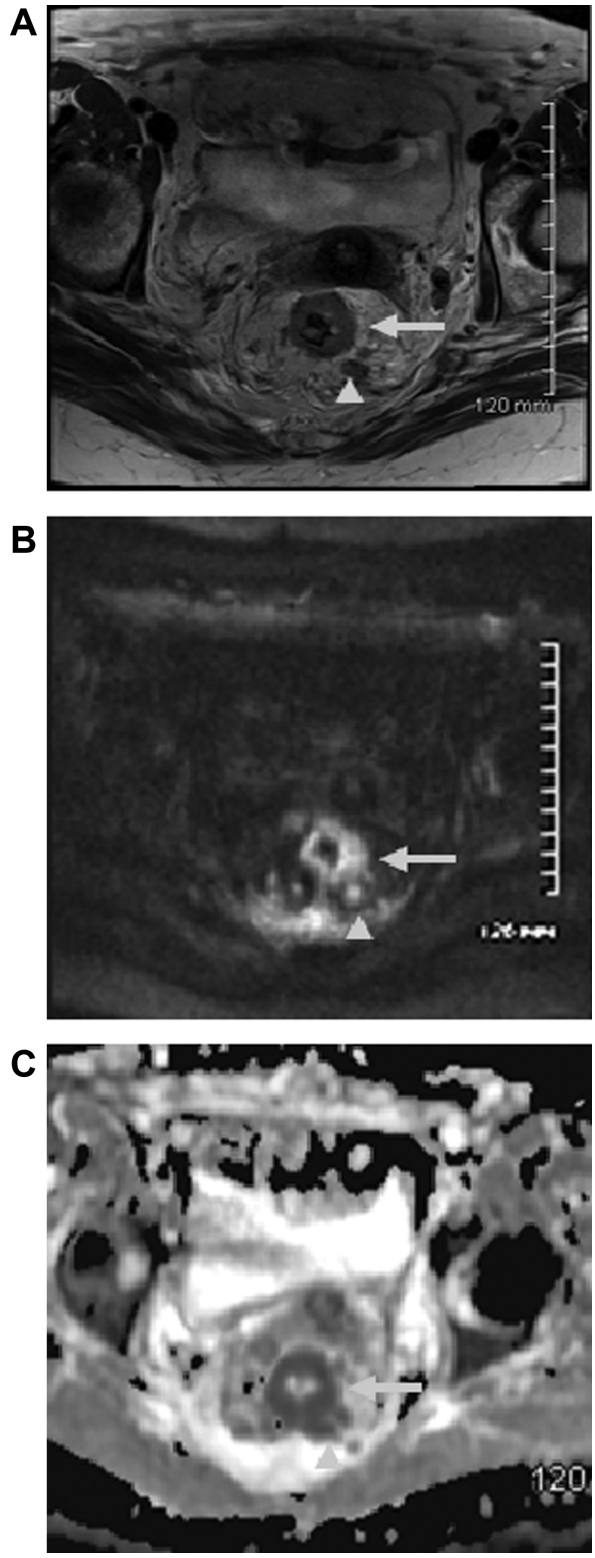

FIGURE 7. T3N2 Rectal Cancer Pretreatment Imaging. (A) T-2 Weighted image. T3 lesion extending beyond the muscularis propria (arrow) with adjacent lymph nodes demonstrating an abnormal heterogenous T2 signal (large, marked with an arrowhead). (B) Axial diffusion-weighted imaging demonstrates high signal-restricted diffusion in an area of hypercellular tumor. (C) Axial apparent diffusion coefficient (ADC) image. The ADC images are derived from the diffusion-weighted images. The ADC images demonstrate decreased ADC confirming that these lesions are indeed restricting diffusion and not just T2 "shine through" artifact which would indicate tissue fluid rather than tumor.

Radiologic Studies

While the accuracy of T category determination by MRI and ERUS declines substantially after nCRT (often reported in the 50% range), distinguishing good from poor responses to nCRT is more promising. A recent study using high-resolution MRI was able to distinguish patients with posttreatment tumors confined to the muscularis propria or more superficially (ypT0-2N0) from those with more advanced tumors with greater than 90% accuracy.[137] No reliable distinction between ypT0, ypT1, and ypT2 was possible with this methodology. Another MRI technique that shows promise for post-CRT restaging is diffusion-weighted MRI (DWI), which may distinguish viable tumor from fibrosis. Preliminary data suggest that while sensitivity detecting pCR is suboptimal (52%-64%), specificity is greater than 90% with DWI and improved by 16% to 52% over standard MRI (Fig. 7).[138]

PET-CT imaging is being explored as a tool for grading response to CRT. PET-CT is a functional study that highlights areas of increased glucose metabolism, including viable tumor. Metabolic activity is recorded as the standard uptake value (SUV). Early studies comparing the accuracy of posttreatment staging by PET-CT with other imaging modalities for determining pCR have described the superior accuracy of PET-CT when the percentage change SUV pre- and posttreatment (ΔSUV) was used rather than absolute values.[139-142] While errors overestimating response were less common than underestimations, the accuracy of PET-CT performed 6 weeks after completing nCRT has not been sufficiently reliable for identifying pCR. A Danish prospective study of 30 patients showed disappointing negative predictive values of PET-CT for identifying pCR. Less than 50% of PET-CT complete responders (no abnormal residual uptake) were ypT0.[143] Recently, a prospective trial performed assessment of tumor response with PET-CT at 12 weeks from CRT with an overall accuracy of complete response detection of 85%.[144] However, there was poor correspondence between small reductions in metabolic activity halfway through CRT, reductions seen after completing therapy, and pathologic response.[145]

How Is the Posttreatment Assessment Used?

As was discussed earlier in this section, the posttreatment assessment often enables sphincter preservation that was not anticipated at the time of initial clinical assessment due to tumor downsizing and T or N downshifting. A natural extension of this finding would be that clinically locally advanced but LN-negative tumors might be treated with CRT and FTLE, but there are no trials showing whether cT3N0 tumors can be safely managed by nCRT and FTLE even if downshifting to ypT1 or ypT0 occurs.

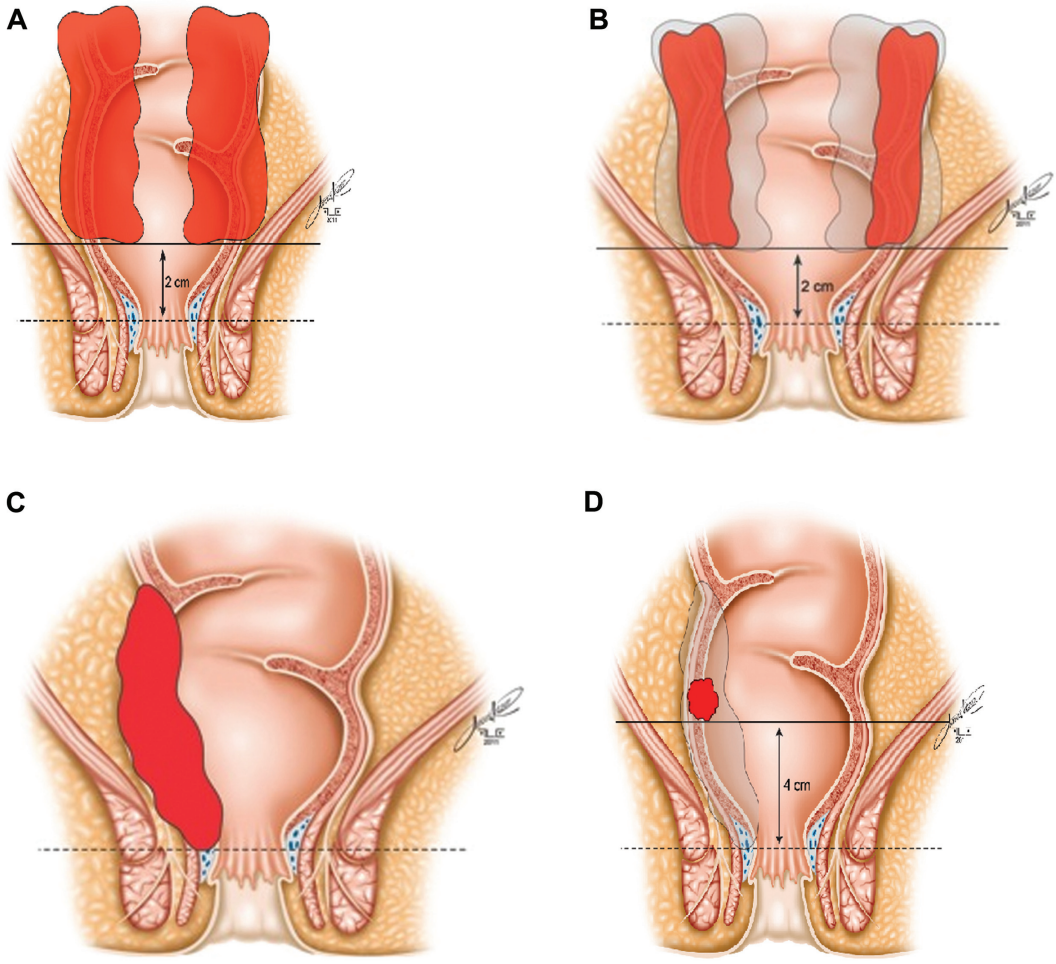

FIGURE 8. Downsizing, Downstaging, and Sphincter Preservation After Neoadjuvant Chemoradiation. (A) A bulky low rectal tumor such as that shown here has sufficient length distally to achieve an acceptable longitudinal margin, but the tumor size would impede mobilization of the rectum and distal transection (B) The same tumor after neoadjuvant chemoradiation is less bulky but as shown did not recede from the original distal margin and is the same T category (area of fibrosis within the black line). However, the reduced bulk enables mobilization and controlled distal transection so that sphincter-preserving surgery can be performed. (C) The tumor before treatment is not bulky but approaches the anorectal ring and threatens sphincter preservation. (D) Tumor regression leaves a smaller focus of invasive cancer (red), which may be the same T category as before treatment, and an area of fibrosis (within the black line). The transection line (dashed line) is now 4 cm from the invasive component but very close to (or even across) the original tumor bed.

Soon-to-be-published data from ACOSOG trial Z6041, a single-arm study evaluating the oncologic outcome of patients with T2N0M0 distal rectal cancer treated with nCRT and then FTLE, may make progress toward clarifying this issue.[146] The observation that the complete mucosal response often corresponds to LN negativity and might serve as a proxy for the mesorectal LN response is the foundation of ongoing studies of less surgically aggressive treatment strategies in which TME has been eliminated.

Evaluation of Neoadjuvant Treatment Change

Acceptable Margin

The 2-cm longitudinal margin rule (see "Surgical Approach to Rectal Cancer," above) can be decreased in the irradiated patient to 1 cm (and possibly less).[147-149] This small adjustment in the acceptable macroscopic margin can improve the rate of sphincter preservation, but the larger contribution likely results from tumor regression such that the 1-cm longitudinal resection margin and the 1-mm CRM are made close to or even within the original tumor bed (Fig. 8). This would suggest that downsizing has occurred even if the remnant tumor, although smaller, is the same T category as at pretreatment staging.

Data supporting the practice of basing the surgical resection margin on the posttreatment status are provided by the German Rectal Cancer Study Group trial comparing nCRT with aCRT in patients with locally advanced disease.[22] The surgeons' pretreatment surgical recommendation was recorded and then compared with the actual surgical procedure performed after nCRT. Forty percent of patients originally determined to need APR before nCRT actually underwent a sphincter-preserving procedure without oncologic compromise at a median follow-up of 45 months. The shift from planned APR to sphincter-preserving surgery was significantly more likely to occur after long-course nCRT

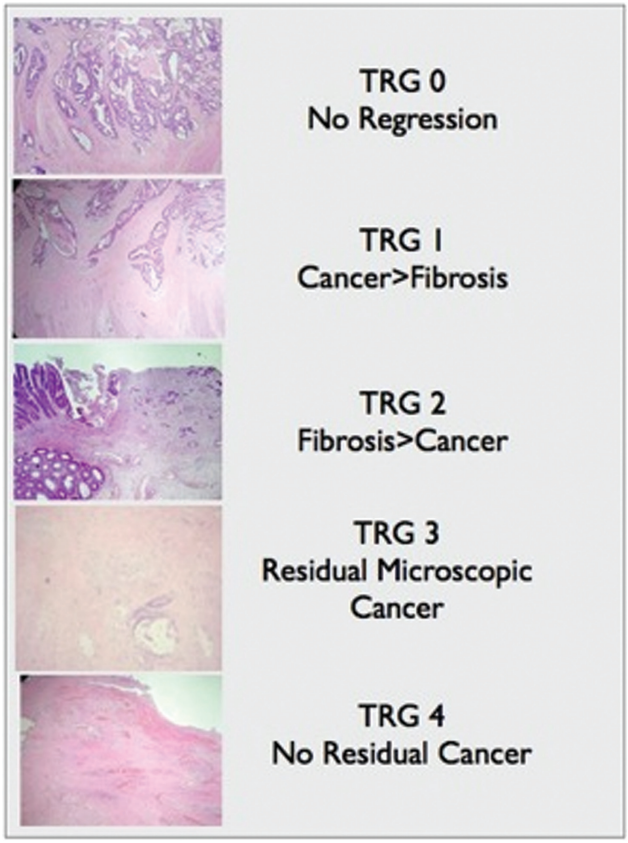

FIGURE 9. Tumor Regression Grade (TRG).[151]

with a 6-week interval to surgery than in the immediate surgery arm, in which a shift to sphincter-preserving surgery occurred in less than 20% of cases. Another group that studied sphincter preservation rates among patients who had very low rectal tumors deemed to require APR before treatment but that were earlier T category tumors (cT2N0) than patients in the German trial. They also found improved sphincter preservation rates: of all patients initially considered for an APR, less than 25% actually underwent such a procedure. The remaining 78% of patients were managed by a sphincter-sparing procedure with no oncological compromise.[150]

Tumor Regression Grade

Besides downsizing and downshifting, posttreatment changes can also be characterized according to the relative volume of residual viable tumor cells (Fig. 9).[151] A residual microscopic focus of T3 tumor represents a better treatment response than a larger nest of tumor cells does. CRT causes tumor necrosis, which is then replaced by inflammation and ultimately by fibrosis. Pathologists can quantify the ratio of viable tumor cells to fibrosis to generate a TRG. Several classifications with subtle differences have been proposed, but they all include the 2 extremes: complete replacement of viable cancer cells by fibrosis (ie, pCR) at one pole and at the other pole, the persistence of viable cancer cells in the absence of fibrotic changes (poor response).[152] In between the 2 poles, a distinct group of "near-complete responders" who have microscopic foci of residual cancer cells in the presence of significant fibrotic change is also recognized in all the classification systems. Patients in this group have significantly improved oncological outcomes compared with patients with an incomplete pathological response or gross residual cancer. Moreover, each degree of tumor response reflected by the TRG, regardless of the classification system used, appears to correlate with the risk of metastatic LN and possibly with oncological outcome.[152-155] TRG has not yet been incorporated into the AJCC/UICC classification system for colorectal cancer and therefore does not contribute to conventional, stage-directed treatment planning at this time.

Acellular Mucin Pools

Mucin pools, with or without viable tumor cells, are a fairly common histologic finding after nCRT. Acellular mucin pools are found in almost one-third of patients with pCR. While mucin pools are thought to be a vestige of a previously viable mural or LN tumor, the primary tumor need not have been of mucinous type. In fact, among 100 pCR specimens studied, 27 had mucin deposits even though pretreatment biopsies identified only 3 mucin-producing tumors.[156,157] Despite the observed association of acellular mucin with higher tumor grade at initial presentation in this series, its presence had no negative impact on OS or DFS. A 2010 review of mucin pools in patients with pCR also noted no increased risk of LR, distant failure, or decreased survival when acellular mucin pools were at the resection margin or in mesorectal LNs.[158] In contrast to these reports, a statistically nonsignificant association between acellular mucin pools and increased distant failure and decreased OS was noted in a Cleveland Clinic retrospective review.[159] At present, acellular mucin pools are not considered residual tumor according to AJCC/UICC criteria or the College of American Pathologists 1999 consensus statement, which has been incorporated into the synoptic reporting protocol for colorectal cancer.[37,160]

Mucosal Response as a Proxy for LN Response

Presently, the only way to determine mural and LN tumor response to nCRT with 100% accuracy is by pathologic evaluation of a TME specimen. The exact relationship between mucosal and LN response is not completely defined, but a few observations support that LNs respond to RT and that involved LNs respond in tandem with the mucosal primary tumor. That even nonmetastatic LNs respond to pelvic RT is evidenced by their decrease in both number and size following treatment. It also appears there is a close correlation between primary tumor posttreatment T category and risk of persistent metastatic perirectal LN disease.

TABLE 7. Qualified Therapy Treatment Planning Matrix

TUMOR TYPE	HIGH-RISK LOCATION[a] (DISTAL RECTUM AND/OR SURGICAL ANAL CANAL)	LOW-RISK LOCATION (MID- OR UPPER RECTUM)
High-risk tumor[b] T3, T4, any N+	Neoadjuvant CRT plus radical resection.	Consider neoadjuvant CRT plus radical resection.
Low-risk tumor T1, T2, N-	Radical resection; FTLE for T1 tumors but consider neoadjuvant CRT.	Radical resection, FTLE for T1 tumors.

CRT indicates chemoradiation therapy; FTLE, full-thickness local excision.

[a]Proximity to levators, threatened sphincter preservation.

[b]Unfavorable features such as tumor grade, threatened mesorectal fascia, or lymphovascular invasion.

When primary tumor regression is complete (ypT0) and there is a longer interval to resection, the incidence of LN metastasis decreases to close to 5% (range, 0%-12% reported in other studies). For ypT2 tumors, the risk of LN positivity is approximately 20%. This response pattern persists when ypT categories are grouped: the risk for LN metastases is lower for ypT0-2 than for ypT3-4 tumors.[126-130,161]

Pathologic Complete Response

As was noted earlier, there is a strong association between pCR (ypT0N0M0 or TRG0) and improved survival.[162,163] Even though the reported incidence of pCR may be influenced by factors such as case mix, initial staging, radiological staging modalities, pathology technique, RT technique, and CTx agents, it has become a useful primary endpoint in many clinical studies.[49] pCR was initially attributed only to radiation-induced necrosis, but as was presented above, it has subsequently also been observed after systemic CTx alone. Regardless of the process underlying this phenomenon, pCR has been reported in 5% to 42% of patients undergoing nCRT.[109]

Treatment Planning

A 4-Tiered Process

Evidence-based, stage-directed therapy based only on pretreatment staging for every rectal cancer is delineated by the National Comprehensive Cancer Network (NCCN) guidelines (see Web site[164]), yet it is a practical matter that each clinician must evaluate those treatment recommendations in the context of a particular patient with a particular tumor. Contravening medical issues, patient disposition, and pattern of tumor involvement can all motivate modifications to the standard treatment plan. Not all contingencies are well mapped out in the current literature. For example, standard treatment of a T1N0M0 tumor could include either FTLE or radical resection. Ten percent or more of locally excised pT1 tumors will recur in the pelvis, but evidence is not yet strong enough to stratify these tumors into higher or lower risk groups. Larger size, superficial ulceration, poor differentiation, and invasion into the submucosa are associated with poorer prognosis. Tumors in the distal one-third of the rectum are more likely to recur locally than tumors in the mid- or upper rectum. The stakes are also higher with regard to sphincter preservation options for the most distal tumors. A full-thickness local excision (FTLE) at the level of the anorectal ring that discloses an unexpected pT2 lesion rather than a pT1 lesion may result in an APR since the excision scar must be included in the resection, whereas a radical resection with sphincter preservation out front might have assured GI continuity. The NCCN treatment guidelines do not take into account stage of disease after neoadjuvant therapy and instead are based only on stage at presentation.

The development and execution of a treatment plan is really a 4-step process that is conducted at 2 time points if nCRT is provided: before and after treatment. The 4 tiers of assessment are:

1) Conventional therapy: identification of stage-directed, standard therapy for the tumor;
2) Qualified therapy: modification of the conventional therapy plan based on evaluation of tumor features that define higher or lower oncologic risk within the stage grouping or present particular surgical challenges;
3) Tailored therapy: recommendations based on assessment of patient factors that influence the feasibility or suitability of the qualified therapy plan;
4) Actual therapy: the treatment that is actually provided.

The actual therapy delivered may diverge from the tailored therapy plan for many reasons. The tailored plan may be derailed by arbitrary events like a motor vehicle accident during nCRT, or it can be entirely treatment related such as cardiac complications of firstline CTx, technical issues in the operating room, or an anastomotic leak leading to a delay in initiating adjuvant therapy.

Qualified Therapy

Qualified Therapy Treatment Planning Matrix

This matrix is suggested as a tool to help integrate tumor features not represented in standard TNM staging or NCCN guidelines but that still might modify the conventional treatment plan (Table 7). Currently, this matrix is

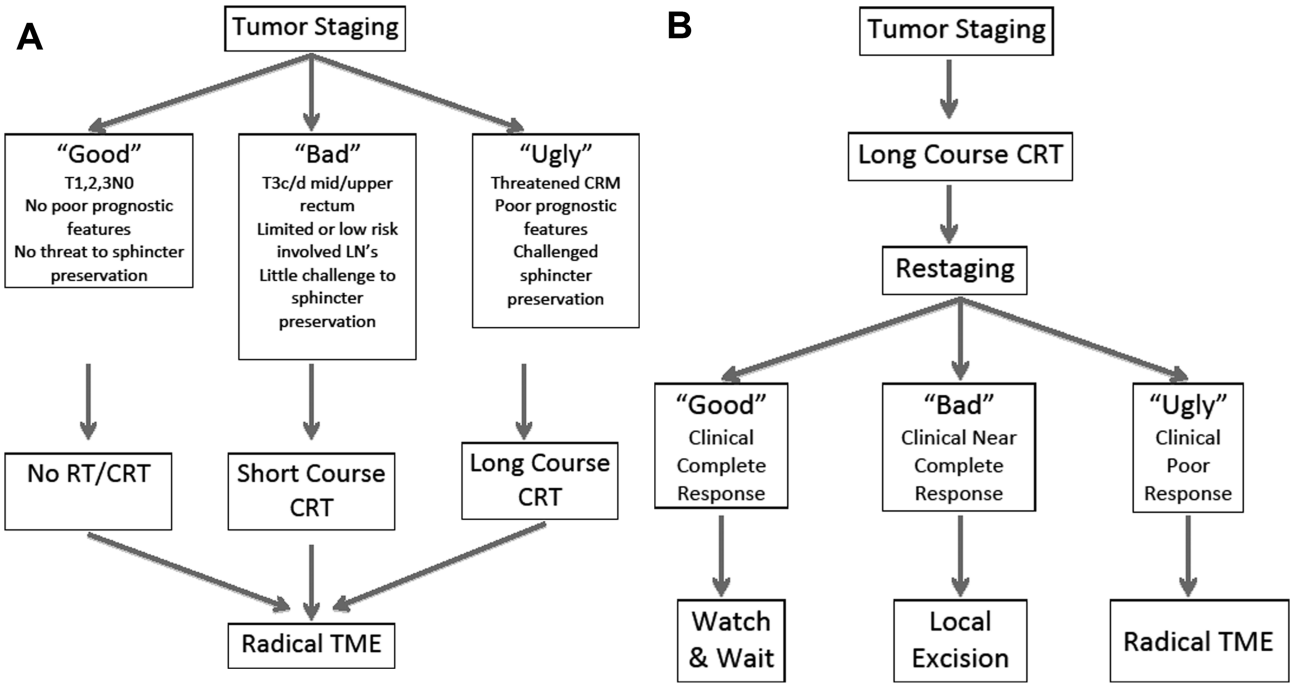

FIGURE 10. "The Good, the Bad and the Ugly." (A) Selection of neoadjuvant regimen. (B) Selection of surgical approach. LNs indicates lymph nodes; CRM, circumferential (radial) resection margins; RT, radiation therapy; CRT, chemoradiation therapy; TME, total mesorectal excision.

most applicable after the initial clinical assessment has been performed to help identify whether neoadjuvant therapy might add benefit or to choose among surgical options. It does not specifically direct the choice of neoadjuvant regimens and also is limited by its failure to incorporate the important prognostic information derived from tumor response to therapy. If data mature enough to support basing adjuvant therapy exclusively on posttreatment rather than pretreatment stage, the current matrix would be adapted.

"The Good, the Bad and the Ugly"

The choice of neoadjuvant regimen has been largely based on local practice pattern. Short-course nRT has prevailed in the European trials and practice while long-course nCRT has been the preferred regimen in the United States. While there appears to be less morbidity with the short-course regimen and better downsizing with the long-course regimen, neither is clearly superior. An algorithm described in Europe that makes a cultural reference to Clint Eastwood's classic film "The Good, the Bad and the Ugly" proposes that both regimens be in the armamentarium of rectal cancer experts and that the decision whether to administer neoadjuvant therapy and what type to recommend could be based on the tumor characteristics: good, bad, and ugly (Fig. 10A). "Good" tumors were defined as T1,2N0 with no radiologic poor prognostic features or challenges to sphincter preservation with radical resection. "Bad" tumors included cT3 lesions, those with limited LN metastases or low-risk involved LNs (eg, not threatening the MRF), and those with little challenge to sphincter preservation. Tumors were designated as "ugly" if sphincter preservation was challenged, there was a threatened CRM, or there were other poor prognostic factors such as LN metastases or vascular invasion.[165] This algorithm's proposal to modulate CRT exposure and give priority to radical resection is not validated yet reflects current practice standards and highlights a preeminent question in rectal cancer care: if oncologic outcomes are equivalent, is it more beneficial to patients to avoid aggressive surgical resection or to avoid aggressive neoadjuvant regimens? We also present an alternative algorithm that modulates surgical approach based on response to neoadjuvant therapy. Like the first algorithm, it is not validated but it does provide a framework for the incorporation of treatment response in operative planning and sets the stage for considering less radical operative strategies or even the nonoperative management of highly selected rectal cancers (Fig. 10B).

Sphincter Preservation

Data supporting the deferment of a final assessment for sphincter-preserving radical resection until after neoadjuvant therapy as well as the selection of operative techniques allowing for sphincter preservation even for very low rectal tumors have been presented above. Nevertheless, none of the randomized trials was able to objectively demonstrate an increase in sphincter preservation, suggesting that technical and surgical issues are probably the reasons for an increase in conservative procedures.[166] In experienced hands, intersphincteric resection (also reported as a

transabdominal transanal resection) can avoid permanent colostomy for tumors with a distal margin one cm above the dentate line (or even lower if the entire internal anal sphincter is sacrificed). Because of the variability of measurement of tumor level (see the "Anatomic Considerations" section), there is no consensus regarding requirements for sphincter preservation.

Tailored Therapy

Once a qualified treatment plan has been developed that integrates the features of a given patient's tumor with conventional therapy directives, the plan is further tailored to incorporate patient factors. As was outlined earlier in the "Initial Clinical Assessment" section, issues such as a patient's general condition, history of prior pelvic RT, diabetes, cachexia, fecal incontinence, mobility, and manual dexterity may alter the qualified treatment plan. High genetic risk or inflammatory bowel disease comorbidities also will strongly affect management recommendations. Social issues such as the patient's support system, outlook, and lifestyle may also influence final recommendations.

The Final Management Plan: Putting It All Together

An Argument for Multidisciplinary Treatment Planning Conferences

The amount of data rendered by staging studies and initial physical examination, the determination of weight to be given to each finding (especially when there are contradictory data), and the varied expertise required to interpret these findings to help shape a plan are complicated, indeed. Assembling the experts to review findings and formulate a management plan that reflects the tiers of decision-making makes sense and may expedite the rendering of a plan for each patient.[3] The application of this framework to particular patients is illustrated with case examples in Table 8.

Outcomes in Rectal Cancer

The most important endpoints in rectal cancer management are local disease control and survival. There are 2 main reasons why local control is so much more significant for rectal than for colon cancer. First, rectal cancer LR rates have historically been high and have varied widely among centers. Second, LRs may both negatively affect survival and have a devastating effect on quality of life for these patients. They are frequently unresectable, difficult to manage, and symptomatic.[167]

Local Recurrence

Surgical technique was one of the first factors recognized as improving LR rates. Although TME was introduced after the first Swedish nRT trials were done, the magnitude of the improvement in the LR rate called into question the salutary effects of nRT reported and posed the question of whether nRT merely compensated for less effective surgery rather than being efficacious independently.[168] In Sweden, the introduction of TME in 1994 led to an improvement in local disease control after 5 years when compared with the non-TME Stockholm I and II trials.[45] Indeed, a Dutch survey of rectal cancer LR rates before, during, and since the more widespread adoption of the TME technique shows graded improvement of LR rates.[169] Likewise, a Norwegian program that studied the effect of training a subset of surgeons in the TME technique and centralizing the surgical management of rectal cancer demonstrated marked reductions in LR as well.[44] For many years it was believed that use of TME would significantly limit the need for any additional therapy.[170] The aggregate effects of proper TME performance together with nRT were demonstrated by the Dutch Rectal Cancer TME trial and German Rectal Cancer Study Group trial; in each case, the addition of neoadjuvant therapy to TME reduced the LR rate by approximately 50%.[22,171] Up to this point, all studies included patients only with radiologically staged cT3-4 or N+ disease. More recently, the CR07 trial included patients with stage I to stage III disease and demonstrated a benefit in local disease control in the preoperative RT group. However, in patients exclusively with stage I disease who were treated by nRT, improvements in local disease control were not statistically significant.[101] The available data clearly support the idea that nRT or CRT further decreases LR rates, even in the setting of proper TME for patients with radiological evidence of stage II and III disease.

LR rates can be adversely affected even in the setting of proper TME and neoadjuvant therapy. CRM+ has been identified as an independent, and perhaps most important, risk factor for the development of LR.[46,172] It is commonly used as a surrogate marker for LR even though other pathological features may play a role.[173] APR has also been considered a risk factor for CRM+ and LR. Of note, a review of the Dutch Rectal Cancer TME trial indicated that patients treated with APR had an increased risk of CRM+ and LR even among those with early (T2) cancers with or without preoperative RT.[174] (See "Surgical Approach to Rectal Cancer" section for a discussion of the APR surgical technique modifications recommended to address the problem of CRM+.)

Overall Survival

Changes in the regional management of rectal cancer have had a much more measurable impact on LR than on OS. Improved OS rates were only observed in the Swedish nRT trials when patients aged older than 80 years were excluded[175] and in the Dutch Rectal Cancer TME trial after longer term follow-up.[171] Final pathological stage, even

TABLE 8. Initial Clinical Assessment: Patient Factors

INITIAL CLINICAL ASSESSMENT	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5
Presentation	73-year-old woman with a 1-cm rectal tumor and biopsy-proven, moderately differentiated adenocarcinoma by gastroenterologist.	54-year-old man with low rectal cancer, biopsy-proven adenocarcinoma by gastroenterologist.	80-year-old man seeking third opinion for small biopsy-proven cancer at anorectal ring. Question of involved LNs by prior ERUS.	43-year-old woman with biopsy-proven sigmoid adenocarcinoma. Second opinion sought after recommendation for immediate sigmoid colectomy.	61-year-old man with a 4-mo history of episodic pelvic pain, change of bowel habits, and bleeding. Now in ER with fever (101°F), mild abdominal tenderness, WBC of 15 mm^3, gas and phlegmon in retrorectal space.
Tumor features	1-cm (<25% of circumference) ulcerated tumor at the middle rectal valve; anterior, caudal aspect at 8 cm from anal verge (5 cm from anorectal ring).	75% circumference, 4-cm longitudinal dimension, ulcerated, anteriorly tethered mass; caudal margin 6 cm from anal verge (1 cm above the anorectal ring); suspicious LNs at mesorectal fascia.	1-cm ulcerated nodule at the anorectal ring posteriorly; indurated but not fixed.	40% circumference, 3-cm longitudinal dimension, ulcerated tumor at distal aspect of upper rectal valve; not palpable transanally.	Posterior, contained perforation of upper rectal cancer; circumferential tumor palpable at tip of examining finger. Endoscopy not performed.
PATIENT FACTORS					
Comorbidities	None.	Diabetic, moderately obese.	COPD but no home O2.	None.	None.
Fecal continence	Good.	Good.	Occasional flatus, incontinence, and soilage.	Good.	Good.
Personal history of pelvic radiation, inflammatory bowel disease, or prior colorectal resection	None.	None.	Had seed implantation RT for prostate cancer 4 y previously.	None.	None.
Personal or family history of colorectal cancer or other cancer	None.	None.	None.	Tested positive for HNPCC.	None.
Outlook, lifestyle issues	Active gardener and volunteer.		Patient refuses permanent stoma.	Pilates instructor with 2 adolescent children.	Robust, athletic.
Staging	cT1N0M0 by ERUS and CT of chest, abdomen, and pelvis: stage I	cT3N1M0 by MRI of pelvis and CT of chest, abdomen, and pelvis: stage IIIB	cT1N1M0 by 3-Tesla MRI of pelvis and CT of chest, abdomen, and pelvis: stage IIIA	cT2N0M0 by ERUS and CT of chest, abdomen, and pelvis: stage I	cT4bN1M0 by CT of chest, abdomen, and pelvis: stage IIIC
Conventional therapy	FTLE or LAR.	Neoadjuvant CRT then APR.	APR.	LAR.	LAR or APR.
Qualified therapy	FTLE or LAR; favor LAR if known high-risk features (poorly differentiated, lymphovascular, or perineural invasion, SM3).	Neoadjuvant CRT then ISR by experienced surgeon or APR.	APR.	LAR.	Diverting transverse colostomy, antibiotics, then CRT. Avoid percutaneous drain. LAR after neoadjuvant therapy.
Tailored therapy	FTLE or LAR.	Neoadjuvant CRT then ISR or APR.	CRT, reevaluate for FTLE.	Total abdominal proctocolectomy, ileal J-pouch reconstruction. Consider total abdominal hysterectomy and bilateral salpingoophorectomy.	Same.

TABLE 8. (Continued)

PATIENT FACTORS					
Treatment planning matrix	Low-risk tumor in low-risk location.	High-risk tumor in high-risk location.	High-risk tumor in high-risk location.	Low-risk tumor in low-risk location but with modifying circumstances.	High-risk tumor in low-risk location but with modifying circumstances.
Neoadjuvant CRT regimen	None per NCCN guidelines (but some controversy about FTLE alone given LN involvement rate of 10%-20%)	EBRT with concurrent 5-FU ("bad" tumor–could consider short-course RT without concurrent chemotherapy).	EBRT with concurrent 5-FU (consider IMRT, consider contact radiation).	None.	EBRT with concurrent 5-FU, boost to presacral space (consider IMRT, consider IORT).
Posttreatment assessment: response to neoadjuvant therapy	No nCRT	Incomplete response but no longer tethered anteriorly.	Slight induration at tumor site at 6 wk after completion of neoadjuvant therapy. No residual induration or scar at 12 wk.	No nCRT	Incomplete response to treatment. Follow-up CT shows no residual abscess cavity; transmural tumor/scar evident posteriorly; no extrapelvic LNs or liver or lung lesions. No additional lesions on colonoscopy.
Recommended therapy	FTLE or LAR.	ISR	APR recommended at 6-wk assessment.	Total abdominal proctocolectomy, ileal J-pouch reconstruction.	LAR.
Actual therapy	FTLE by TEM.	ISR	Observation.	Total abdominal proctocolectomy, ileal J-pouch reconstruction.	LAR.
Pathologic staging	pT1cN0cM0	ypT3(focal)pN0(0/13)cM0 (TRG 1)	NA	pT2pN1(1/17)cM0	ypT2pN0(0/14)cM0
Follow-up	Flexible or rigid proctoscopy in office and CEA level every 3 mo for 3 y, then every 6 mo for 2 y, and then annually. Colonoscopy at 1 y postop then at 3 y. CT of chest, abdomen, and pelvis; LFTs, and CBC annually. Additional workup for symptoms.	Office visit and CEA level every 3 mo for 3 y, then every 6 mo for 2 y, and then annually. Colonoscopy at 1 y postop then at 3 y. CT of chest, abdomen, and pelvis; LFTs; and CBC annually. Additional workup for signs or symptom of recurrence.	Flexible or rigid proctoscopy and DRE in office every 6 wk for 1 y, then every 3 mo for 2 y, then every 6 mo for 2 y, and then annually. CEA every 3 mo for 3 y, then every 6 mo for 2 y, and then annually. Colonoscopy at 1 y postop and then at 3 y. CT of chest, abdomen, and pelvis; LFTs; and CBC annually. Additional workup for symptoms.	Adjuvant CRT recommended. Risk of poor neorectal function. Office examination and CEA level every 3 mo for 3 y, then every 6 mo for 2 y, and then annually. Proctoscopy to evaluate rectal remnant at staple line every 6 mo. CT of chest, abdomen, and pelvis; LFTs; and CBC annually. Additional workup for symptoms. Also needs surveillance for other HNPCC-associated malignancies.	Office visit and CEA level every 3 mo for 3 y, then every 6 mo for 2 y, and then annually. Colonoscopy at 1 y postop then at 3 y. CT of chest, abdomen, and pelvis; LFTs; and CBC annually. Additional workup for symptoms.

APR indicates abdominoperineal resection; CBC, complete blood count; CEA, carcinoembryonic antigen; COPD, chronic obstructive pulmonary disease; CRT, chemoradiation therapy; CT, computed tomography; DRE, digital rectal examination; EBRT, external beam radiation therapy; ER, emergency room; ERUS, endorectal ultrasound; 5-FU, fluorouracil; FTLE, full-thickness local excision; HNPCC, hereditary nonpolyposis colorectal cancer; IMRT, intensity-modulated radiation therapy; IORT, intraoperative radiation therapy; ISR, intersphincteric resection; LAR, low anterior resection; LFTs, liver function tests; LN, lymph node; MRI, magnetic resonance imaging; NA, not applicable; NCCN, National Comprehensive Cancer Network; O2, oxygen; Postop, postoperative; RT, radiation therapy; SM3, submucosal level 3; TEM, transanal endoscopic microsurgery; TRG, tumor regression grade; WBC, white blood cell count.

among patients undergoing nCRT and experiencing variable degrees of tumor downstaging, is the sole best predictor of survival and is in fact independent from initial clinical (radiological) stage.[176] Interestingly, a subset analysis of the EORTC trial found that the improved survival among patients who received aCRT occurred preferentially among those whose tumor downshifted after nCRT (ypT0-2). In other words, responders to nCRT appeared to benefit more from adjuvant systemic CTx than nonresponders.[177] This observation challenges the accepted logic that higher risk patients (those with worse prognostic features and a high risk of recurrence) are more likely to benefit from adjuvant therapy than lower risk patients. Perhaps we are offering the right treatment to the wrong patients.

Since distant failure rates have not improved to the same extent that LR rates have and rectal cancer patients still die of systemic disease, it has been postulated that the early treatment of micrometastases with induction CTx before administering standard nCRT might improve OS. As was discussed earlier, treatment-related toxicity and mortality have limited the investigation of this regimen.[112]

Local Excision Outcomes

High LR rates and decreased survival after FTLE of LN-negative T1 and T2 cancers compared with radical resection were reported in a study from the University of Minnesota in 2000. With a mean follow-up of 4.4 years, the LR rate after FTLE was 18% for T1 tumors and 47% for T2 tumors versus 0% and 6%, respectively, for radical resection at 4.8 years. The OS rate was 69% in the FTLE group and 82% in the radical surgery group.[178] Recently reported from the Cancer and Leukemia Group B (CALGB) 8984 study (the only prospective study of T1 and T2 rectal cancer FTLE to date) were LR rates of 8% and 18%, respectively, at a median of 7 years of follow-up.[179] It has been suggested that TEM local excision of T1 cancers results in improved LR compared with conventional transanal excision,[86,180,181] but the University of Minnesota LR rates after TEM excision were still 10% for T1 tumors and 23% for T2 tumors.[181] An even more disappointing 20% LR rate was reported from another group after TEM excision of 88 pT1 rectal cancers. Not only was the LR rate high, survival was compromised even though salvage procedures were possible in the majority of the LR cases.[182]

Limited retrospective reviews have suggested that the addition of aCRT, especially for T1 tumors, can improve the results of transanal excision.[183] When CRT is given neoadjuvantly, LR rates as low as 6% and OS rates as high as 86% have been reported for cT3 tumors.[184] A small prospective trial randomized favorable cT2N0M0 patients after nCRT to either laparoscopic radical resection or TEM. At a median follow-up of 84 months, 5.7% of the TEM patients had a LR versus 2.8% in the radical resection group; the actuarial survival rate was 94% in both groups.[185] Data from ACOSOG trial Z6041 prospectively evaluating FTLE after nCRT for cT2N0M0 tumors will soon be available and hopefully will clarify this issue.

If FTLE local treatment failures could be reliably salvaged by radical resection, LR would be less of a problem. However, salvage of LR following FTLE continues to be a concern. Weiser et al reported that 55% of salvage surgery patients required extended resections, and the actuarial survival rate was 53%, which is quite low compared with expected survival for this group with T1 to T2 tumors at initial presentation.[186]

New Developments, Future Directions

Nonoperative Management of Rectal Cancer: "Watch and Wait"

In patients who have a pCR after nCRT, not a single cancer cell is removed by surgery. In these patients, one could argue that surgery might be unnecessary and might ask whether radical TME and its attendant complications are justified only for the sake of confirming pCR. The nonoperative approach, known as "watch and wait," has been used by Habr-Gama et al for many years.[187-189] Even though good long-term results have been reported, this approach has been minimally embraced by other institutions and remains highly controversial, principally because of concerns about the inaccuracies of posttreatment clinical staging and uncertainty regarding the potential oncologic benefit of resection even when there is pCR.[188,190,191]

The clinical determination of CR is more elusive than the pathological determination due to limitations of imaging, particularly after CRT. Lack of consensus about the timing of assessment (see "When Should Posttreatment Assessment Be Done," above) and physical examination criteria are factors. Habr-Gama et al would suggest that studies evaluating pCR rates after less than an 8-week waiting period may detect residual disease in patients who could have developed a pCR had more time elapsed between the completion of nCRT and radical resection.[187-189] Likewise, inaccuracies of clinical detection of CR (typically demonstrating clinical underidentification of pCR) may be the consequence of a short (6 weeks) waiting period. Nonetheless, the clinical assessment of tumor response is a complex clinical task that requires uniform criteria and expertise.[133] There is definitely a learning curve. When assessment was performed by a group of surgeons with disparate experiences and caseloads and no shared standards for identifying CR, there was interobserver variability.[190] The extent to which accurate assessment rests on training and expertise could limit the usefulness of nonoperative management even if other issues were resolved.

The "watch and wait" strategy is really a "no-immediate-resection" approach that is applied to highly selected tumors and requires intensive follow-up by an experienced colorectal surgeon using digital rectal and endoscopic examinations at 4- to 6-week intervals for the first year after completing nCRT (Fig. 11).[192] Strict criteria are used to identify potential complete responders, but the final designation of cCR is not made until a full 12 months after nCRT. Full excisional rather than endoscopic biopsy must be used in equivocal cases. Patients are advised that disease detection during the first 12 months (ie, failure to meet cCR criteria) or recurrence after 12 months requires surgical salvage. A retrospective review of no-immediate-surgery patients who were initially identified as having a cCR but

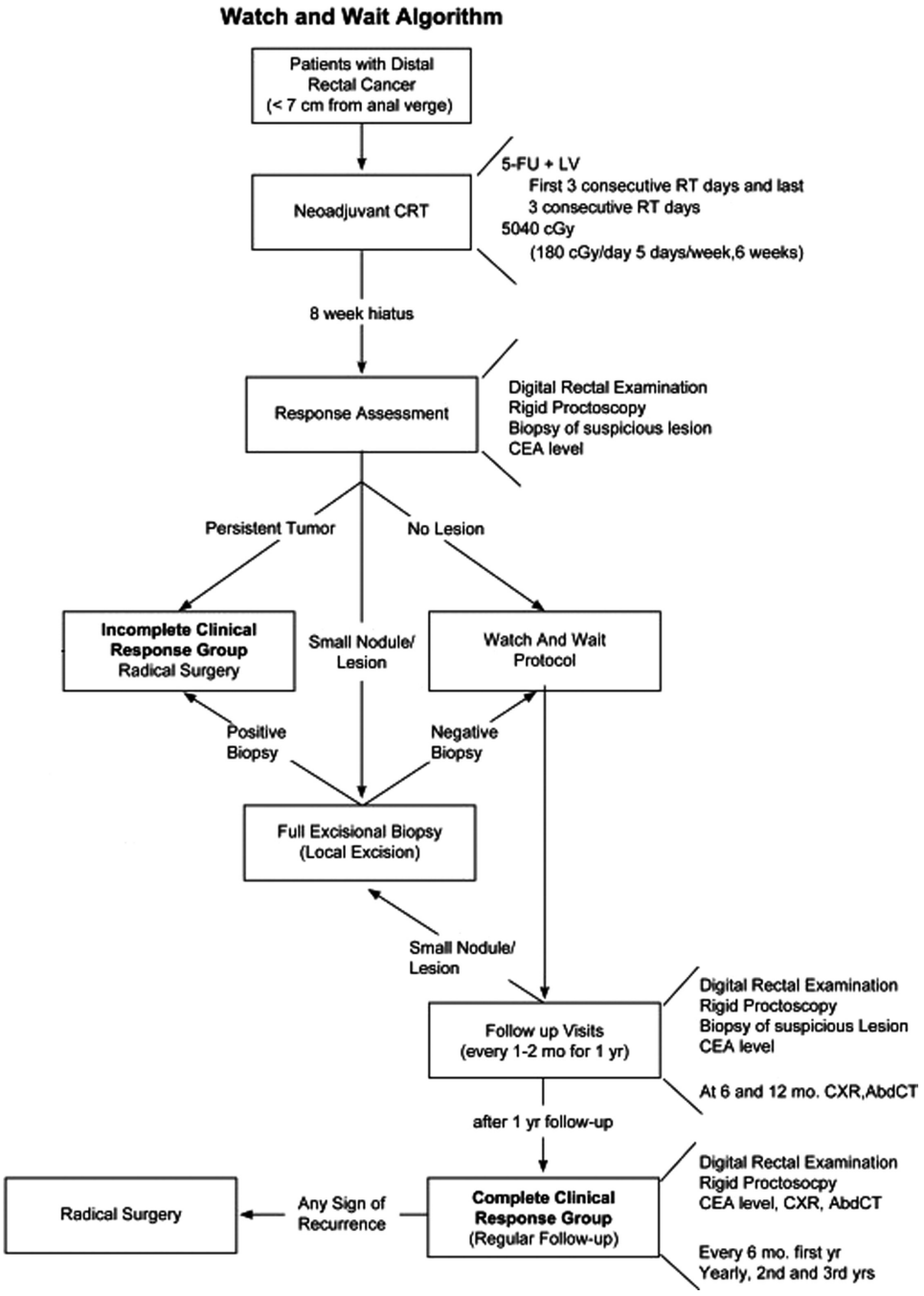

FIGURE 11. Watch and Wait Algorithm. CRT indicates chemoradiation therapy; 5-FU, fluorouracil; LV, leucovorin; RT, radiation therapy; cGy, centigrays; CEA, carcinoembryonic antigen; ERUS, endorectal ultrasound; AbdCT, abdominal computed tomography; PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance imaging; CXR, chest x-ray. Reprinted with permission from Habr-Gama A, Perez RO, Proscurshim I, et al. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? *Int J Radiat Oncol Biol Phys*. 2008;71:1181-1188.[192]

subsequently required delayed (salvage) radical resection showed no oncologic compromise compared with patients operated on immediately after posttreatment assessment.[192] Local recurrence after the first 12 months was amenable to salvage surgery 100% of the time. There were no oncologic benefits in terms of OS or disease-free, cancer-specific survival between patients who underwent radical resection because they did not meet criteria for cCR but were in fact ypCR and those who did meet criteria for cCR, which was sustained for 12 months or longer, and who were managed nonoperatively.[189] Even though there are encouraging data, no randomized controlled trials have been conducted to help substantiate these observations. In addition, this program clearly favors nCRT to radical resection even for "good" tumors. The reports are intriguing, and there is growing interest in organizing a multisite trial; at least one study is currently underway in the United Kingdom.

Prediction of Tumor Response: Genetic Studies

There is great hope that molecular studies will shed some light on the issue of prediction of response to nCRT in patients with rectal cancer. Few studies have attempted to identify gene expression signatures by microarray platforms capable of predicting "good" versus "bad" responses to CRT. Unfortunately, these studies use diverse definitions of good response, including pCR, near-complete pathological response, or even any T-category downshift. In addition, all studies assessed tumor response at the relatively short interval of 4 weeks to 6 weeks from CRT completion.[193-195] Given that retrospective studies have suggested that longer intervals may increase complete tumor regression rates, these rather short intervals may have influenced the results of all studies. Also, there were absolutely no overlaps with respect to genes included in the gene signatures that might predict survival in each of the studies. Perhaps newer protocols using high-throughput sequencing for gene expression analysis may provide additional molecular and genetic information about the prediction of tumor response to nCRT.

Conclusions

Multimodal treatment of rectal cancer has improved LR rates and can increase the opportunity for sphincter preservation. Moreover, response to neoadjuvant treatment has provided information about tumor behavior that challenges conventional management strategies and is shifting the foundations of our understanding about rectal tumors. The complexity of factors contributing to tumor behavior and the spectrum of treatment options demand multidisciplinary conferences to plan and implement treatment and to review outcomes. These issues multiply in the setting of metastatic disease. Proper staging of rectal cancer relies on imaging, and there is an increasing role for MRI and possibly for PET-CT, not just for initial staging but also for the assessment of response to treatment. Nonetheless, staging inaccuracies continue to be a problem and, due to concerns about the limitations of the clinical identification of pCR, have presented the main obstacle to the adoption of alternative treatment strategies. Treatment planning is a tiered process that incorporates evidence-based standards for stage-directed therapy and also tumor and patient factors not described by current AJCC/UICC staging criteria. Increasingly, this dynamic process may incorporate downsizing and potentially downshifting into the final operative decision. It would seem that longer wait times, perhaps on the order of 8 weeks to 12 weeks between the completion of nCRT and surgery, improve both the rate of pCR (ypT0N0M0) as well as the potential for sphincter preservation. However, the limitations of a "one-size-fits-all" approach may derail the definition of an optimal interval and steer us instead toward a more conditional plan for reassessment. To what extent neoadjuvant therapy either alters tumor biology or discloses it remains to be determined. There is clear evidence that pathologic stage after nCRT more accurately indicates prognosis than initial clinical stage. Efforts are underway using molecular biology technology to identify tumor markers that predict response to nCRT so that the expense and morbidity of that therapy can be avoided. The overreaching goals of rectal cancer investigations are to establish truly individualized treatment plans that are minimally invasive and preserve function for patients with rectal cancer. ■

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