Optimal Methods for Staging Rectal Cancer

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Abstract

At present, several modalities exist for the preoperative staging of rectal lesions, including computed tomography (CT), body coil or endorectal coil magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS) done by rigid or flexible probes, and positron emission tomography (PET). Staging accuracy for CT ranges from 53% to 94% for T-stage accuracy and from 54% to 70% for N-stage accuracy. Improved CT accuracy is observed at higher disease stages. Body coil MRI has shown T- and N-stage accuracy ranging from 59% to 95% and 39% to 95%, respectively. Endorectal coil MRI has shown improved T- and N-stage accuracy, with rates of 66% to 91% and 72% to 79%, respectively. The development of phased-array MRI, combining high spatial resolution with a larger field of view, offers promise to improve on these rates. EUS, considered the current gold standard, has shown T-stage accuracy ranging from 75% to 95%, with N-stage accuracy ranging from 65% to 80%. Flexible EUS probes have the advantage of being able to access and sample iliac nodes. Recent studies also suggest that three-dimensional EUS may provide greater accuracy than conventional two-dimensional EUS. Limited studies exist on the use of PET in primary tumor staging. PET may upstage disease in 8% to 24% of patients and has also been used in posttreatment restaging and surveillance. Postradiation edema, necrosis, and fibrosis seem to decrease restaging accuracy in all modalities. This article reviews the current literature about the staging accuracy of the various modalities and suggests a staging algorithm for rectal cancer.

Accurate staging of rectal cancer is necessary to provide the optimal treatment strategy. Staging information includes extent of tumor involvement of the rectal wall and adjacent structures, presence or absence of adjacent lymphadenopathy, and determination of distant metastasis. Preoperative radiation therapy and total mesorectal excision (TME) are increasingly used in the treatment of locally advanced rectal cancer to reduce tumor recurrence. Recent data have shown that preoperative radiation therapy can reduce tumor recurrence from 27% to 11% (1). In addition, TME (a surgical technique that removes the rectum and surrounding mesorectal fat and perirectal lymph nodes and surrounding mesorectal fascia) has been shown to reduce postoperative recurrence to 10% without radiation therapy (2). A recent randomized controlled trial has shown that the combination of these techniques may reduce recurrence to 2.4% at 2 years compared with 8.2% with TME alone (3). Thus, accurate local staging information is paramount for stratifying patients who would benefit from neoadjuvant therapy as well as for predicting the surgical approach. Figure 1 illustrates major decision points that should be addressed in the staging process.

At present, several modalities exist for the preoperative staging of rectal cancer: computed tomography (CT); magnetic resonance imaging (MRI) with traditional body, endorectal, or phased-array coils; endorectal ultrasonography (EUS) with rigid or flexible probes; and positron emission tomography (PET) with and without CT fusion. Typically, a combination of these modalities is used to provide complete staging information. The choice of modality is often influenced by local expertise and availability. This article reviews the current literature about staging accuracy, strengths, and limitations of these modalities and suggests a staging algorithm for rectal cancer.

CT Imaging

CT imaging allows visualization of the entire abdomen and pelvis. Initial data showed CT T-staging accuracy of 79% to 94% in patients with primarily advanced T-stage disease (4–9). T-staging accuracy fell to 52% to 74% when a broader spectrum of tumor sizes was analyzed (10–17). The decrease in accuracy may have been due in part to the lack of detailed spatial and contrast resolution offered by standard CT imaging techniques, leading to diminished accuracy for early-stage lesions confined to the rectal wall. These data suggest that CT T-stage accuracy improves in more locally advanced tumors. Nodal staging accuracy has ranged from 54% to 70% (11, 18). Although improvement in CT imaging (e.g., multidetector row spiral CT) has occurred, data are limited on whether such advances will result in improved locoregional staging accuracy (19). Yet, CT is used routinely in the staging of rectal cancer, mostly for the
evaluation of distant metastasis. Figure 2 illustrates CT staging of a rectal cancer.

**Magnetic Resonance Imaging**

The use of MRI in staging rectal cancer was first reported in 1986 (7, 10). Since that time, MRI has gradually surpassed CT for locoregional rectal cancer staging. The initial studies of MRI in rectal cancer staging were done with a body coil, which lacked the ability to differentiate the layers of the rectal wall. Consequently, T-staging accuracy of 59% to 88% was reported, which was similar to that reported for CT imaging (7, 10, 14, 15, 18, 20, 21). The development of endorectal coils made detailed imaging of the rectal wall possible, with a corresponding improvement in T-staging accuracy of 71% to 91% (22–27). Comparative studies of endorectal coil MRI and EUS have shown similar T-staging accuracy (27–29). However, endorectal coil MRI is hampered by limited availability, high cost, and a diminished field of view due to signal attenuation at a short distance from the coil that can prevent full evaluation of the mesorectal fascia and surrounding tissue (9). In addition, positioning the endorectal coil is difficult in patients with proximal or nearly obstructing tumors, leading to failed coil insertion in up to 40% of patients (30).

The advent of dedicated external coils (e.g., phased-array coils) allowed for high spatial resolution and an enhanced imaging field. Although initial studies of this multiple-surface coil technique in rectal cancer staging revealed disappointing results, compared with standard body coil or CT staging, recent studies with a new generation of coils have improved T-stage accuracy to 65% to 86% (31–39). Nonetheless, these results are less than initially anticipated, and interobserver variability with respect to study interpretation has been substantial. Figure 3 illustrates MR imaging of a rectal cancer.

As is common with other modalities, the primary staging inaccuracy of MRI occurs in differentiating T2 from T3 lesions. Because of the desmoplastic reaction seen adjacent to tumors, MRI typically overstages T2 lesions (9), which makes it difficult to determine whether an irregular outer border of the rectal wall represents perirectal fat being invaded by inflammation alone or a combination of tumor and peritumoral fibrosis.

Nodal staging in rectal cancer is complicated by the fact that micrometastasis can occur in normal-sized nodes (40–43). Although radiologic imaging may detect nodes as small as 2 to 3 mm in size, morphologic criteria alone are poor predictors of whether a node is reactive or metastatic. Consequently, the nodal staging accuracy of MRI has been highly variable, ranging from 39% to 95% (7, 10, 20, 23, 24, 28, 44–48). Recently, MRI with the use of contrast agents, such as ultrasmall superparamagnetic iron oxide, has been proposed as a method of improving nodal staging (49). Ultrasmall superparamagnetic iron oxide undergoes phagocytosis by macrophages in lymph nodes and results in a shortening of the T2 relaxation time and a decrease in signal intensity of normal lymph nodes, which theoretically should improve the detection of micrometastatic nodal disease. Although previous studies in patients with head and neck and urologic tumors have been encouraging, published studies using this agent in staging rectal cancer are lacking.

As mentioned above, predicting a clear circumferential margin at the time of TME is becoming the new standard for
staging accuracy. A recent European study of 408 patients undergoing body coil MRI showed 88% accuracy in predicting whether an clear circumferential margin could be achieved at the time of operation (50). These results are particularly impressive, given that about one fourth of the patients evaluated had undergone neoadjuvant therapy, which is known to reduce staging accuracy.

Rectal EUS

Intraluminal rectal ultrasound examination of rectal lesions can be done with a rigid probe or a flexible echoendoscope. For the purpose of this discussion, both techniques are considered EUS.

EUS has been used to stage rectal cancer since the early 1980s. A recent publication evaluating all EUS studies from 1986 to 2003 in which more than 50 patients were enrolled showed an overall accuracy of 81.8% (51). Although most of the studies had accuracies of 85% to 95%, the composite number was influenced by two large studies, each of which contained more than 400 patients; in these studies, accuracy was lower (i.e., 63.3% and 69%; refs. 52, 53). As with MRI, most inaccuracy results from overstaging of T2 lesions, as EUS cannot reliably distinguish an irregular outer rectal wall image as being due to peritumoral inflammation or transmural tumor extension. Stenotic lesions may present difficulty, as the probe may not be able to traverse the lesion, leading to suboptimal staging. This problem is greater with rigid probes. Catheter probe EUS, which can be done with a standard endoscope, may aid in obtaining accurate tumor staging in the setting of a malignant stenosis. A well-known clinical caveat is that obstructing tumors usually represent at least T3 disease.

EUS nodal staging accuracy is less than that of tumor staging and ranges from 70% to 75% (47, 54, 55). Flexible probes have the ability to evaluate the iliac region for adenopathy, which is clinically important because these nodes are retained in standard TME resection. In one study, up to 28% of lymph node–positive distal tumors showed iliac adenopathy, with 6% of patients having only iliac adenopathy (56). Thus, failure to evaluate this region could lead to inadequate surgical margins in up to 6% of patients with low rectal lesions. Morphologic characteristics suggestive of malignant involvement include hypoechoic appearance, round shape, peritumoral location, and size >5 mm (57). An early study showed that lymph nodes >5 mm in size have a 50% to 70% chance of being malignant compared with only 20% of nodes <4 mm (58). EUS-guided fine-needle aspiration (FNA) allows confirmation of malignancy in suspicious nodes during the same examination, as long as the primary tumor does not lie in the path of the needle. Although initial studies differed on the role of EUS-guided FNA, a recent study of 457 patients showed the value of FNA, particularly in identifying distant malignant adenopathy (59). Seven percent of patients (32 of 457) had iliac adenopathy, with 47% of the nodes (15 of 32) having confirmed malignancy by FNA. Of note, only 47% of patients (7 of 15) with malignant adenopathy had adenopathy on CT. Figure 4 illustrates EUS imaging and the role of EUS-guided FNA in rectal cancer staging.

Three-dimensional EUS consists of the traditional transverse scan as well as coronal and sagittal scans that allow for a multiplanar display. This procedure has been found to be superior to CT and two-dimensional EUS in accurately determining tumor margins. The three-dimensional reconstruction is also thought to improve visualization of subtle protrusions of tumors infiltrating into adjacent tissues and organs, allowing for improved T and N staging. An initial study of 25 patients undergoing three-dimensional EUS, two-dimensional EUS, and endorectal MRI showed no significant difference in T- or N-stage accuracy, but it was thought that endorectal MRI and three-dimensional EUS improved understanding of the spatial relationship of the tumor due to their ability to obtain multiplanar imaging (30). A more recent study of 86 patients who underwent three-dimensional EUS, two-dimensional EUS, and endorectal EUS (using a rigid probe), and four-channel multidetector CT showed T-stage accuracy of 78%, 69%, and 57%, respectively; N-stage accuracy was 65%, 56%, and 53%, respectively (60). However, examiner errors in interpretation were found in 47% of two-dimensional EUS studies and 65% of three-dimensional EUS studies. When these images were correctly interpreted, T-stage accuracy improved to 91% for three-dimensional EUS and 88% for two-dimensional EUS and N-stage accuracy improved to 90% and 76%, respectively. This study shows promise for three-dimensional EUS while highlighting the highly operator-dependent nature of EUS data.

Positron Emission Tomography

PET uses the glucose metabolism of malignant cells to discriminate tumor from benign fibrosis. In rectal cancer, PET has been used primarily in detecting recurrent disease. Although not routinely used for the staging of primary rectal...
tumors, PET is increasingly being used in combination with CT to aid in the detection of nodal and distant metastasis. Limited data exist in the preoperative setting, but recent studies have found preoperative PET to change preoperative management in 17% of patients (61), predict postoperative survival (62), and improve staging accuracy in combination with CT (63). Figure 5 illustrates PET imaging in rectal cancer.

Staging Accuracy Post-Neoadjuvant Therapy

As neoadjuvant therapy has become more common in the treatment of rectal cancer, restaging studies before planned operative resection are being done with increasing frequency. A recent study comparing EUS staging accuracy in patients not receiving neoadjuvant therapy with patients receiving neoadjuvant therapy noted a decrease in T-staging accuracy from 86% to 72% and a slight improvement in N-staging accuracy from 71% to 80% (64). However, EUS in the post-treatment setting predicted T0N0 disease correctly in only 50% of patients, and similarly, poor results have been observed with CT and MRI. The reduction in staging accuracy is due to postradiation edema, inflammation, fibrosis, and necrosis. A recent study of 29 patients undergoing neoadjuvant therapy and pretreatment and posttreatment staging with CT, MRI, and PET showed that PET was 100% sensitive in predicting response to therapy (compared with 54% for CT and 71% for MRI; ref. 65). Corresponding specificity for predicting tumor response to treatment was 60%, 80%, and 67% for PET, CT, and MRI, respectively. The investigators opined that PET was superior to CT and MRI in predicting response to neoadjuvant therapy. At present, staging post-neoadjuvant tumors remains problematic and will likely require improved imaging techniques and a combination of structural (CT, MRI, and EUS) and functional (PET) imaging to achieve improved staging accuracy.

Suggested Algorithm

Based on the currently available literature, EUS or phased-array MRI seem to be appropriate initial studies for local tumor
staging. EUS seems to provide more accurate staging for mobile T1 and T2 lesions, whereas MRI seems to be superior for fixed, more locally advanced disease. However, both modalities provide comparable overall T- and N-staging, with EUS currently being the less expensive of the two. Recent studies support the high accuracy of MRI in predicting a clear circumferential resection margin in patients undergoing TME. Both modalities are limited by issues of availability and operator dependence. In contrast, CT scanning cannot be considered appropriate for local tumor staging at present, although additional studies with multidetector CT are warranted. CT is the current standard for distant staging, but the combination of CT and PET offers the promise of both anatomic and functional imaging over a wide area and is rapidly gaining acceptance.

Conclusion

Accurate staging of rectal lesions is critical in determining both the need for preoperative therapy and when a local or more radical excision is needed. Currently, a combination of locoregional staging with EUS and/or MRI with CT or CT-PET for evaluation of distant metastasis seems to be the best approach for obtaining accurate clinical staging. Posttreatment staging before operation continues to be suboptimal, and enhancements to current techniques and the use of PET will hopefully improve these results. Future improvements should be pursued for a single test, such as phased-array MRI or multidetector CT in combination with PET, to provide complete and accurate staging information.

References


Discussion: Diagnostic Issues in Early-Stage Disease

Dr. Carolyn Compton: Is node suspiciousness based on size alone?

Dr. Kenneth Chang: Yes, but on endoscopic ultrasonography (EUS), size, shape, and echotexture are used to determine criteria for malignancy.

Dr. Al Benson: Do you report tumor volume as a moment in time or a continuum? How would you actually calculate volume in terms of the entire tumor volume?

Dr. Chang: Work is being done on three-dimensional EUS where you can recreate the entire tumor in 3-D and calculate a true volume. Currently, we are taking two-dimensional, real-time images in cross-section.

Dr. Benson: So, you only have a moment in time?

Dr. Chang: Yes, we pull back and forth multiple times from one end of the tumor to the other and determine the largest area of involvement. We freeze that picture and highlight the circumference of the tumor using a tracer. The surface area is calculated in centimeters squared and is called T max. Studies have shown that reducing T max by 50% after neoadjuvant therapy is a predictor of favorable outcome and surgical response. Furthermore, it’s far better than merely comparing at pre- and post-T stage.

Dr. Daniel Haller: Studies on operator dependency of EUS and magnetic resonance imaging (MRI) come from experts at one institution. However, in real life, we know from the German trial that 20% of patients were treated because of EUS results and did not need such treatment (i.e., the group assigned to receive surgery first did not have the disease that they were thought to have). It’s my understanding that people are more likely to be over- than understaged by EUS or MRI, especially with regard to T stage.

Dr. Chang: Operator dependency is definitely a major consideration in EUS. However, even with CT or MRI, there is some degree of operator dependency with interpretation.

Dr. Haller: Is overstaging from the T standpoint more likely when patients undergo surgery?

Dr. Chang: With a true T2, there tends to be more of a chance to overstage, whereas with T3, there is more of a chance to understage. CT can sometimes be confusing if you are trying to determine lymph node status. This is improved somewhat with CT/PET fusion. CT is probably the most commonly used staging modality. However, the literature suggests that CT is not as accurate for local staging, compared with MRI or EUS. CT is obviously still useful for assessing distant metastasis, but MRI may be more accurate for distant staging, as well as local staging, and assessing the circumferential resection margin. EUS is still the best modality for T staging. CT/PET may have a role in assessing response to neoadjuvant therapy. We have many options, and the question becomes: which modality or combination is the most efficient and effective? Currently, in our center, we are relying on the combination of CT and EUS for preoperative staging.

Dr. Patrick Lynch: Could you comment further on the factors that conspire to the overstaging of T2 tumors?

Dr. Chang: If you have a tumor that is deep into the submucosa, but not obviously going into the muscularis propria, you may be inclined to say that it is a T3 because the outer border of the muscularis propria is somewhat irregular.

This irregularity could be an inflammatory or desmoplastic reaction to the tumor. If I don’t see contiguous, hypoechoic infiltration through the submucosa into the muscle layer, despite an irregular outer border of the muscularis propria, I would still interpret it as a T1 lesion. However, if I see contiguous infiltration into the muscle plus irregularity on any other side with some break away lesions, I feel very comfortable calling it a T3.

Dr. Haller: Has an endoscopic ultrasound society established recommendations for what one calls a T2 or T3 tumor or is this completely operator dependent?

Dr. Heidi Nelson: It’s completely operator dependent. As a believer in neoadjuvant and even postoperative adjuvant therapy, I think that if a tumor is node negative, you get down to the fine points. If it is T2, how much T2? If it is T3, how much T3?

Dr. Haller: It seems as though every institution and ultrasonographer has a different definition of T2 and T3. As imperfect as it is, at least the American Joint Committee on Cancer presents a common definition. Overtreating with radiation is even more expensive and toxic than adjuvant chemotherapy.

Dr. Nelson: Again, you are right, so if my ultrasonographer says it’s node negative and T3, I ask, how much T3? Is it just barely T3?

Dr. Compton: The critical cut point is 5 mm. There is a big difference in risk between a tumor that is 5 mm beyond the muscle wall.

Dr. Nelson: If a tumor is node negative, barely T3, and a few millimeters outside of the muscularis, I may go ahead with surgery and not administer neoadjuvant therapy because there is a 20% chance of overstaging. A patient would then receive radiation that he or she didn’t need.

Dr. Haller: Right, especially if sphincter preservation is not the issue.

Dr. Michael Stamos: The problem is that more of these patients are likely to be node positive than are over staged by EUS, at least at our institution. The patient will now receive postoperative radiation, which has more complications than preoperative radiation.

Dr. Compton: The College of American Pathologists has a proficiency testing program for many tests whereby the people who are performing the tests are tested for competence. Is there an equivalent test here?

Dr. Compton: A pathology report on a resection specimen that has no report of any lymph node status should never be accepted. If less than 12 lymph nodes are found, the pathologist should be dissatisfied with the number and reexamine the specimen. If on reexamination, which can be anything from fat clearing to carving off all of the extramural fat and putting all through for microscopic elevation, 12 lymph nodes are still not found, the pathology report must be appropriately documented, as it is a permanent part of the medical record. It is important for the pathologist to explain why the magic number is not being found. The primary responsibility should fall with the pathologist.

Dr. Lee Rosen: Let me push further. We have 10 lymph nodes. The pathologist has done a great job and both the surgeon and medical oncologist have asked questions. Does this suffice to make treatment decisions?

Dr. Robert Beart: If all of the lymph nodes in the specimen have been examined and there was an adequate resection and
no positive lymph nodes, we have adequate information. If for some reason the resection was inadequate, I don’t think we know.

**Dr. Compton:** We have all agreed about the fictional flavor of operative reports and that it’s virtually impossible to determine if the resection is adequate from reading such reports. If the pathology exam of the specimen is a form of quality control, the argument is circular. The very fact of finding fewer than the magic number may be an indicator of poor-quality surgery, which is the circular argument and a difficult issue to resolve. Surgeons need to be more meticulous about reporting the surgical parameters of the resection in the operative report.

**Dr. Axel Grothey:** We are not talking about the completeness or radicality of the surgery when we talk about lymph nodes only. If only 10 lymph nodes are found, it’s 10 lymph nodes. But, does this convey information about immune status? It’s a prognostic parameter independent of the resection and is more of an independent statement on prognosis (i.e., how many lymph nodes a patient is able to produce in response to the tumor). So, if there are 10 lymph nodes, is the prognosis poor from all that we know? The answer is “yes”. When I see a patient with stage II disease, if there is one high-risk factor from a primitive point of view (obtained from the surgical report, pathology report, patient characteristics, perforation, etc.), I place this patient in a high-risk category.

**Dr. Anton Bilchik:** Let’s say that the pathology report comes back as moderate differentiation in a 63-year-old patient with a T3 lesion and 8 negative lymph nodes. Should you this patient receive chemotherapy or would you ask the pathologist to reexamine the specimen first?

**Dr. Grothey:** I would definitely ask the pathologist to reexamine the specimen. The responsibility should rely with the pathologist in the first place, but we medical oncologists should have a gatekeeper function.

**Dr. Beart:** I don’t view the operative report as fiction, but do think that it often lacks critical information. I think that the surgeon should dictate where the vessels were ligated.

**Dr. Lynch:** Saying that the operative report is fictional is like saying that the pathology report is fictional. I think we have to assume the integrity of the people with whom we are dealing.

**Dr. Rosen:** We are talking about checks and balances.

**Dr. Compton:** If there is no statement in the operative or pathology report about nodes or ligation levels, the person reading the report has no idea what really happened and whether the person doing the procedure had any notion of the importance of their role. At that point, it’s not meaningful, and you always have to assume the worst.

**Dr. Rosen:** How do we rank the importance of the various prognostic factors?

**Dr. Bilchik:** At present, lymph node evaluation is the single most important prognostic factor in colon cancer.

**Dr. Compton:** Given the data overall, I agree. We must establish some kind of stable yardstick by which to measure the benefit of using proteomic or genomic approaches and define the benefits of the comparators. If we don’t have a really well-defined baseline, the “compared to what” question cannot be answered, and we are in that position right now. We have not yet established any objective criteria.

**Dr. Rosen:** The criteria are not equally weighted, which is a very important point.

**Dr. Lynch:** In the average pathology department, is the gross specimen maintained well enough that one could go back and address the adequacy of the lymph nodes?

**Dr. Compton:** Yes, the specimen is retained for a certain amount of time until the final diagnosis has been issued. This procedure is addressed by laboratory accreditation standards.

**Dr. Bilchik:** In what percentage of reevaluated patients are more lymph nodes found?

**Dr. Compton:** In one study, 21 lymph nodes were found on average during diligent gross examination. On reexamination of every specimen, all of the extramural soft tissue was stripped off. On microscopic examination, the number of lymph nodes tripled.