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Clinical Practice Guidelines – Gastrointestinal Disease Site

Guideline Title:	Pre-operative Staging of Primary Rectal Cancer	**Date:**	**(O):** **(R):**	Nov 30, 2011
Tumor Group:	G. I. Disease Site Group	**Page:**		1 of 8
Issuing Authority:	Dr. Jehann Siddiqui Clinical Chief, Cancer Care Program	**Date Signed:**		Oct 21,2013
Adapted From:	New Zealand Guidelines Group "Management of early colorectal cancer" guideline, May 2011 (32).			

Introduction:

Colorectal cancer is the second leading cause of cancer related deaths in Canada (8900 estimated deaths in 2011) and the fourth most common cancer diagnosis overall (22,200 estimated new cases in 2011) (1). The location of the tumors within the bowel has a major impact on its management and prognosis. About one third of all colorectal cancers in Canada originate in the rectum. The anatomical definition of rectal cancer is any tumor located 15cm or less from the anal verge. Rectal cancer is associated with a poorer prognosis when compared to colon cancer, presumably due to its location within the narrow confines of the pelvis and proximity to other organs and nerves. The primary aim of treating rectal cancer is cure, but consideration must be given to quality of life issues, such as anal sphincter preservation, genitourinary function and sexual function, where this is possible.

Total mesorectal excision (TME) refers to the en bloc removal of the rectum and mesorectal contents within an intact mesorectal envelope. The use of TME and the introduction of preoperative radiation and chemotherapy have been successful in reducing local recurrence in locally advanced rectal tumors. Even with radical treatment, there is still the risk of local failure. Until recently, pre-operative imaging wasn't consistently capable of discerning which patients would require neoadjuvant therapy, potentially leading to overtreatment in some cases (2). However, advances in pre-operative imaging now allow for the identification of those patients likely to benefit from these new preoperative or neoadjuvant therapies.

Question:

What are the optimal staging investigations for patients with rectal cancer?

Target Population:

These recommendations apply to all patients with a newly diagnosed primary cancer of the rectum.

Supporting Evidence:

The benefits of preoperative concurrent chemoradiotherapy in the treatment of locally advanced rectal cancer include reduced local recurrence and potentially improved overall survival (3-5). In North America, patients with clinical Stage I rectal cancers are treated with surgical resection alone, while those with stage II and III lesions may undergo preoperative combined chemoradiation, followed by surgical resection. Preoperative therapy may also be considered for those with earlier stage cancer to increase the opportunity for sphincter preservation (3). Pre-operative staging provides crucial information such as:

- the T stage or extramural depth,
- circumferential resection margin of the tumor (CRM) (tumor <1mm to mesorectal fascia),
- extramural vascular invasion (present or not),
- lymph node involvement,
- peritoneal perforation by tumor,
- location of the primary tumor with respect to the anal sphincter and peritoneal reflection,
- possible evidence of distant metastatic disease (6).

This information enables the colorectal team to rationalize the potential benefits of neoadjuvant therapy.

Imaging Modalities

There are many different imaging modalities that could be used for rectal cancer staging and tumor localization but not all have the same level of accuracy. These include:

- Intraluminal Endoscopic Ultrasound (EUS) - is carried out with the aid of a flexible or rigid ultrasound probe. In studies *excluding fixed tumors, tumors of the upper rectum, and bulky or stenosing tumors*, the accuracy of T staging has been reported to be 90% using EUS (6). A study of 1184 patients with rectal cancer confirmed that EUS is very accurate for early-stage low tumors (T1 and T2) with a sensitivity of 94% and specificity of 86%, but it performs less well in cases of advanced rectal cancer (7).

A recent study concluded that the overall accuracy in determining metastatic nodal involvement by EUS is approximately 70% to 75%. This is compared with 55% to 65% for CT and 60% to 70% for MRI (8). However, another study which reviewed the pathological technique used during EUS found that while EUS can detect lymph nodes that are 5mm or greater in size, its accuracy decreases for metastatic lymph nodes <5mm in diameter. This is a disadvantage since early data has determined that an estimated 50% of metastatic lymph nodes associated with rectal cancers are smaller than 5mm (9).

In a retrospective study of over 17,000 patients with rectal cancer, CRM was found to be a better predictor of local recurrence for patients undergoing surgery as initial therapy than for those receiving preoperative therapy (10). EUS cannot visualize the mesorectum and peritoneum and thus cannot determine CRM status or degree of peritoneal involvement. EUS is not always reliable in being able to distinguish between fibrosis and tumor or whether the mesorectal fascia is involved. One of the main criticisms of this technique is that it is

operator dependent, with less experienced sonographers providing less accurate results. Even in the hands of an expert, a technically difficult EUS may give an inconclusive or inaccurate result for both T stage and N stage (11).

Another disadvantage of the EUS is that it is an invasive procedure and potentially uncomfortable for the patient. However, when compared to magnetic resonance imaging, EUS is relatively widely available and inexpensive.

- Magnetic Resonance Imaging (MRI) – is able to very accurately delineate rectal cancer size, location and mural extension. Several studies have established agreement between MRI findings and histopathology with respect to T stage, one of which was a prospective study that showed a 94% agreement between MRI and pathologic assessment (12). The Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) study was a multicenter prospective study which evaluated the accuracy of MRI in depicting the extramural depth of tumor invasion in 211 patients with histopathologic results as the reference standard (13). This study showed MRI and histopathologic measured tumor depth to be equivalent.

Some studies suggest that the accuracy of MRI when predicting lymph node involvement is as high as 85% (13). Others suggest it is less efficacious, with a sensitivity and specificity of 66% and 76%, respectively (14). No imaging modality can reliably identify lymphatic micrometastasis. Another prospective observational study by the MERCURY Study Group, involving 408 consecutive patients from 12 colorectal units in 4 European countries, investigated the accuracy of high-resolution MRI to detect involvement of the surgical CRM (15). The MERCURY radiologists defined CRM involvement as tumor within 1mm of mesorectal fascia. The results found the technique to be highly accurate and reproducible in the multicenter setting with 92% specificity.

MRI also has the ability to detect extramural vascular invasion (EMVi), which is believed to be an important prognostic factor that identifies patients at risk of both local and distant metastases. A retrospective study which reviewed 142 patients with a median follow-up of 3.3 years revealed a 4-fold higher risk of distant metastases (52% versus 12%) and a decreased 3-year relapse-free survival of 35%, when EMVi was present on preoperative MRI versus no EMVi (16).

According to the MERCURY Study Group, peritoneal infiltration can be identified by MRI as an intermediate signal intensity protrusion through and beyond the anterior peritoneal surface of the rectum (13).

- Computed Tomography (CT) – in patients with advanced T-stage disease, the accuracy of CT T-staging was found to be 79% to 94%, but decreased to 52% to 74% when smaller tumor sizes were included due to lack of spatial and contrast resolution (17).

Routinely, the size of lymph nodes on CT imaging predominantly determines whether metastases are likely, with nodes larger than 1cm being considered abnormal. The sensitivity of CT detection of lymph node involvement for rectal cancer is very poor at only 22% to 73%, since a large proportion of metastatic lymph nodes are smaller than 5mm (18).

The sensitivity and specificity of determining CRM status remains unacceptably poor while other prognostic factors such as EMVi, nodal assessment of the mesorectum, and peritoneal perforation are not reliably assessed (19-21). The evidence suggests that CT is most helpful for staging distant metastatic spread but provides only limited local staging information.

- Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)/CT Scanning – allows visualization of metabolic changes within cancer cells. FDG-PET has poor spatial resolution and therefore cannot provide detailed anatomy which prevents an accurate determination of the degree of local tumor spread, EMVi, CRM status, or the relationship to the sphincter complex. Studies have shown that PET/CT scanning can reliably detect colorectal cancer but not its depth of invasion and hence, T stage. Also, FDG-PET has a reported sensitivity of only 29% at predicting lymph node involvement. Therefore, it is not recommended for local staging of the primary tumor (22).

Comparative Evidence of Imaging Modalities

Several systematic reviews and meta-analyses of varying qualities were reviewed which examined the use of imaging techniques in the preoperative staging of rectal cancer.
One of these systematic reviews completed a **high-quality** review of 90 studies encompassing 299 data sets and reported pooled diagnostic performance for each of the modalities at different stages of the disease. For muscularis propria invasion, EUS and MRI had similar sensitivities; specificity of EUS (86%) was higher than MRI (69%). For perirectal tissue invasion, sensitivity of EUS (90%) was significantly higher than that of CT (79%) and MRI (82%); specificities were comparable. For adjacent organ invasion and lymph node involvement, estimates for EUS, CT and MRI were comparable. The summary receiver operating characteristic (ROC) curve for EUS of perirectal tissue invasion showed better diagnostic accuracy than that of CT and MRI. Summary ROC curves for lymph node involvement showed no difference in accuracy (14).

The other systematic review, of **average quality**, compared the ability of MRI, CT and EUS to detect CRM involvement and nodal status in the staging of rectal cancer. Seven studies reviewing CRM status were identified. All used MRI and demonstrated sensitivity ranging from 60% to 88% and specificity ranging from 73% to 100%. The summary ROC curve suggested a false positive rate of approximately 20%. Eighty-four studies of nodal status were included (EUS=54, MRI=29, CT=18), with EUS having a better pooled diagnostic odds ratio than CT or MRI. When summary ROCs were compared, there was no significant difference in the performance of the three modalities in predicting nodal status. MRI was recommended as the only modality that detects CRM involvement with any accuracy (23).

The diagnostic performance of MRI in predicting CRM involvement in rectal patients was examined by one **good-quality** systematic review. Nine studies were included with both pooled sensitivity (94%, 95% CI 90-97%) and specificity (85%, 95% CI 81-89%) being relatively high. Subgroup analyses indicated that study quality, the type of magnet and coil that were used, and the number of interpreters of the imaging affected how well MRI predicted CRM involvement. However, the number of studies included in some of these subgroup analyses was small. The authors suggested MRI should be used as the primary imaging modality in local staging of rectal cancer (24).

Several National and International clinical practice guidelines were reviewed in the development of this guideline. Though there was disagreement between studies, with regards to the best overall primary imaging modality in local staging of rectal cancer, the New Zealand Guidelines Group (NZGG) agreed that MRI appears to be the only imaging modality that can detect CRM involvement. Some authors suggest that EUS and MRI should be used as complementary modalities: EUS as a general diagnostic tool and MRI to detect CRM involvement. Saskatchewan Cancer Agency (SCA) based its guideline on the recommendations of the European Society of Medical Oncologists (ESMO) which recommends EUS for the earliest tumors (cT1-T2) or rectal MRI for all tumors, including the earliest ones, in order to select patients for preoperative treatment and extent of surgery (25). The National Cancer Institute of United States (NCI) recommends MRI to determine depth of penetration and the potential for achieving negative CRM, as well as to identify locoregional nodal involvement and distant metastatic disease. The National Comprehensive Cancer Network (NCCN) notes that a disadvantage of EUS is a high degree of operator dependence. An advantage of MRI is its ability to provide accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia. Hence, MRI evaluation of patients with more advanced rectal cancer has the potential to provide information useful in the prediction of the CRM prior to radical surgery.

Recommendations:

The following recommendations of the Eastern Health G. I. Disease Site Group apply to patients with a pathologically confirmed cancer of the rectum:

- All patients should undergo history and physical exam, complete blood count, renal and liver function tests, and carcinoembryonic antigen (CEA) tumor marker testing.
- All patients should also undergo digital rectal examination (DRE), rigid proctoscopy (to determine tumor location and distance from the anal verge), and total colonoscopy (to rule out synchronous lesions or other pathological conditions).
- All patients should undergo biopsy of the rectal primary tumor.
- A baseline CT scan of chest/abdomen/pelvis should be performed on all patients with ≥ T2 disease.
- MRI of the pelvis is recommended to confirm T stage and assist in nodal staging. Patients with obvious T3/T4 or node positive disease based on other clinical findings may forego the MRI, if this is an obstacle to timely management.
- Routine use of PET/CT scanning as part of baseline staging is not recommended at this time.

Search Strategy:

Literature searches were conducted in PubMed, Embase, and the Cochrane Library, using keywords “rectum” AND “neoplasms” AND “neoplasm staging”, as well as an extensive manual search of the reference lists of available literature articles. Guideline searches were also carried out on the websites of the world’s most highly respected cancer organizations and agencies. All selected literature articles and source guidelines were in English and dated after the year 2000 (unless the selection was an earlier landmark study) up to November 2011. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Twelve source guidelines were identified and conformed to our search criteria (25-36), from which five were selected due to currency, quality of content and/or were Canadian in origin (28,32-34,36).

The six identified source guidelines were put through the ADAPTE process (37) with an AGREE II assessment (38), and the New Zealand Guidelines Group (NZGG) “management of early colorectal cancer” guideline was chosen to be adapted for use in our guideline (32). The NZGG guideline was selected as the optimal choice due to its applicability, quality and currency of content.

There has been much debate but no consensus on the ‘grading of evidence’ in Canada. Presently, Canadian experts in the field of guideline development are involved in an ongoing in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.
No competing or conflicts of interest were declared.

Disclaimer:

These guidelines are a statement of consensus of the G.I. Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

Contact Information:

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