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Rectal cancer staging

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ABSTRACT

Recommendations for the management of rectal cancer have been incredibly dynamic over the last several decades and accurate staging is required to make informed decisions and guide patient discussions. A complete staging evaluation should include a physical examination, complete colonoscopy, serum carcinoembryonic antigen level, and imaging to include a CT chest, MRI of the pelvis, and either a CT or MRI of the abdomen. Assessment of the circumferential resection margin with a rectal cancer protocol MRI is the cornerstone of this staging workup. Accurate staging is of paramount importance when considering treatment options for this complex disease.

Rectal cancer staging

Recommendations for the management of rectal cancer have been incredibly dynamic over the last several decades as new treatment paradigms and new imaging techniques have been investigated and adopted. While surgery remains the cornerstone of treatment for most cases of rectal cancer, the addition of neoadjuvant chemoradiotherapy has dramatically changed the way we approach this disease. With such emphasis on neoadjuvant treatment, and the emerging possibility non-operative management of rectal cancer, establishing an accurate clinical stage is of utmost importance. Furthermore, accurate staging is required to make informed decisions and guide patient discussions regarding the intent of treatment as either curative or palliative.

Unlike colon cancer, where preoperative staging is mainly for the determination of distant metastatic disease, accurate preoperative staging of rectal cancer is fundamental to guide a more nuanced approach to treatment. The implications of over or under-staging patients with a diagnosis of rectal cancer can dramatically impact the treatment that is delivered, and ultimately, patient outcomes. This chapter aims to provide a review of the relevant anatomy related to rectal cancer staging, current recommendations, and will discuss the various staging modalities with particular emphasis on imaging.

Anatomy and nomenclature

Rectal cancer is staged according to the American Joint Committee on Cancer (AJCC) TNM staging system, Eighth Edition.[1] The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology define the rectum as beginning at a virtual line drawn between the sacral promontory and symphysis pubis on MRI, and ending at the palpable upper border of the anorectal ring.[2] This most proximal definition of the rectum is important to correlate clinically, as treatment may align more with colon cancer or rectal cancer depending on which side of this "line" the tumor lies. Educated decision-making in this regard has implications for oncologic outcomes, as the risk of recurrence is worse and overall survival poorer in rectal cancer.

Furthermore, when discussing the staging of rectal cancer, an important distinction should be made between the *clinical* stage and the *pathologic* stage, and the proper nomenclature be used by all treating providers both in discussion and in all documentation as to avoid confusion. *Pathologic* stage can only be determined after a specimen is removed, and is denoted with a "*p*," for example, *p*T4N1M0. *Clinical* stage, however, is a determination that is made preoperatively based upon multiple modalities of investigation, including physical examination and imaging studies. It is denoted with a "*c*," for example, cT4N1M0. The utility of designating and treating based upon a clinical stage in rectal cancer is predicated on the fact that the accuracy of the clinical staging is comparable to the pathologic stage. The accuracy of various imaging modalities will be discussed later in the chapter.

In general, a complete clinical staging evaluation for a patient who presents with rectal cancer includes a physical examination (anorectal examination and palpation of inguinal lymph nodes), complete colonoscopy with histopathologic evaluation via biopsy, serum carcinoembryonic antigen level (CEA), and imaging to include a CT chest, MRI of the pelvis, and either a CT or MRI of the abdomen. Endoscopic ultrasound is recommended only if the patient is unable to undergo MRI. Refer to Table 1 for specific information gained from each modality.

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Table 1
Staging studies and the specific information gained.

Staging Modality	T,N,M Stage	Specific Information Gained
Physical Examination		
• Digital Rectal Examination	T	Location (distance from verge and circumferential location); Is the lesion fixed or mobile?
• Anoscopy/Rigid Proctoscopy	T	Location (distance from verge and circumferential location)
• Inguinal Lymph Node Palpation	M	Presence or absence of concerning enlarged distant nodes
Serum Markers		
• Carcinoembryonic Antigen (CEA)	–	Baseline level; Used to raise suspicion for metastatic disease or detect recurrence
Endoscopy		
• Colonoscopy	T	Depth; Histopathologic information
	–	Presence of synchronous lesions
		*Consider CT colonography if cannot be completed.
• *Transrectal Endoscopic Ultrasound (TRUS)	T	Depth; Regional lymph nodes
		*Only recommended when MRI contraindicated
Imaging		
• CT Chest	M	Identification of lung nodules concerning for metastases
• CT or MRI Abdomen	M	Distant nodes; Liver or peritoneal metastases
• MRI Pelvis	T, N	Depth; Distance from verge; Circumferential Resection Margin (CRM); Regional Nodes

Transrectal endoscopic ultrasound (TRUS)

Transrectal ultrasound (aka endorectal ultrasound) had been a mainstay in rectal cancer staging for the better part of the last 30 years, but because of its operator dependence, technical challenges, and only moderate accuracy, it has been eclipsed in the last decade by the MRI of the pelvis. Nonetheless, in experienced hands, TRUS is able to provide detailed information about a tumor's relationship to other pelvic structures, provides excellent anatomic resolution, and can assess nodal status, contingent upon the probe being able to pass beyond the tumor.[3] The probe is typically inserted with the patient in left lateral decubitus position after they have completed an enema bowel preparation. A 30–60 cc water-filled balloon provides acoustic contrast within the lumen and the probe is scanned through the entire length of the tumor to acquire all of the information necessary for complete staging. What makes TRUS technically challenging is the necessity to constantly adjust the angle of the probe in relationship to the rectal wall, accounting for the topography of the tumor itself and/or any blood clots, fecal matter, or necrotic material, for example, that may prevent perfect apposition.

When relying heavily upon the traditional TNM staging system for rectal cancer, TRUS is well suited for distinguishing the T stage because of its ability to depict the individual layers of the bowel wall, and for N stage. A 2004 meta-analysis that compared EUS, CT and MRI and found that TRUS was superior to MRI for the determination of T2 tumors (sensitivities of both were 94% but specificity of TRUS was 86% whereas MRI was 69%) and T3 tumors (sensitivity of EUS 90%, MRI 82%; specificities of 75% and 75%). EUS and MRI were found to be comparable in identifying T4 tumors (approx. 70% sensitive, 96% specific) and lymph node involvement (approximately 66% sensitive, 76% specific).[4] The overall accuracy of TRUS for T stage has been reported as near 85.2% and for N stage, 75.0%, but these are likely an overestimation and subject to at least some degree of publication bias.[5] However, an important limitation of TRUS is its inability to visualize the mesorectal fascia (MRF) except at the level of the seminal vesicles/vagina, which renders it ultimately suboptimal for determination of the circumferential resection margin (CRM), arguably the most important, although not included, component of staging (more on the CRM in the following sections on MRI). Overall, TRUS is an acceptable alternative to MRI in those patients for whom an MRI is contraindicated or who cannot tolerate the study.

Magnetic resonance imaging for staging in rectal cancer

Pelvic MRI with contrast is now the recommended imaging modality for the accurate local staging of rectal cancer.[2] It provides information regarding tumor size and location, the relationship of the tumor to the sphincter complex and peritoneal reflection, evidence of extramural vascular invasion and bony metastasis. Most importantly, though, MRI has been shown to provide an excellent assessment of the circumferential resection margin (CRM), which is perhaps the most important prognostic factor for local recurrence, the development of distant metastasis and disease free survival.[6–9] Neither CT nor TRUS are able to reliably assess the CRM.[4]

The circumferential resection margin (CRM), also known as the lateral or radial resection margin, is defined as the closest distance of the tumor to the mesorectal fascia (MRF) by MRI. Defining this becomes more complex when one considers the anatomy of the rectum, which must be considered when interpreting the MRI. In the lower parts of the rectum (less than about 5 cm from the anal verge), the mesorectal fat surrounding the rectum is circumferentially bound by the MRF, whereas in the upper portions, the peritoneum covers the anterior portion of the mesorectal fat (anterior peritoneal reflection) and posteriorly, the peritoneum extends gradually upward to encircle the rectosigmoid. The CRM is generally considered positive when the tumor extends within 1 mm or less of the MRF, or for lower tumors, invasion into the intersphincteric plane.[2,10] The significance of the CRM, and more specifically CRM positivity, to local recurrence and overall survival in rectal cancer patients has been elucidated with increasing clarity over the past three decades, beginning with the Basingstoke experience. Heald and Ryall, in 1986, described a 3.7% cumulative risk of local recurrence using the technique of total mesorectal excision (TME), whereby the mesorectal fascia is left intact with the specimen, sharply dissected out of the pelvis.[11] This was critical to show that tumor penetrance into the mesorectal fat was an important, and at that time underappreciated, prognostic indicator. Since then, numerous studies have corroborated the importance of the CRM. The local recurrence is significantly higher in patients with a positive CRM than without, ranging from 78% vs. 10% in the earliest studies, to 22% vs. 5% respectively in more contemporary reports.[8,12] Furthermore, with decreasing distance to the CRM, there is an exponential increase in rates of local recurrence, metastasis and death.[12]

In the era of neoadjuvant chemoradiotherapy for rectal cancer, the CRM becomes even more important because tumor retraction from the CRM as a result of treatment portends an improved prognosis.[13] CRM determination at diagnosis is imperative to appropriately guide preoperative treatment planning, and has meant an increasing emphasis on reliable imaging methods. MRI has emerged as consistently superior to either TRUS or CT scan for CRM assessment, while offering comparable assessment of both T and N stage, because of its ability to identify the mesorectal fascia. The MERCURY trial, first

published in 2007, prospectively evaluated the accuracy of MRI for determining the extramural tumor depth of invasion. In this, they found that the imaging and pathology correlation was equivalent to within 0.5 mm.[14] In a pooled analysis from 2012, the sensitivity of MRI for CRM involvement was 77%, while the specificity was 94%.[15] The 5 year follow up to MERCURY investigated the prognostic significance of high-resolution MRI CRM assessment and found that a positive CRM by MRI was the only preoperative staging parameter that remained significant for the prediction of local recurrence (LR), disease-free survival (DFS) and overall survival (OS). The hazard ratio for LR with an involved CRM was 3.50 (95% CI 1.53–8.00); the 5-year DFS was 67.2% for an uninvolved CRM versus 47.3% with a positive CRM; and the OS for an uninvolved CRM 62.2% versus 42.2% with a positive CRM by MRI.[9]

The accuracy of T stage identification by MRI has been well demonstrated, and was 84% in a 2009 study by Akasu and Iinuma, et al.[16] It should be noted, however, that the accuracy of the T stage improves with increasing stage. For instance, differentiation between T1 and T2 is challenging, especially without an endorectal coil (which is not recommended), but characterization of T3 and T4 tumors have an overall accuracy of nearly 100% (96 and 99%, respectively).[16,17] Low rectal tumors represent a unique staging challenge because of their proximity to the sphincter complex and thin mesorectum. A T staging system for tumors at this location in particular has been proposed and is denoted in Table 2 with a star.[18]

Table 2
Staging of rectal cancer, according to both pathologic and radiologic information.

Stage	Description
T Stage	
T0	No evidence of primary tumor
Tis	Carcinoma in situ; intramucosal carcinoma-no extension through the muscularis mucosae
T1	Invades submucosa (not into the submucosa)
	*[a]Confined to bowel wall, does not extend through full thickness; intact outer muscle coat
T2	Invades muscularis propria
	*[a]Tumor replaces muscle coat but does not extend into intersphincteric plane
T3	Invades through muscularis propria into the pericolorectal tissues
	*[a]Invades intersphincteric plane or lies within 1 mm of levator muscle
*T3a	<5 mm into perirectal fat or extramural
*T3b	5–10 mm into perirectal fat or extramural
*T3c	>10 mm into the perirectal fat or extramural
T4	Organ invasion
	*[a]Invades external anal sphincter and is within 1 mm and beyond levator muscle with or without invading adjacent organs
T4a	Penetrates to surface of visceral peritoneum
T4b	Directly invades or is adherent to other organs/structures
N Stage	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node (LN) metastasis
N1	Metastasis in 1–3 regional LN
N1a	Metastasis to 1 regional LN
N1b	Metastasis to 2–3 regional LN
N2	Metastasis to 4 or more regional LN
N2a	Metastasis to 4–6 regional LN
N2b	Metastasis to 7 or more regional LN
M Stage	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (ex. Liver, lung, ovary, non-regional LN)
M1b	Metastasis in more than one organ/site or the peritoneum

*Radiologic classification adapted from Taylor FG, Swift RI, Blomqvist L, and Brown G. A systematic approach to the interpretation of preoperative staging MRI for rectal cancer. *AJR* 2008; 191:1827–1835 and Jhaveri KS and Hosseini-Nik, H. MRI of Rectal Cancer: An Overview and Update on Recent Advances. *AJR* 2015; 205:W42-W55.
*[a]Specific for low rectal tumors, defined as <5 cm from the anal verge.

The identification of involved regional (mesorectal and/or internal iliac) and/or distant (inguinal) lymph nodes is important for preoperative chemoradiation planning and overall prognosis. The size (5–8 mm) and morphology (irregular contour, mixed signal intensity) of these lymph nodes on MRI are used to infer the presence of nodal metastasis.[19] These imaging characteristics perform moderately with regard to the sensitivity and specificity of MRI, and are roughly equivalent to that of TRUS, ranging from 54–94% and from 67–83%, respectively.[17] Specifically, a 2012 meta-analysis of 21 studies found a sensitivity of 77% and a specificity of 71% for the detection of metastatic lymph nodes with MRI.[15] Park et al. performed a histopathologic node-for-node validation study of MRI for the detection of nodal metastasis in 2014 and found a sensitivity of 58.0%, a specificity of 88.4% and a positive predictive value of 61.7%.[20] Nodes <3 mm, however, are infrequently identified by MRI, but as many as 15% harbored disease. Despite only moderate detection rates, excellent interobserver agreement for the interpretation of nodal involvement (0.959) highlights another advantage of MRI—the user independence of this modality—provided the correct protocols are ordered and utilized.

Rectal cancer MRI protocol

In order to garner the most information about a rectal tumor using MRI, the appropriate study must be ordered by the physician, the correct protocol and sequences performed by the technologist, and the relevant information interpreted by the radiologist. In addition, the surgeon should attempt to convey the location of the tumor from the anal verge in the referral note to the radiologist. In 2013, the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) published consensus guidelines for the use of MRI in the staging of rectal cancer which were updated by the Society of Abdominal Radiology (SAR) in 2017.[21,22] A minimum of a 1.5T field strength MRI system with pelvic phased-array multichannel coils should be used to provide high spatial resolution, high signal-to-noise ratio and a larger field of vision to include the lateral pelvic structures and nodes.[17,18,23] The specific MRI protocols included in most rectal cancer studies and the tumor information gained from each are shown in Table 3. What is universally and critically important is that the angulation of the coils in relationship to the tumor be in proper arrangement. This typically occurs in the T2-weighted imaging series, where the images are obtained perpendicular to the tumoral axis in sagittal plane, and in as many perpendicular planes as necessary depending on tumor size and shape to get optimal images. Proper angulation can mean the difference between the radiologist reading an involved CRM or not. The T2 images are the most important component of the protocol.

Patients are placed supine in the MRI machine, and a flexible coil is placed tightly around the patient's pelvis. While a variety of enhancement techniques have been attempted in the past to improve resolution, none are currently recommended. Endorectal coils have been shown to be costly, limited by patient tolerability, and provide improved signal contrast in only a relatively small area. Therefore, their use is not recommended.[23] Similarly, endorectal filling with gel or contrast is not recommended, as rectal distention compresses the mesorectal fat and compromises visualization of the mesorectal fascia and lymph nodes. Similarly, a pre-study bowel preparation in unnecessary.

The role of gadolinium-enhanced MRI is controversial, but the current ESGAR and SAR guidelines do not recommended its routine use based upon literature, which has found no clear advantage.[24,25] It is worth mentioning that several studies have shown some improved clarity with its use. One study from Memorial Sloan Kettering in 2018 showed that 24% of patient's treatments could have been altered due to either upstaging or downstaging of tumors based on the addition of gadolinium.[26] In addition, there is some evidence which shows that gadolinium enhancement can improve detection of extramural vascular invasion.[27]

Table 3
MRI protocols and the specific information gained from each series type.

Series		Tumor Information
T1-weighted pulse sequences		Pelvic bony involvement and incidental findings.
FSE T2-weighted imaging	***Sagittal***	Initial images for localizing the tumor.
	Axial	
	Coronal	
	High-Resolution Oblique	Optimal anatomic information regarding tumor depth, and relationships to surrounding structures.
DWI		Improve accuracy for detection of tumor. Accuracy for lymph node detection. Assessment of response to chemoradiation.

Adapted from AJR 2015; 205:W42-W55 and Gollub MJ, Arya S, et al. Abd Radiol 2018;43(11):2893–2902. FSE = fast-spin echo, DWI = diffusion-weighted imaging.

MRI reporting

Given the specifics of the MRI rectal cancer protocol and the work that is involved in obtaining high-resolution images, the physician should be mindful that all of the necessary information is conveyed by the radiologist in the report. There are published guidelines for standardized MRI reporting of rectal cancer, and these reports should include the information provided in Table 4.

CT chest and/or abdomen

Imaging of the chest and abdomen is important for the determination of metastatic rectal cancer, because 19%–30% of patients will have distant metastatic disease on initial presentation, most commonly to the liver and lung.[28–30] Interestingly, rectal cancer patients exhibit a slightly higher frequency of lung metastasis and lower frequency of peritoneal metastasis then in colon cancer.[31] Multidetector CT scan has been shown to be the most sensitive test (between 67% and 85%) for the detection of asymptomatic hepatic lesions (specificity 96%), and up to 100% accurate for the differentiation of hepatic metastases from other lesions (as is MRI).[32,33] The accuracy of CT for hepatic metastasis decreases with lesions less than 1 cm.[34] Metastasis are best visualized in the portal venous phase, and appear as heterogeneously hypoattenuating.[35]

CT chest without contrast is the most sensitive test for the detection of pulmonary colorectal metastasis, which occurs in 10–15% of those with metastatic disease, and is recommended over chest X-ray.[36] CT chest is able to detect nodules smaller than 5 mm with an overall sensitivity of 78%.[37] Marron et al. found that 78% patients had concordant imaging and pathology; predictors of discordance were the number of radiologic nodules and bilateral involvement.[38]

Table 4
Standard information to be included in an MRI report of rectal cancer.[21,22]

Distances
• From the anal verge or the anorectal junction to the most distal aspect of the tumor • Shortest distance between tumor and MRF (and location), i.e. CRM • Involvement of mesorectal fascia?
Sizes • Tumor length
T Stage • Overall stage • Extent of extramural growth if ≥T3 • Mesorectal tumor deposits • +/- morphological pattern of growth • Presence/absence of EVMI
N Stage • Overall N stage • Presence or absence of extramesorectal nodes • Absolute number of suspicious nodes

MRF = mesorectal fascia; EVMI = extramural vascular invasion.

Restaging

Due to multiple acceptable treatment strategies for rectal cancer, there are no absolute recommendations for restaging. One should consider restaging pelvic MRI to evaluate the response to neoadjuvant therapy of a positive CRM, or when considering non-operative management after neoadjuvant therapy. The majority of tumors can be downstaged, and 15–27% will have a pathologic complete response after neoadjuvant treatment.[39,40] Just as in the initial staging, MRI plays a major role in this reassessment, although there is some skepticism regarding its accuracy following neoadjuvant treatment compared to the initial staging. Any decreased accuracy is thought to be due to several factors, including difficulty with differentiating desmoplastic reaction or radiation changes from tumor infiltration, leading to overstaging.[17,41] The CRM remains of paramount importance in restaging, and has shown a 76% sensitivity and 86% specificity in a previously radiated pelvis.[42] A 2013 meta-analysis of 33 studies of rectal cancer restaging found that the sensitivity and specificity for MRI overall was 50.4% and 91.2%, respectively, and that the addition of diffusion-weighted imaging and experienced radiologists improved the interpretation of MRI in this setting significantly.[42] In 2015, Maas et al. published their results of a prospective cohort study which evaluated restaging modalities, both individually and in composite, for their ability to predict a complete pathologic response. They found that with a combination of clinical assessment (digital rectal and endoscopy) and T2-weighted/Diffusion-weighted MRI, the positive predictive value for a complete response when both tests show a complete response was 98%.[43]

Conclusion

This is an incredibly exciting and dynamic time in the management of rectal cancer. Improvements in imaging technology have made it possible to preoperatively stage patients with such accuracy that providers can make confident decisions about treatments, which sometimes even include a non-operative approach. Like most gastrointestinal cancers, the traditional AJCC TNM staging system is utilized in rectal cancer. However, the circumferential resection margin (CRM), as a somewhat more descriptive extension of the T stage, has proven itself as the most important predictor of local recurrence, disease-free and overall survival. Because of its high resolution and ability to reliably identify the mesorectal fascia (therefore assess the CRM), the T stage and the N stage, the rectal cancer protocol MRI has become the principal staging modality. Of all the MRI sequences obtained, the T2 weighted images are most important. In addition to MRI for locoregional staging, abdominal imaging (via MRI or CT) and chest imaging (CT) are necessary to assess for metastatic disease given the relatively high proportion of patients who will present with distant disease. Ultimately, a multidisciplinary approach to all phases

of rectal cancer management is critical to ensure the highest standards of care.

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