27 Rectal Cancer: Preoperative Evaluation and Staging

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Key Concepts

- Accurate preoperative staging of patients with rectal cancer helps identify patients at risk for local or distant metastasis and guides treatment decisions.
- Endorectal ultrasound (ERUS) is effective for staging the depth of invasion (T stage), especially for early-stage rectal tumors (uT0, uT1) that may be considered for local excision.
- Magnetic resonance (MR) has the ability to delineate the extent of locally advanced tumors and estimate the involvement of the mesorectal fascia.
- ERUS and MR use surrogate markers to estimate nodal involvement—size and node morphology—and are not particularly accurate in predicting nodal metastatic spread unless there are multiple large nodes in the mesorectum.
- The potential for understaging and overstaging of patients should be realized and taken into account when making treatment decisions.
- High-resolution computed tomography (CT) can detect distant metastatic lesions greater than 1 cm in diameter.
- Positron emission tomography (PET) scan is the most accurate assessment of total body tumor burden, especially when combined with CT (PET-CT).
- PET-CT is indicated when there are equivocal findings on CT and finding distant metastatic disease would alter therapeutic decisions.

Introduction

Careful pretreatment evaluation of the patient with rectal cancer is paramount for the successful management of their disease. By identifying the location of the tumor and its stage at the time of presentation, the surgeon is best prepared to discuss treatment options and prognosis with the patient and his or her family. As such, all healthcare providers caring for patients with rectal cancer should have a thorough understanding of the evaluation and staging of this disease.

Preoperative staging is performed according to the TNM classification of malignant tumors, estimating the depth of invasion into the rectal wall (cT), the presence or absence of lymph node metastasis (cN), and the presence of distant metastasis (cM). Also of importance is the determination of invasion of the anal sphincter and pelvic floor musculature, adjacent pelvic organs, or pelvic sidewall, all with significant consequences of planning and treatment to the patient.

The prefix “c” is used to indicate clinical staging, which is the estimate of stage based on physical examination and radiographic studies. Unfortunately, there is often confusion regarding this distinction, with some authors describing treatment recommendations for “T3N0” tumors as determined by pretreatment staging, when instead they should describe the tumor as “cT3N0.” The difference at first glance appears trivial but can have significant consequences if the clinician fails to understand that estimates of tumor stage are just that, estimates, and that treatment planning must take into account the potential inaccuracy of these estimates. For example, understaging of the cancer preoperatively may result in the omission of preoperative radiotherapy/chemoradiotherapy and lead to an increased risk of local recurrence. Conversely, overstaging may lead to overtreatment, increasing the overall morbidity and cost of treatment.

Pretreatment evaluation begins with physical examination and colonoscopic evaluation. Radiographic studies may include computed tomography (CT), endorectal ultrasound (ERUS), magnetic resonance imaging (MRI), and PET. These tests are complementary, each with their own advantages and disadvantages, and may be used in combination. Laboratory evaluation includes determination of the carcinoembryonic antigen (CEA) level.

Physical Examination

When evaluating a patient diagnosed with rectal cancer, the patient’s history is recorded, and an inquiry is made as to the duration of symptoms, changes in weight, bowel habits, bowel control, and presence of pain. If restorative proctectomy

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or local excision is to be contemplated, a detailed assessment of anal sphincter function and prior trauma (e.g., obstetrical history, prior anal operations) should be obtained. A general physical examination is performed with special attention for signs of muscle wasting, abdominal distension, hepatomegaly, and lymphadenopathy. A careful digital rectal examination is performed, noting the distance of the tumor from the anal verge and its proximity to the anal sphincter and pelvic floor. Tumors located in the anterior portion of the rectum have the risk of invasion into the genital structures, and special attention should be made to the potential for fixation to adjacent structures (i.e., prostate, vagina, sacrum, puborectalis). In a woman with an anterior rectal cancer, a pelvic examination should be done to ensure there is no invasion of the vaginal wall that may affect treatment. When the tumor is located in the posterior or lateral rectal wall, pelvic sidewall invasion should be considered. In addition, assessment of anal sphincter bulk and tone should be performed.

The texture of the tumor also gives a clue as to the stage. Benign adenomas are soft and the tumor may occasionally be difficult to detect on digital rectal examination. When a tumor invades the rectal wall, a desmoplastic reaction occurs and the resulting fibrosis will be felt as firm tissue. Evaluating the mobility of the tumor can also give information on how deep the tumor invades. A tumor tethered to the rectal wall, but that is otherwise mobile, is likely to invade into but not through the wall. Tumors that are fixed within the pelvis and are not mobile are locally advanced, deeply invading the full thickness of the rectal wall and possibly invading surrounding pelvic structures. Using these qualities of adherence of the tumor to the rectal wall and pelvis based on the digital rectal examination, Mason proposed a clinical staging system (CS-I to CS-IV) and recommended treatment options for patients with rectal cancer [1]. The digital rectal examination may occasionally also detect peritumoral lymphadenopathy, though this is often difficult. It should be noted that digital rectal examination has limitations in that only tumors of the distal rectal rectum can be adequately assessed. Furthermore, accuracy in staging depth of invasion is better for advanced tumors than for early tumors and improves with the surgeon's experience [2].

Clearance of the proximal large bowel, preferably by complete colonoscopy, should be performed in all patients with rectal cancer to exclude synchronous lesions and to confirm the histopathology of the tumor via biopsy. Other radiological testing may occasionally be used (i.e., CT colonography, air-contrast enema), though each has inherent limitations that providers should be aware of such as the need for an adequate preparation or failure to identify small lesions. Patients that are unable to be cleared prior to surgery due to an obstructing lesion should undergo proximal evaluation within 6 months after their operation. The endoscopic appearance of a tumor also gives a clue as to the relative degree of invasion, with benign tumors being soft to manipulation with the colonoscope or endoscopic forceps and malignant tumors being firm. Ulceration of the tumor implies invasion into the rectal wall, while deep ulceration may be a sign of transmural invasion.

Limiting pretreatment evaluation to digital rectal examination and colonoscopy prior to surgery for a rectal tumor is only appropriate for lesions that are considered benign. For patients with known or suspected rectal cancer, additional pretreatment locoregional imaging to stage depth of invasion and body scanning to detect distant metastasis should be performed prior to starting any treatment—whether with surgery, chemotherapy, or radiation.

Locoregional Imaging

Computed Tomography

Computed tomography (CT) is widely available and is one of the primary modalities used in preoperative staging of rectal cancer. CT accuracy is improved by administering oral, intravenous, and rectal contrast. CT can localize the tumor in the rectum but is not able to accurately delineate the layers of the rectal wall. For locally advanced tumors, CT may show extension beyond the rectal wall and invasion into surrounding structures. The addition of multidetector-row CT (MDCT) has improved accuracy for local staging of rectal cancer but still lacks the detail required. By including multiplanar (coronal, sagittal) images to standard axial images, this provides improved accuracy rates for higher T staging and N staging of rectal cancer than axial images alone [3].

Limitations to CT scanning for local staging of rectal cancer include the limited ability to define the mesorectal fascial layers and layers of the rectal wall. Although the mesorectal fat (MRF) surrounding a tumor can be clearly visualized on CT, perirectal fat stranding or induration secondary to rectal inflammation or peritumoral fibrosis cannot be definitively differentiated from tumor extension. In addition, the diagnosis of T4 tumors can be difficult due to lack of soft tissue resolution in the pelvis. Tumor involvement of an adjacent organ or the pelvic sidewall is also not accurate and is inferred by the loss of the fat plane between the tumor and the adjacent organ or structure.

Endorectal Ultrasound

On endorectal ultrasound (ERUS), the bowel wall is defined by five distinct sonographic layers of alternating hyper- and hypoechoic qualities [4]. Extending from the lumen outward, these layers correspond to (1) the interface between the ultrasound probe and the mucosa, (2) the interface between the mucosa and muscularis mucosa, (3) the submucosa, (4) the muscularis propria, and (5) the serosa or pericolic fat. The prefix "u" is used to describe ERUS T and N staging of rectal cancer (Figure 27-1, 27-2, 27-3, 27-4, and 27-5) [5].

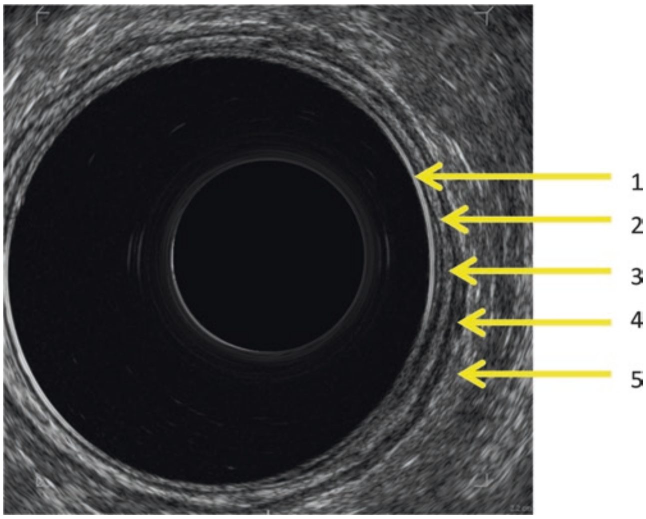

FIGURE 27-1. Endosonographic layers of the rectal wall. (1) Interphase of endoscopic balloon with mucosa. (2) Interphase of mucosa/submucosa. (3) Submucosa. (4) Muscularis propria. (5) Serosa and pericolic fat.

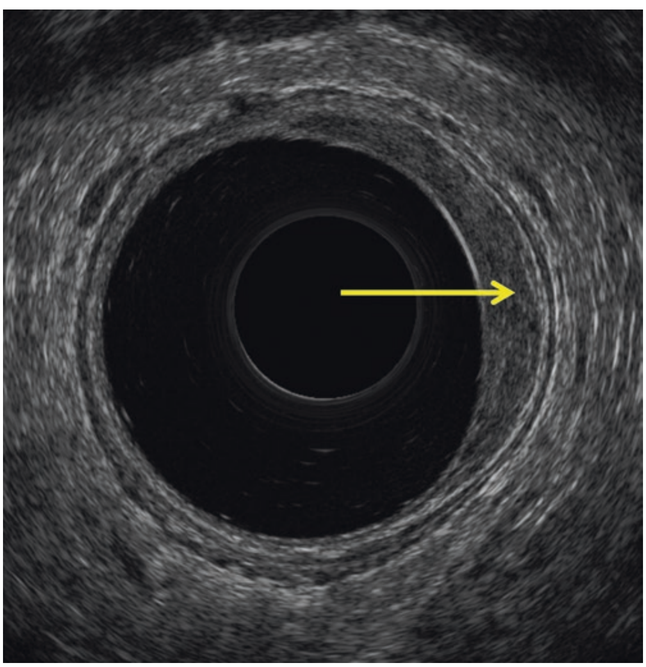

FIGURE 27-2. ERUS of uT0 tumor. Hypoechoic tumor (*arrow*) does not invade into the first hyperechoic layer. Notice that the submucosa (*white layer*) remains intact.

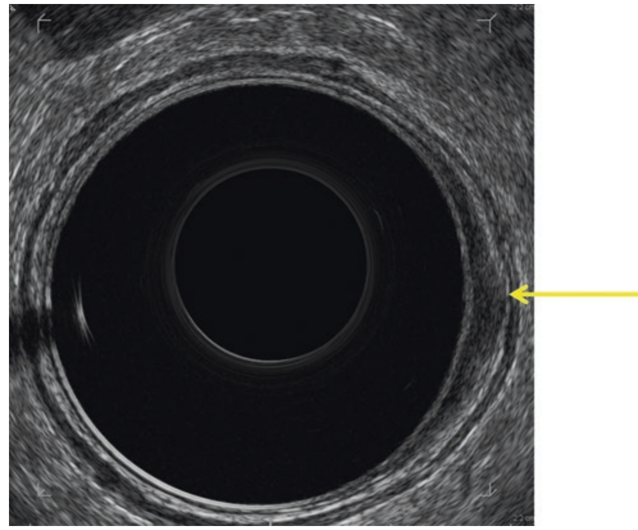

FIGURE 27-3. ERUS of uT1 tumor. Hypoechoic tumor invades into the middle hyperechoic layer (*arrow*) but does not invade the outer hypoechoic layer.

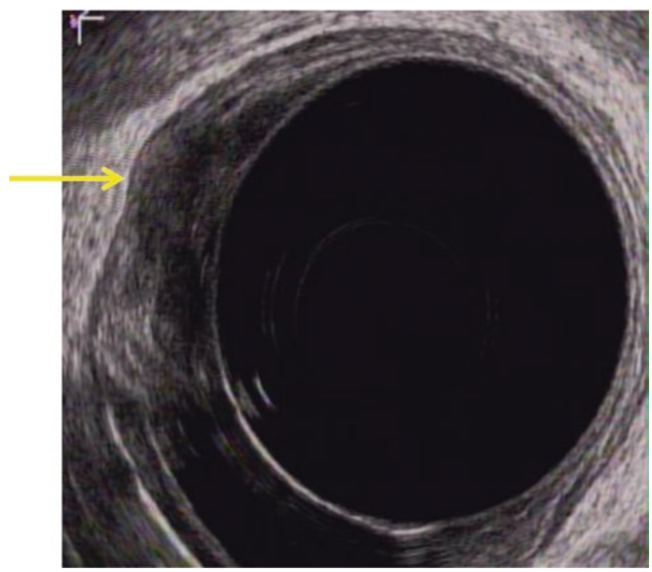

FIGURE 27-4. ERUS of uT2 tumor. Hypoechoic tumor invades through the middle hyperechoic layer and into the outer hypoechoic layer.

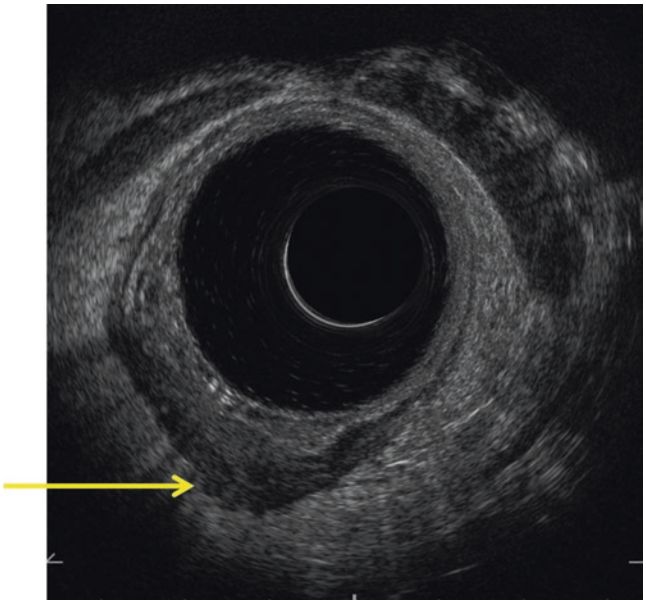

FIGURE 27-5. ERUS of uT3 tumor. Tumor extends through the second hypoechoic layer and into the outer hyperechoic layer (*arrow*).

ERUS has advantages in that it is simple to perform and inexpensive compared to CT or MR. The patient is given an enema to evacuate the rectum prior to the procedure. The procedure is often combined with a flexible or rigid proctosigmoidoscopy. Some patients require sedation to allay discomfort or anxiety. The ultrasound probe needs to pass proximal to the tumor in order to evaluate the entire extent of the tumor, thus making it difficult or impossible with obstructing lesions. 3-D ultrasonography records the image in real time and allows for subsequent manipulation of the image for axial, coronal, and sagittal evaluation. Malignant lymph nodes appear as hypoechoic and rounded peritumoral structures, whereas benign lymph nodes are less likely to be detected as they are isoechoic with the perirectal fat.

T Staging

There is variation in the reported accuracy of ERUS in accessing the T stage of rectal cancer, with an overall accuracy of about 84 % (ranging from 63 to 96 %), while the reported accuracy of CT and MRI is lower, 65–75 % and 75–85 %, respectively [6]. The accuracy of ERUS T staging in rectal cancer was analyzed in a meta-analysis of 42 studies ($N = 5039$) where ERUS T stage was compared to pathological stage (Table 27-1) [7]. The authors reported that ERUS has a sensitivity of 81–96 % and a specificity of 91–98 %, showing a higher sensitivity for locally advanced rectal cancer or LARC (95 %), compared with early cancer (88 %). The authors concluded that ERUS should be the preferred test for preoperative tumor staging rectal cancer.

As with many interpretive studies, operator experience plays a significant role in staging accuracy. In a prospective, multicenter study conducted in 384 hospitals in Germany, investigators analyzed the diagnostic accuracy of preoperative ERUS (uT) with pathological (pT) findings in 7096 patients with rectal cancer who had not received neoadjuvant therapy [8]. The overall accuracy of uT to pT was found to be 65 %, with understaging occurring in 18 % and overstaging in 17 % of patients. The hospital volume of yearly ERUS procedures performed was found to affect the accuracy for staging, with uT-pT correlation of 63 % for hospitals undertaking ≤10 ERUS/year, 65 % for those performing 11–30 ERUS/year, and 73 % for hospitals where more than 30 ERUS/year were performed. The poorest correlation was found for T2 and T4 rectal cancers. The authors cautioned that ERUS is a useful tool for guiding the therapeutic strategy of rectal cancer only when performed by expert diagnosticians.

Several investigators have demonstrated a lower accuracy of ERUS in detecting T2 tumors compared to T1, T3, or T4 [9–11]. Reasons for this include difficulty in differentiating those tumors that have deep invasion into the muscularis propria from those with microscopic invasion into the perirectal fat and in differentiating peritumoral inflammation and edema from neoplastic infiltration. One group retrospectively subdivided patients with preoperative T2 tumors into uT2a, for tumors with focal invasion into the muscularis propria, and uT2b, for tumors with extensive invasion into the muscularis propria, and found improved weighted kappa accuracy (from 0.89 to 0.94) when the uT2b tumors were included in the enlarged uT3 group [12].

ERUS has been studied for the selection of patients with early-stage rectal cancer (T0, T1) who may benefit from transanal excision instead of traditional transabdominal rectal resection. In a study of 552 patients undergoing transanal excision of rectal tumors, investigators evaluated the accuracy of ERUS to clinical staging and found that ERUS had a sensitivity of 95 % vs. 78 % and a positive predictive value of 93 % vs. 85 % in detecting adenoma or T1 rectal carcinoma as compared to clinical staging, whereas specificity was similar in both (62 % vs. 58 %) [13]. A meta-analysis designed to evaluate the accuracy of ERUS in T0 staging of rectal cancers found 11 studies ($N = 1791$) which met the inclusion criteria. The pooled sensitivity of ERUS in diagnosing T0 was 97.3 % (95 % CI: 93.7–99.1) and a pooled specificity of 96.3 % (95 % CI: 95.3–97.2) [9].

N Staging

Accuracy for detecting metastatic lymph nodes by endorectal ultrasound is less precise than for T staging, with a variable accuracy in reported studies of 63–85 % [6]. Differences in accuracy among studies may be due in part to differences in criteria used in defining nodal metastases. Hildebrandt et al. reported that hypoechoic, sharply demarcated nodes and those with heterogeneous pattern are more indicative of metastasis [14]. Katsura and associates found that nodes

Table 27-1. ERUS accuracy compared to histological stage.

Meta-analysis of 42 studies, $N = 5039$ patients		
T stage	Pooled sensitivity	Pooled specificity
T1	87.8 % (95 % CI 85.3–90.0 %)	98.3 % (95 % CI 97.8–98.7 %)
T2	80.5 % (95 % CI 77.9–82.9 %)	95.6 % (95 % CI 94.9–96.3 %)
T3	96.4 % (95 % CI 95.4–97.2 %)	90.6 % (95 % CI 89.5–91.7 %)
T4	95.4 % (95 % CI 92.4–97.5 %)	98 % (95% CI 97.8–98.7 %)

Adapted from Puli S, Bechtold M, Reddy J, Choudhary A, Antillon M, Brugge W. How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. Ann Surg Oncol 2009; 16:254–265 [7]

>5 mm, with well-defined boundaries and uneven and greatly hypoechoic patterns, were more likely to represent metastasis [15]. Akasu related the size of the short axis diameter of the largest lymph node to the rate of metastasis and found that for nodes <2 mm, the incidence of nodal metastases was 9.5 %, increasing to 47 % for nodes 3–5 mm in diameter and 87 % for nodes larger than 6 mm [16]. A meta-analysis of 35 studies evaluating the accuracy of EUS in diagnosing N stage in patients with rectal cancer showed a sensitivity of 73 % and specificity of 76 %. The data analyzed supported the hypothesis that ERUS is more accurate in excluding nodal involvement, rather than diagnosing it [17].

Staging accuracy for lymph node metastasis improves when the findings are associated with the T stage, with a higher risk of metastasis correlating with higher T stage. In a retrospective review of 134 patients with rectal cancer who underwent ERUS followed by radical surgery without neoadjuvant therapy, the accuracy of ERUS for N staging was 48 % for pT1 cancers, increasing to 84 % for pT3 cancers [18]. Notably, early rectal lesions are more likely to have lymph node micrometastases not detected by endorectal ultrasound. This may explain the somewhat high recurrence rates seen after local excision of early-uT-stage rectal cancer. On the other hand, CT has an accuracy of 55–65 % and MRI has an accuracy of 60–65 %. ERUS is more reliable than CT in being able to detect lymph nodes smaller than 1 cm and has comparable sensitivity and specificity to MRI [19].

Limitations to ERUS for staging rectal cancer include incomplete exams due to tumors that are bulky or stenotic. In women, these limitations may be overcome by vaginal insertion of the ultrasound probe [20]. Other causes of inadequate contact of the ultrasound probe with the tumor may be air or stool in the rectum or angulation of the tumor. Operator experience has also been shown to play a role in the accuracy of ERUS staging [21, 22].

Magnetic Resonance

High-resolution magnetic resonance (MR) with phased array pelvic coils is being increasingly used in the preoperative assessment of rectal cancer given its improved ability to evaluate the at-risk surgical circumferential resection margin. The pelvic coil is a wraparound surface coil placed around the pelvis. Patients are prepared with an enema on the morning of the examination. Thin-section (3 mm) T2-weighted fast spin-echo sequences are obtained in a plane orthogonal to the tumor [23]. Higher-resolution MRI allows improved definition of bowel and tumor infiltration [24]. MRI with endorectal coil is no longer recommended. Although endorectal MRI can show five layers of the rectal wall, the field of view is limited and the mesorectal fascia is not always visible. Additionally, the endorectal coil is more uncomfortable to the patient than the external coil and cannot be inserted in stenosing tumors [25]. Endorectal coil also has the potential to distort the tissues.

Three layers of the rectal wall are visible on a phased array external MRI. The innermost mucosa is thin and hypointense, the middle submucosa is hyperintense, and the outer muscularis propria is darkly hypointense. Below the peritoneal reflection, the rectum is surrounded by the MRF which is limited by the thin mesorectal fascia, which fuses with the rectoprostatic or rectovaginal fascia anteriorly and the presacral fascia posteriorly. The MRF surrounds the rectum completely only in the lower third and is best seen laterally as a thin hypointense line on T2W sequences. Inferiorly, the MRF thins out as it reaches the levator ani, which forms the roof of the ischiorectal fossa. MR is the best imaging modality to identify this avascular plane surrounding the mesorectum, which includes the mesorectum in its fascial envelope—the circumferential radial margin (CRM) (Figure 27-6).

In a meta-analysis of 21 studies designed to determine the accuracy of MR for T category (T1–2 vs. T3–4), lymph node metastases, and circumferential resection margin (CRM) involvement in primary rectal cancer that did not undergo preoperative chemoradiotherapy, MRI specificity was significantly higher for CRM involvement (94 %) than for T stage (75 %) or nodal metastases (71 %) [26]. Diagnostic odds ratio was significantly higher for CRM (56.1) than for nodal metastases (8.3) but did not differ significantly from T category (20.4) (Table 27-2). The authors concluded that MRI has good accuracy for both CRM and T category and should be considered for preoperative rectal cancer staging (Figure 27-7).

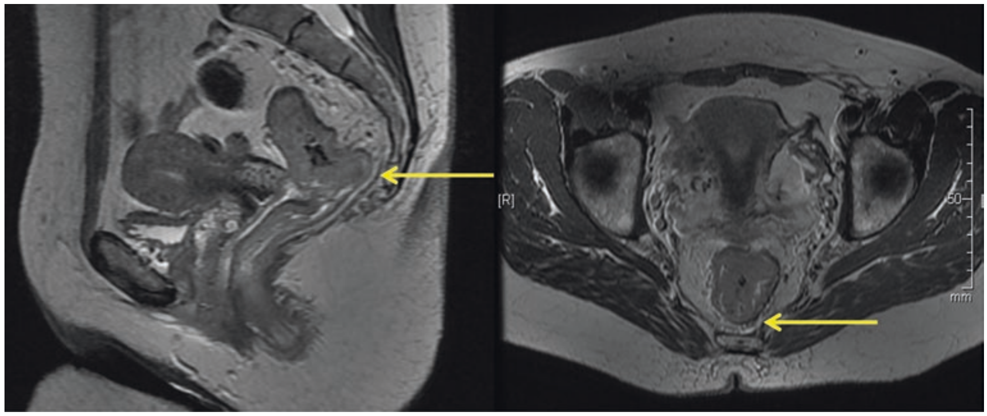

FIGURE 27-6. MR of cT3 tumor. Circumferential resection margin is preserved (*arrows*).

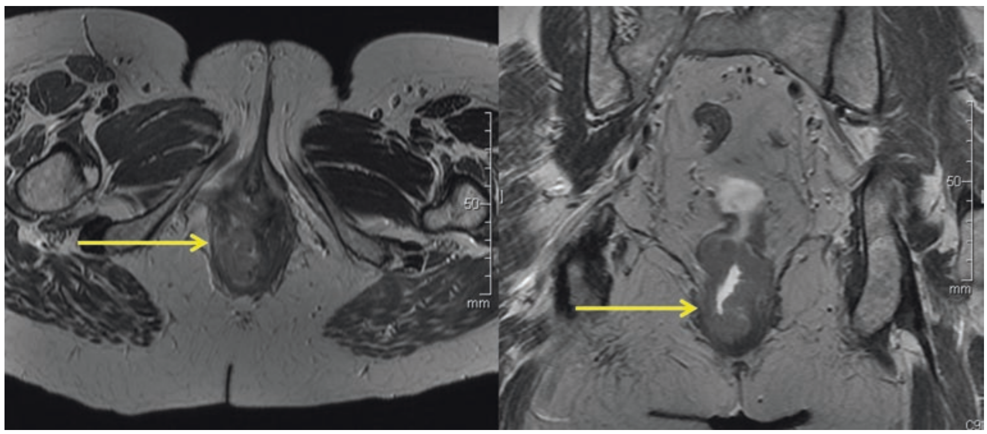

FIGURE 27-7. MR of cT4 tumor. Tumor invades the anal sphincter and levator ani (*arrows*).

TABLE 27-2. Meta-analysis of magnetic resonance accuracy in T stage, N stage, and circumferential resection margin (CRM)

	Specificity
T stage 19 studies (*N*=1986)	75 % (95 % CI 68–80)
N stage 12 studies (*N*=1249)	71 % (95 % CI 59–81)
CRM 10 studies (*N*=986)	94 % (95 % CI 88–97)

Adapted from Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor J, Schmocker S, Brown G, McLeod R, Kennedy E. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surge Oncol 2012; 19:2212-2223 [26]

Park et al. [27] evaluated the accuracy of preoperative MRI in predicting pN stage by doing a node-for-node matched histopathology evaluation. The overall success rate of matching between the two techniques was 91 %. Preoperative MRI revealed a node-by-node sensitivity and positive predictive value of 58.0 and 61.7 %. Of the 341 nodes harvested, 120 were too small (<3 mm) to be depicted on magnetic resonance images, and 18 of these contained metastasis (15 %).

MR limitations include foreign bodies in patients that are MR incompatible. Foreign bodies that are compatible, such as surgical clips, may also obscure images. Movement-related artifacts may preclude accurate visualization of the rectal wall. MR is not portable to the operating room and is more expensive than ERUS [28].

Many referral centers with an expertise in rectal cancer treatment are now utilizing MR as the preferred locoregional staging evaluation, especially for locally advanced tumors.

ERUS is utilized for evaluation of early-stage lesions or used in combination with MR for select patients.

Whole Body Imaging

Computed Tomography

CT of the chest, abdomen, and pelvis is indicated in patients with rectal cancer to evaluate for distant metastasis, primarily of the liver and lung (Figure 27-8) [29]. The overall sensitivity of MDCT for liver metastases ranges from 77 to 94 % [30–32]. Most lesions measuring over 1 cm in size can be reliably differentiated from benign liver lesions (such as cysts or hemangiomas). However, for lesions under 1 cm in size, sensitivities drop to as low as 41.9 % [33]. The finding of small nonspecific hypodensities measuring <1 cm (also known as "too-small-to-characterize" hypodensities) is very common, perhaps present in as many as 17 % of all patients [34]. In the majority of cases, even in those patients with a known underlying malignancy, these small hypodensities in the liver are likely to be benign (~90 %) and can be followed over time.

Evaluation of lung metastases is also an important component of MDCT distant staging. In one study of 56 patients with rectal cancer, 18 % had evidence of at least one pulmonary metastasis on MDCT, with an increasing risk of pulmonary metastasis with rising tumor grade [35].

Positron Emission Tomography

PET is a whole body nuclear medicine imaging examination utilizing 2-(^{18}F) fluoro-2-deoxy-D-glucose (FDG) that exploits the increased rate of glycolysis in tumor cells to detect tumor. FDG is a glucose analog that is taken up by cellular glucose transport mechanisms and is phosphorylated by hexokinase. Most malignant cells have an increased metabolism of glucose and thus take up the FDG at a greater rate than surrounding tissues. FDG-6-phosphate then becomes metabolically "trapped" intracellularly, because of the relative lack of glucose-6-phosphatase activity in tumor cells. PET detects the increased FDG uptake. This uptake can be assessed both qualitatively (via visual examination of the degree of uptake of a tumor relative to other tissues) and quantitatively (via an SUV value). While PET was traditionally performed as a stand-alone examination, these studies are now typically performed in conjunction with CT to allow for more precise correlation of FDG activity with anatomy [30].

FIGURE 27-8. CT of the abdomen demonstrating two liver metastases.

Although PET has been demonstrated to be more accurate in the assessment of whole body tumor burden than a combination of conventional imaging [31], it does have limitations. There is a limit to the resolution of the scan, and lesions less than 1–2 cm may be missed. This makes accurate assessment of nodal metastases difficult. In addition, the activity of the primary tumor may interfere with detection of mesorectal lymph nodes due to the proximity of the primary rectal tumor. Lastly, mucinous adenocarcinomas may not be detected, given that the FDG uptake per unit volume of tissue is reduced as compared to non-mucinous tumor [31].

The role of PET in the management of patients with primary rectal adenocarcinoma is to investigate equivocal findings on CT, when the detection of metastatic disease would change treatment strategy. In addition, PET should also be performed prior to consideration of resection of distant metastatic disease or local pelvic recurrence, to exclude incurable occult disease that would make the operation palliative rather than curative. PET is extremely useful in the differentiation of pelvic scar from recurrent tumor in those patients who have undergone proctectomy for rectal adenocarcinoma.

In one study, PET-CT showed a diagnostic accuracy of 92 % (as opposed to 87 % for MDCT), changed the patient's stage in 13.5 % of cases, identified previously unknown disease in 19.2 % of cases, changed the patient's planned surgery in 11.5 % of cases, and changed the patient's therapy in 17.8 % of cases [32]. Another study found that PET-CT upstaged 50 % of patients, downstaged 21 % of patients, and changed the patient's treatment plan in 27 % of patients [36]. This study noted that PET-CT was particularly likely to identify "discordant" findings (i.e., findings not identified on MDCT) in patients with low rectal cancers due to the propensity of this group of lesions to metastasize to local lymph nodes in the pelvis (particularly nodes in the inguinal, femoral, or iliac chains), as PET-CT identified metastatic lymphadenopathy in 13.5 % of patients in this study which were not diagnosed on MDCT.

PET has been evaluated as a potential technique to determine histologic response to neoadjuvant chemoradiotherapy and better identify patients for local excision or nonoperative therapy, but like CT, MR and ERUS have not been found to be accurate in the assessment of residual tumor in the pelvis [37]. At present, PET is not recommended in the routine evaluation of patients presenting with primary rectal adenocarcinoma

[38] but is utilized to evaluate equivocal findings on CT when finding distant metastatic disease would alter management.

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