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 involvement of the mesorectal fascia.
- ERUS and MR use surrogate markers to estimate nodal involvement—size, 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

- 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 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

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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 positron emission tomography (PET). These tests are complimentary, each with their own advantages and disadvantages, and may be used in combination. Laboratory evaluation includes determination of the carcinoembryologic antigen (CEA) level.

History and 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 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.
- If restorative proctectomy is being considered, assessment of anal sphincter bulk and tone is important as it may help predict postoperative function.
- 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.
- 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.

Endoscopic Evaluation of the Rectum

- Flexible sigmoidoscopy or proctoscopy should be performed to help localize the tumor anatomically and assess its appearance.
- The endoscopic appearance of a tumor also gives a clue as to the relative degree of invasion, with benign tumors soft to manipulation with the endoscope 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.
- Distance to the anal verge is best assessed by rigid proctoscopy, although this measurement is of limited utility as it can vary greatly based on differences in body habitus. It is more important to assess the distance of the distal margin of the tumor from the anorectal muscular ring as this will often guide the decision between restorative and non-restorative proctectomy. Another assessment which is helpful is the relationship of the tumor to the folds of Houston.
- As noted in other chapters, the surgeon should always examine the rectum of any patient referred with a lesion in the left colon prior to operation, as flexible endoscopic measurements of distance by non-surgeons are notoriously inaccurate. Many lesions described as being proximal to "15 cm" are actually in the true rectum. This discovery may fundamentally alter treatment planning.

Total Colon Evaluation

- Evaluation of the proximal colon, 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) for patients who cannot undergo complete colonoscopy, 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 colon evaluation within 6 months after their operation.
- In select cases of an apparent benign lesion, pretreatment evaluation may be limited to digital rectal examination, colonoscopy, and CEA prior to surgery.
- For patients with known or suspected rectal invasive adenocarcinoma, additional pretreatment staging is appropriate.

Locoregional Imaging

Computed Tomography

- Although computed tomography (CT) is routinely performed to exclude distant metastatic disease, it has limited ability to define the mesorectal fascial layers and layers of the rectal wall. Although CT can suggest tumor invasion into surrounding structures, tumor involvement of an adjacent organ or the pelvic sidewall is not entirely accurate and is only 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. 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 (Figs. 27.1, 27.2, 27.3, 27.4 and 27.5).
- The advantage of ERUS is that it can be performed in the surgeon's office as part of the initial evaluation of the patient, and it is 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. The probe can be passed through a rigid proctoscope to assess proximal tumors.
- 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.

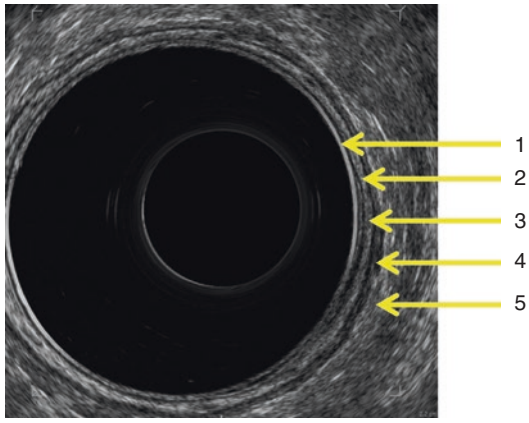

Fig. 27.1 Endosonographic layers of the rectal wall. (1) Interphase of endoscopic balloon with mucosa. (2) Interphase of mucosa/submucosa. (3) Submucosa. (4) Muscularis propria. (5) Serosa and pericolic fat

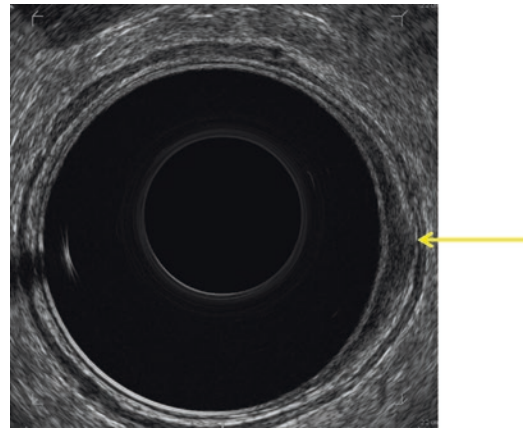

Fig. 27.3 ERUS of uT1 tumor. Hypoechoic tumor invades into the middle hyperechoic layer (arrow) but does not invade the outer hypoechoic layer

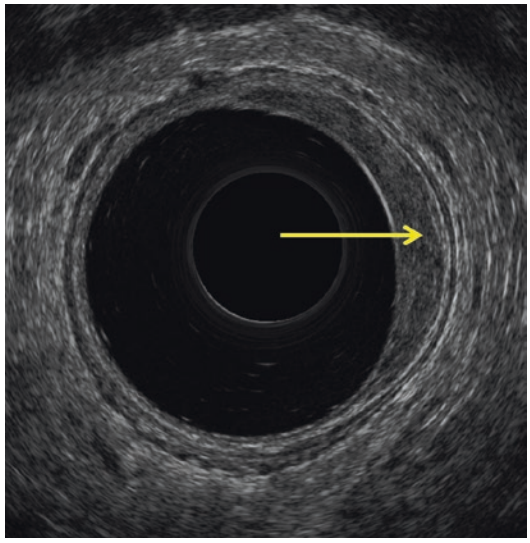

Fig. 27.2 ERUS of uT0 tumor. Hypoechoic tumor (arrow) does not invade into the first hyperechoic layer. Notice the submucosa (white layer) remains intact

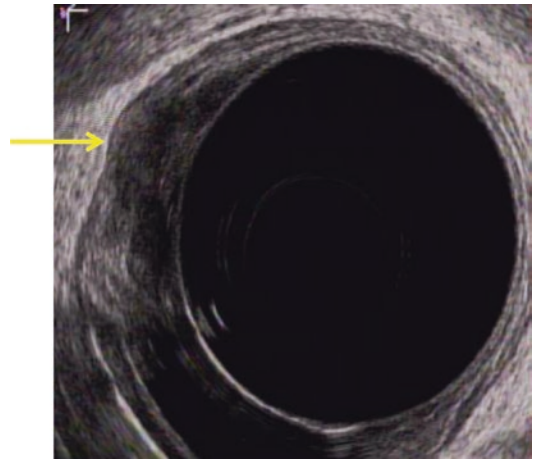

Fig. 27.4 ERUS of uT2 tumor. Hypoechoic tumor invades through the middle hyperechoic layer and into the outer hypoechoic layer

- 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.
- Limitations to ERUS for staging rectal cancer include incomplete exams due to tumors that are bulky or stenotic and inadequate contact of the ultrasound probe with the tumor due to 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. Some patients require sedation to allay discomfort or anxiety.

T Staging

- The reported accuracy of ERUS in accessing the T stage of rectal cancer ranges from 63% to 96% (Table 27.1).

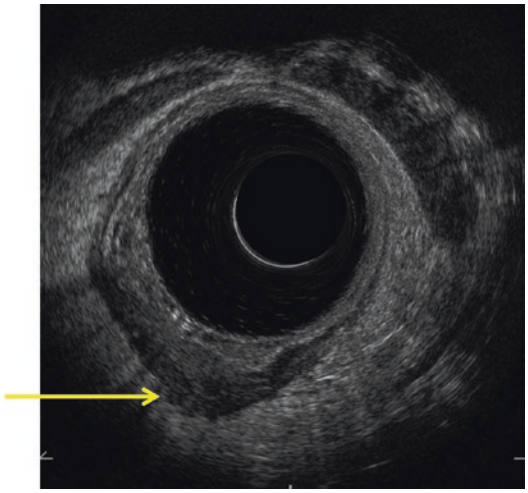

Fig. 27.5 ERUS of uT3 tumor. Tumor extends through the second hypoechoic layer and into the outer hyperechoic layer (arrow)

Table 27.1 ERUS accuracy compared to histological stage

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%)	98.3% (95% CI 97.8–98.7%)

Meta-analysis of 42 studies, $N = 5039$ patients
Adapted from Puli S, et al. How good is endoscopic ultrasound in differentiating various t stages of rectal cancer? Meta-analysis and systematic review. Ann Surg Oncol. 2009; 16:254–65

- As with many interpretive studies, operator experience plays a significant role in staging accuracy.
- Several investigators have demonstrated a lower accuracy of ERUS in detecting T2 tumors compared to T1, T3, or T4.
- However, other investigators have demonstrated the utility of ERUS in the selection of patients with early-stage rectal cancer (T0, T1) who may benefit from transanal excision instead of traditional transabdominal rectal resection.

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, et al. 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; 19:2212–23

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%.
- Further complicating the analysis is that different investigators have used different size and morphology criteria for nodal involvement with tumor.
- 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.

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 (Table 27.2).
- 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. Higher-resolution MRI allows improved definition of bowel and tumor infiltration.
- MR 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. Endorectal coil also has the potential to distort the tissues.

- Three layers of the rectal are visible on a phased array external MR. 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 mesorectal fat (MRF) which is limited by the thin mesorectal fascia, which fuses with the retroprostatic or retrovaginal 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) (Fig. 27.6) and invasion of the anal sphincter musculature (Fig. 27.7).
- As with other radiographic techniques, prediction of N stage is less accurate than for T stage. However, MR appears to be the most

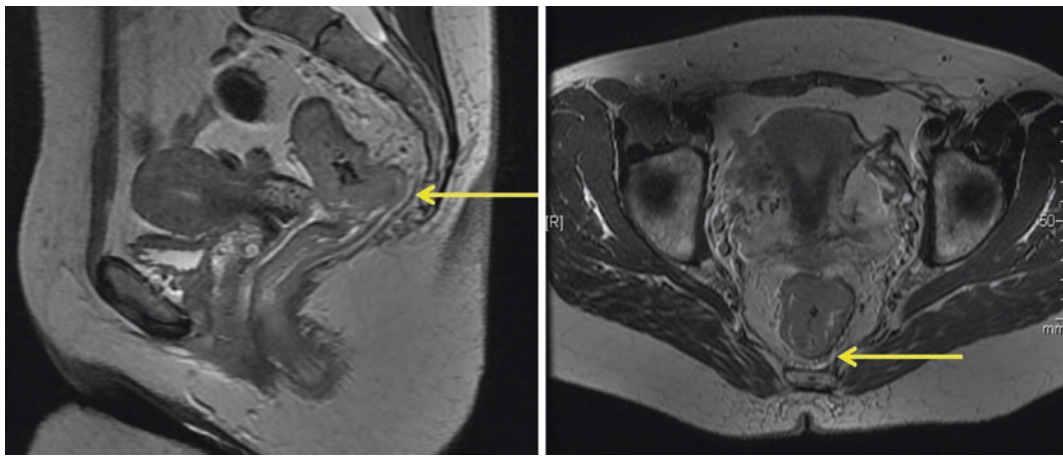

Fig. 27.6 MR of cT3 tumor. Circumferential resection margin is preserved (arrows)

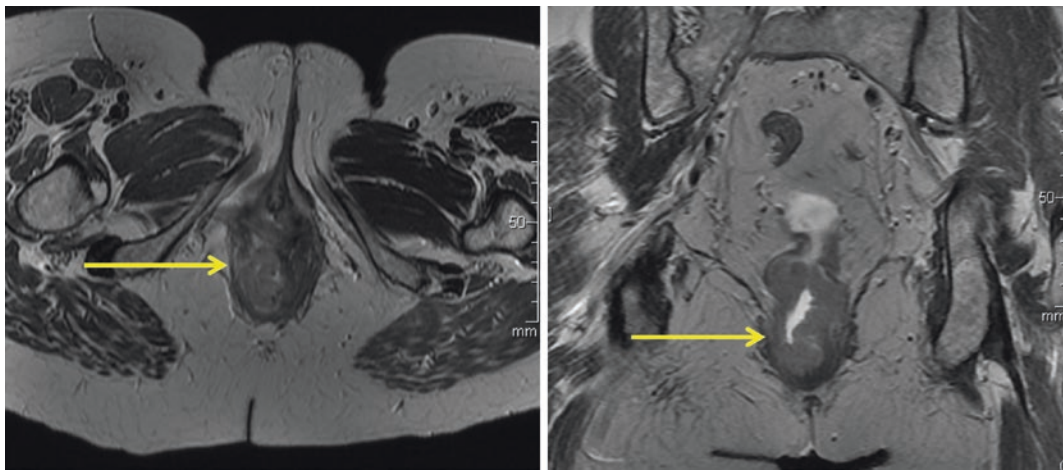

Fig. 27.7 MR of cT4 tumor. Tumor invades the anal sphincter and levator ani (arrows)

accurate of the imaging modalities currently employed. A variety of advanced techniques are being employed by various investigators in an attempt to improve nodal staging accuracy with MR.

- 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.
- 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 (Fig. 27.8). The overall sensitivity of CT for liver metastases ranges from 77% to 94%. 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 40%. 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. 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 further evaluated with liver MR or simply followed over time.
- Evaluation of lung metastases is also an important component of CT staging.

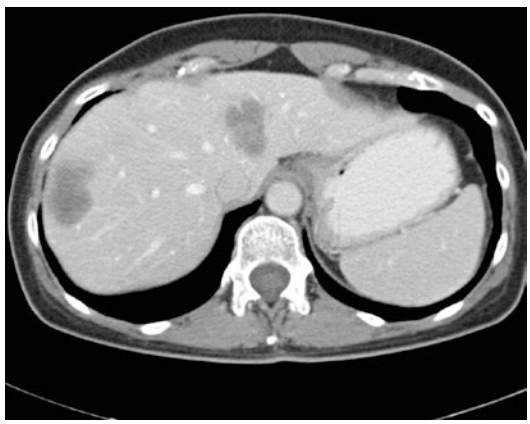

Fig. 27.8 CT of the abdomen demonstrating two liver metastases

Positron Emission Tomography (PET)

- PET is a whole-body nuclear medicine imaging examination utilizing 2-[18F] 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.
- FDG uptake can be assessed both qualitatively (via visual examination of the degree of uptake of a tumor relative to other tissues) and quantitatively (via a 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.
- Although PET has been demonstrated to be more accurate in the assessment of whole-body tumor burden than a combination of conventional imaging, 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.

- 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 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.
- 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, has not been found to be accurate in the assessment of residual tumor in the pelvis. At present, PET is not recommended in the routine evaluation of patients presenting with primary rectal adenocarcinoma but is utilized to evaluate equivocal findings on CT when finding distant metastatic disease would alter management.