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A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Optimization of Preoperative Assessment in Patients Diagnosed with Rectal Cancer

*E. Kennedy, E. Vella, D. B. MacDonald, S. Wong, R. McLeod, and the Preoperative Assessment
for Rectal Cancer Guideline Development Group*

Report Date: January 20, 2014

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Section 1: Guideline Recommendations

Section 2: Evidentiary Base

Section 3: Development Methods, Recommendations Development and
External Review Process

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Rectal Cancer**

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Evidence-Based Series #17-8: Section 1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Optimization of Preoperative Assessment in Patients Diagnosed with Rectal Cancer

Guideline Recommendations

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Report Date: January 20, 2014

GUIDELINE OBJECTIVE

To provide the optimal strategy to assess patients diagnosed with rectal cancer prior to treatment. This includes:

1. Investigations [chest X-ray or computed tomography (CT) thorax/abdomen/pelvis, colonoscopy, serum carcinoembryonic antigen] to assess for distant metastases and synchronous lesions in patients with rectal cancer
2. Imaging [magnetic resonance imaging (MRI) pelvis, endoscopic ultrasound (EUS), transrectal ultrasound (TRUS), CT pelvis] for local staging of rectal cancer
3. The optimal MRI protocol to locally stage rectal cancer
4. The optimal MRI criteria to locally stage rectal cancer
5. The optimal MRI criteria to select patients for neoadjuvant therapy
6. The role of multidisciplinary cancer conferences (MCCs)
7. The role of restaging MRI after neoadjuvant therapy

TARGET POPULATION

Newly diagnosed patients with rectal cancer¹ undergoing elective treatment comprise the target population.

INTENDED USERS

This guideline is intended for radiologists, surgeons, radiation oncologists, medical oncologists, and pathologists. This guideline coincides with the introduction of colorectal cancer Diagnostic Assessment Programs in Ontario. Diagnostic Assessment Programs provide coordination of care using a clinical navigator, fast tracking of diagnostic tests and a multidisciplinary team approach. They are an Ontario-wide strategic priority designed to

¹ Rectal cancers are defined as adenocarcinomas that lie between the termination of the sigmoid colon, usually at the level of the sacral promontory, and the dentate line. The mesorectum and its enveloping mesorectal fascia end at the pelvic floor or top of the puborectalis sling, while the most distal aspect of the rectum ends at the dentate line. The rectum is divided into three sections: lower rectum (0-5 cm from anal verge), mid rectum (5-10 cm from anal verge) and upper rectum (10-15 cm from anal verge). Rectal tumours are classified according to their location relative to the peritoneal reflection anteriorly, i.e., entirely above, astride or entirely below the peritoneal reflection.

improve patient access and outcomes, and are outlined in *Ontario Cancer Plan 2005-2011* and *Ontario Cancer Plan 2011-2014* (1).

RECOMMENDATIONS AND KEY EVIDENCE/JUSTIFICATION

RECOMMENDATION 1

- Staging for all rectal cancer patients should include:
 - CT of the abdomen and pelvis
 - CT of the chest or chest X-ray.
- Complete colonic examination by colonoscopy should be performed preoperatively, if possible.
- Serum carcinoembryonic antigen (CEA) should be assessed preoperatively.

Qualifying Statements

- While CT chest is preferred, chest x-ray may be used as an alternative method of chest imaging. The choice of CT of the chest or chest X-ray should be consistent with the modality used for postoperative surveillance. If CT of the chest is used for postoperative surveillance, then CT of the chest should be done at the same time as staging CT of the abdomen and pelvis. If chest X-ray is used for postoperative surveillance, then CT of the chest is recommended only if abnormalities requiring further investigation were found on chest X-ray.
- When CT of the chest is performed in combination with CT of the abdomen and pelvis, intravenous contrast is recommended. However, when CT of the chest is the sole investigation, intravenous contrast is potentially helpful but not required.
- If the use of intravenous contrast is contraindicated, abdominal MRI or ultrasound may be used to supplement CT to further assess for liver metastasis.
- Colonoscopy is preferred but CT colonography can be used to complete the assessment when the colonoscopy is incomplete. If not completed preoperatively, a complete colonoscopy should be performed postoperatively.
- This recommendation applies to patients undergoing elective treatment only (i.e., does not include patients with obstruction or perforation).

Key Evidence/Justification

This recommendation was adapted from the NICE 2011, NZGG 2011, SIGN 2011 and PEBC 2006 guidelines, which were based on consensus, as there were no high-quality studies to support this recommendation (2-5). While NICE 2011 and SIGN 2011 have recommended CT of the chest, NZGG 2011 and PEBC 2006 have recommended chest X-ray. The main advantages of CT of the chest discussed by the Guideline Development Group include: (i) the early detection of pulmonary nodules that may lead to a change in management (i.e., first-line chemotherapy, metastasectomy) (6) and (ii) a baseline CT of the chest for comparison if CT of the chest is used for postoperative surveillance. The main disadvantage of CT of the chest discussed by the Guideline Development Group included the high sensitivity and low specificity of CT to detect indeterminate pulmonary nodules and lack of consensus as to how these nodules should be managed (7). The cost of performing a CT of the chest was discussed by the Guideline Development Group and was considered to be neither an advantage nor disadvantage, as the added cost and time required to conduct a CT of the chest in conjunction with a CT of the abdomen/pelvis is minimal. Although there is limited evidence, the Guideline Development Group has made the recommendation to endorse CT of the chest for pulmonary staging. The main reasons for this were the increased risks of pulmonary

metastases alone with rectal cancer compared to colon cancer (8,9) and the ability to have a baseline CT chest for comparison during the surveillance period.

Serum CEA was recommended preoperatively only by the NZGG 2011 and postoperatively by NZGG 2011, NICE 2011 and SIGN 2011 (2-4). The evidence for these recommendations were based on four meta-analyses that show intensive follow-up programs that include CEA testing lead to significantly improved overall survival and detection of asymptomatic recurrences compared to a less intensive follow-up. The advantages of preoperative CEA testing discussed by the Guideline Development Group include: (i) the recommendation and evidence for CEA testing for postoperative surveillance and (ii) limited value of postoperative CEA testing if no preoperative CEA is available for comparison. The Guideline Development Group did not identify or discuss any disadvantages to use of preoperative CEA testing. Therefore, a recommendation to perform preoperative CEA was made and is consistent with the colorectal cancer Diagnostic Assessment Programs in Ontario.

RECOMMENDATION 2

- Patients with rectal cancer should undergo MRI pelvis in order to assess T and N categories and the distance to the MRF [(i.e., potential circumferential resection margin (CRM))].

Qualifying Statements

- For the purpose of this guideline, the distance to the mesorectal fascia (MRF) will be used and represents the potential CRM. The use of the term MRF is more appropriate, because CRM is a pathologic term determined by the extent of surgical resection.
- For low rectal cancer, defined as 0-5 cm from the anal verge, if local excision (with transanal excision or transanal endoscopic microsurgery) is being considered, transrectal ultrasonography (TRUS) performed by those with demonstrated expertise is preferred to MRI, in order to more accurately discriminate between T1 and T2 lesions. TRUS should not be used to predict CRM involvement.
- For upper rectal cancers, defined as 10-15 cm above the anal verge, in which the mesorectal fascia is not threatened, MRI may not provide significantly more information than CT of the pelvis.
- MRI is used for local staging of the rectum and does not adequately assess regional disease at the level of the inferior mesenteric artery or distant disease; CT of the abdomen and pelvis should be used to assess for distant metastases and regional disease including lymph node involvement along the inferior mesenteric artery.
- If there are contraindications to MRI, CT of the pelvis and/or TRUS are recommended.

Key Evidence/Justification

The evidence for this recommendation was based on the NICE 2011, NZGG 2011, SIGN 2011 and PEBC 2006 guidelines (2-5). These guidelines discussed the results of two systematic reviews by Kwok et al 2000 and Bipat et al 2004 that assessed the diagnostic accuracy of MRI, CT and US for T and N category (10,11). These studies showed that ultrasound had the highest sensitivity and specificity for T-category, followed by MRI and CT, respectively. Two additional systematic reviews assessing the diagnostic accuracy of MRI only to assess MRF involvement have shown that MRI has good sensitivity and specificity to predict MRF involvement (12,13). Taken together, these studies suggest that transrectal ultrasound has the best diagnostic accuracy for T-category, in particular T1 and T2 tumours, followed by MRI and CT, and MRI has the best diagnostic accuracy to detect MRF involvement. Therefore, based on these studies, we have recommended MRI as the modality of choice for preoperative staging of rectal cancer. To date, there are only a few, poor-quality studies that have directly compared the diagnostic accuracy of CT and MRI for the prediction of MRF involvement, and

therefore, there is currently insufficient evidence to support the use of CT to assess distance to the MRF and MRF involvement. However, many experts would likely consider the added benefit of MRI relative to CT relatively small for the assessment of upper rectal and rectosigmoid tumours in which the mesorectal fascia (i.e., potential CRM) is not threatened or involved.

The reviews by Kwok et al 2000, Bipat et al 2004, and Lahaye et al 2005 also show that all modalities have moderate accuracy to detect nodal involvement (10-12). Therefore, the Guidelines Development Group endorsed the recommendations from the NICE 2011, SIGN 2011 and NZGG 2011 guidelines to use MRI for local staging of rectal cancer.

RECOMMENDATION 3

- At a minimum, axial, coronal and sagittal T2-weighted images of the pelvis and high-resolution T2-weighted sequences perpendicular to the long axis of the rectum at the level of the tumour using phased-array coil are required.

Qualifying Statements

- A high-resolution MRI meets the specifications outlined by the MERCURY Group Protocol and is shown in Appendix 1.
- For low rectal cancer, coronal high-resolution images along the long axis of the anal canal should be considered in addition to or instead of the long axis of the rectum in order to better assess the relationship of the tumour to the sphincter components.
- Additional sequences, bowel preparation, anti-peristaltics, luminal distension, and intravenous contrast are believed to be supplemental and are not a mandatory requirement for a high-quality MRI.

Key Evidence/Justification

A review of the literature for MRI protocols including optimal sequences, bowel preparation, enemas, anti-peristaltic agents, and intravenous contrast was performed. There was only one study that suggested rectal distension may improve the accuracy of T-category assessment while having little effect on MRF or lymph node involvement (14).

Four studies assessed use of gadolinium-enhanced T1 images compared to T2 unenhanced images (10,15-17). However, these studies generally found no difference in T or N staging, and therefore, use of gadolinium was not recommended as a mandatory component of the MRI protocol. Two meta-analyses demonstrated that multiple readers resulted in better prediction of T category and MRF involvement than when these criteria were assessed by single readers (13,18). While consensus reading is preferred, due to issues with respect to work load and feasibility, The Guideline Development Group also did not recommend this manoeuvre as a mandatory component of the MRI protocol.

Based on these limited data, the Guideline Development Group endorsed the MRI protocol used by the MERCURY study group, which was a prospective, European, multidisciplinary project that demonstrated the accuracy and feasibility of MRI as a method of assessing rectal cancer. The evidence to support this recommendation can be found in Appendix 1. This is also the MRI protocol endorsed by the Surgical Oncology Program (available here: <https://www.cancercareontario.ca/en/guidelines-advice/modality/surgery>)(19).

RECOMMENDATION 4

- The MRI report for preoperative, local staging of rectal cancer should include the elements outlined in the CCO Synoptic MRI Report for Rectal Cancer (available here: <https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=80771>) (see

Key Evidence/Justification

The Guideline Development Group endorsed the synoptic MRI report, which was based on evidence and multidisciplinary consensus. The evidence and justification to support these MRI criteria are available here <https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=133269> (19). It is important to note that the overall rationale for the synoptic MRI report was to provide clear definition for each item on the synoptic report and to improve overall consistency and completeness (but not necessarily accuracy) of MRI reports across the province.

RECOMMENDATION 5

- According to current practice, patients with stage II or III rectal cancer should be offered preoperative therapy using T and N categories to preoperatively stage patients.

Qualifying Statement

- To date, there is insufficient evidence to change the current selection criteria from T and N categories to distance to the MRF (i.e., potential CRM), extramural depth of invasion (EMD) and/or extramural vascular invasion (EMVI).

Key Evidence/Justification

Several RCTs have been done showing that preoperative radiation or chemoradiation leads to a decrease in the risk of local recurrence (21-24). These RCTs assessed T and N category with digital rectal examination and/or TRUS to select patients for neoadjuvant therapy. While there have been no RCTs that have used MRI criteria to select patients for preoperative therapy, more recently, two prospective non-randomized cohort studies used distance to the MRF of less than 1 mm on MRI to select patients for preoperative therapy (25,26). In these studies, patients with distance to the MRF of greater than or equal to 1 mm on MRI, regardless of T and N category, were treated with surgery alone. The results for these patients suggested that the rate of positive CRM was 1.5% (2/134) (25), and local recurrence was 3.3% (4/122) (26). These studies are clinically relevant because they suggest that preoperative radiation or chemoradiation may not be necessary in as many patients when MRI is used to select patient for preoperative therapy. This has significant clinical implication because preoperative radiation has been shown to lead to poorer bowel and sexual function compared to surgery alone (27). While these findings are important, the Guideline Development Group recommended that higher quality evidence is required before a change in the selection criteria can be recommended.

RECOMMENDATION 6

- All rectal cancer patients in Ontario, independent of their geographic locale, should have their case presented at a multidisciplinary cancer conference (MCC).

Qualifying Statement

- Alternatively, each case should be reviewed through collaborative discussion(s) and/or multidisciplinary clinic with appropriate clinicians (surgeon, radiation oncologist, radiologist, medical oncologist and pathologist). The goal is to provide clinical correlation, decide on an individualized treatment plan, and provide feedback to the radiologist and other members of the team.

Key Evidence/Justification

The effect of having an MCC discussion on patient outcomes was weak and conflicting. One study did find fewer positive CRM rates for those patients who were discussed at an MCC, but another study did not (28,29). Three studies investigated the effect of having an MCC on survival and did not find an association (30-32). Four studies suggested that patients were more likely to receive appropriate therapy if they were reviewed at an MCC (33-36). The Guideline Development Group chose to recommend that all patients with rectal cancer be discussed at an MCC, which is consistent with CCO's MCC standards document (37).

RECOMMENDATION 7

- Restaging MRI following preoperative chemoradiation is optional.

Qualifying Statement

- No recommendation can be made to support or refute the routine use of restaging MRI following neoadjuvant therapy. However, restaging MRI may be appropriate in cases where there is suspected MRF involvement or when complete response would change management, on a per patient basis.

Key Evidence/Justification

The Guideline Development Group did not recommend routine use of restaging MRI following neoadjuvant therapy due to lack of evidence. In particular, there were no studies assessing the effect of restaging MRI on surgical management or patient outcomes. However, two studies have shown that a lower tumour regression grade score (i.e., TRG 1 and 2) on restaging MRI was an independent and positive predictor of overall and disease-free survival (38,39). In addition, one of these studies showed that MRF involvement on restaging MRI was an independent and positive predictor of local recurrence (38). Two other studies found that tumour reduction volume was a significant predictor of disease-free survival (40,41) and overall survival (41). Due to lack of evidence, the Guideline Development Group does not recommend routine use of restaging MRI. However, the Guideline Development group believed that restaging MRI in select patient populations where observation following a complete response on MRI would be considered a reasonable treatment option (e.g., high-risk surgical patients, patients requiring abdominoperineal resection) or in patients with a potentially threatened CRM to ensure adequate response to chemoradiation prior to surgery.

FUTURE RESEARCH

Future high-quality studies need to:

- Assess the effect of preoperative chest CT in the management of rectal cancer patients: in particular how to manage indeterminate pulmonary nodules and the effect of this on clinical outcomes;
- Evaluate new approaches to selection of rectal cancer patients for pre-CRT using MRI to predict distance to the MRF (i.e., potential CRM) instead of T and N category;
- Compare the diagnostic accuracy of CT and MRI to predict distance to the MRF (i.e., potential CRM) for upper rectal tumours above the anterior peritoneal reflection where the improved resolution of MRI may not provide significant advantage over CT compared to mid and low rectal cancers;
- MRI protocols for restaging MRI to assess the diagnostic accuracy for predicting complete clinical response.

RELATED GUIDELINES

- CCO's Radiology: Synoptic MRI Report for Rectal Cancer available here:
<https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=80771> (19)
- CCO's MCC standards document available here:
<https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/286> (37)

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Appendix 1

To achieve optimal visualization of the rectum and surrounding structures for staging of rectal tumours, the protocol utilized by the MERCURY study group¹ is recommended (Table).

Hardware

Different field strengths may be used with equally good results but require adjustment of imaging parameters to obtain an adequate signal-to-noise ratio. Although endoluminal coil MRI may provide superior imaging resolution², due to its limited usefulness in stricturing rectal tumours and increased cost, it is less widely used across Ontario. On this basis, the evidence and recommendations outlined in this document are intended specifically to guide the use of pelvic phased array coil MRI.

Sequences

Four fast-spin echo, T2-weighted sequences without fat saturation are recommended, as summarized below (Table). Sequences 1 and 2 give a crude visualization of the primary tumour, possible sites of nodal involvement, and orientation of the tumour. They are used to plan sequences 3 and 4, which are the high-resolution sequences. These sequences enable characterization of nodes and detailed staging of the extent of the primary tumour. T1-weighted sequences are not mandatory as they prolong the study and do not provide additional information.

Table

Sequence	Imaging plane	TR/T E	FOV (cm)	Section thickness (mm)	Matrix size	ETL	NSA	Comment
1	Sagittal	2500/5000/85	24	5-0	512x256	8	2	Allow visualization of the tumour
2	Axial	4000/ 85	24	5-0	512x256	8	2	Pelvic sidewall to sidewall, from iliac crest to symphysis pubis
3	Oblique axial	4000/ 85	16 (20 for 1.0T machines)	3-0	256x256	8	4	Through tumour and perirectal tissues, perpendicular to long axis of rectum
4	Coronal oblique	4000/ 85	16 (20 for 1.0T machines)	3-0	256x256	8	4	For low rectal tumours (at or below origin of levators)

(Source: MERCURY Study Group. Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. *Radiology* 2007;243:132-9.)

1. Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. *Radiology*. Apr 2007;243(1):132-139.
2. Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. *Radiology*. Sep 2004;232(3):773-783.

Appendix 2



This document was developed by Drs Elsar Al-Sukhni, Laurent Milot, Mark Fruitman, Gina Brown, Selina Schmocker and Erin Kennedy for the Cancer Services Innovation Partnership – a joint initiative of Cancer Care Ontario and the Canadian Cancer Society

1. MRI PROTOCOL

Overall image quality: ☐ Adequate ☐ Suboptimal ☐ Non-diagnostic

2. TUMOUR LOCATION

Tumour location (from anal verge): ☐ Low (0-5.0 cm)
☐ Mid (5.1-10.0 cm)
☐ High (10.1-15.0 cm)

Distance of the lowest extent of tumour from anal verge: _____ cm

Distance of lowest extent of tumour from top of the anal sphincter: _____ cm

Relationship to anterior peritoneal reflection: ☐ Above ☐ At or straddles ☐ Below ☐ Not able to assess

3. TUMOUR CHARACTERISTICS

Circumferential extent/location (clock face): _____

Craniocaudal extent: _____ cm

Mucinous: ☐ No ☐ Yes

4. T-CATEGORY

i) T-category:

- ☐ T1 or T2
☐ T2/early T3 [includes spiculation of the perirectal fat]
☐ T3
☐ T3/possible T4*
☐ T4*

*Please indicate structures with possible invasion: _____ (see list below)

GU	PELVIC SIDE WALL	BONE/VASCULAR	OTHER
bladder	Obturator internus	sacrum (specify level)	Anterior peritoneal reflection
left ureter; right ureter	Piriformis	left internal iliac vessels; right internal iliac vessels	
prostate		left external iliac vessels; right external iliac vessels	
uterus	LEVATOR ANI		
vagina	Pubococcygeus		
	Ileococcygeus		
	Coccygeus		

ii. *For low rectal tumours (0- 5 cm) only:*

Is the lower extent of the tumour at or below the top border of the puborectalis? ☐ No ☐ Yes*

*If yes, please complete the following section for the most penetrating component of the tumour below the top border of puborectalis:

- ☐ Possible confinement to the submucosa; no definite involvement of internal sphincter (suspected T1)
☐ Confined to the internal sphincter; no involvement of intersphincteric fat or external sphincter (early T2)
☐ Through the internal sphincter and intersphincteric fat; possible or definite involvement of the external sphincter (advanced T2)
☐ Through the external sphincter and into surrounding soft tissue; no organ involvement (T3)
☐ Through external sphincter and possible involvement of the adjacent organs (i.e., prostate, vagina) (T3/T4)
☐ Through external sphincter and definite involvement of adjacent organs (i.e., prostate, vagina) (T4)

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5. DISTANCE TO THE MRF AND EXTRAMURAL DEPTH OF INVASION (EMD)

i) Shortest distance of the definitive tumour border to the MRF = _____ mm
[or ☐ unable to estimate or ☐ not applicable (involving the peritonealised portion of the rectum or T4a)]

ii) Extramural depth of invasion (EMD) at this level = _____ mm
[Record 0 mm for T1 and T2 tumours]

iii) Are there any tumour spiculations closer to the MRF? ☐ No ☐ Yes*

*If yes, please specify distance = _____ mm and location _____ (on clock face)

iv) Is there any other component of the tumour (any T2-3) closer to the MRF? ☐ No ☐ Yes*

*If yes, please specify distance = _____ mm and location _____ (on clock face)

6. EXTRAMURAL VASCULAR INVASION (EMVI)

EMVI: ☐ Absent ☐ Equivocal ☐ Present

7. MESORECTAL LYMPH NODES AND TUMOUR DEPOSITS

Any suspicious mesorectal lymph nodes and/or tumour deposits? ☐ No ☐ Yes*
(suspicious = irregular border, mixed signal intensity and/or ≥ 8 mm)

*If yes: (please complete a and b)

(a) Shortest distance of any suspicious mesorectal lymph node/tumour deposit to MRF = _____

(b) Please indicate location of the lymph node/deposit closest to the MRF:

- ☐ At level of tumour; at _____ o'clock
☐ Above tumour; at _____ o'clock
☐ Below tumour; at _____ o'clock

8. EXTRAMESORECTAL LYMPH NODES

Any extramesorectal lymph node(s) with suspicious morphology or signal? ☐ No ☐ Yes*
(suspicious = irregular border, mixed signal intensity and/or ≥ 1 cm)

* If yes, please specific location (free text):

9. FREE TEXT/ADDITIONAL COMMENTS

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Evidence-Based Series #17-8: Section 2

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Optimization of Preoperative Assessment in Patients Diagnosed with Rectal Cancer:

Evidentiary Base

*E. Kennedy, E. Vella, D. B. MacDonald, S. Wong, R. McLeod, and the Preoperative Assessment
for Rectal Cancer Guideline Development Group*

Report Date: January 20, 2014

RESEARCH QUESTIONS

1. What investigations (chest X-ray or CT thorax/abdomen/pelvis, colonoscopy, serum carcinoembryonic antigen) should be performed to assess for distant metastases and synchronous lesions in patients with rectal cancer?
2. What imaging (MRI pelvis, EUS, TRUS, CT pelvis) should be performed for local staging of rectal cancer?
3. What MRI protocol has been shown to have the best accuracy to locally stage rectal cancer?
4. What MRI criteria are necessary to locally stage rectal cancer preoperatively?
5. Which MRI criteria should be used to select patients for neoadjuvant therapy?
6. Does a pretreatment discussion at multidisciplinary cancer conference (MCC) improve patient outcome for patients with rectal cancer?
7. Does a restaging MRI after neoadjuvant therapy improve patient outcomes for patients with rectal cancer?

INTRODUCTION

Rectal cancer is one of the most common cancers in Canada (1). The five-year survival of patients with rectal cancer has increased over the years, most likely due to recent advances in the investigation and management (1). These include improved clinical staging with imaging techniques such as endorectal ultrasound and MRI, the use of neoadjuvant treatments, and surgical approaches such as total mesorectal excision (2-4). However, despite these and other improvements, approximately a quarter of patients with primary rectal cancer still die of recurrent disease in Canada (1).

Appropriate management of rectal cancer relies on the accurate staging including depth of tumour invasion into and beyond the bowel wall (T-category), the presence of metastatic lymph nodes (N-category) and the involvement of the predicted circumferential resection margin (CRM), as these criteria are important for treatment decision making and planning (5-8).

MRI is increasingly becoming the modality of choice for preoperative staging of rectal cancer, and therefore, there is a need to determine the appropriate protocol and minimum

criteria required to accurately stage rectal cancer. In addition, it is also important to determine which MRI criteria should be used to guide neoadjuvant therapy and surgical management, as this will guide discussion and decisions at MCC.

The CCO's Surgical Oncology Program has collaborated with the Program in Evidence-Based Care (PEBC) to develop guidelines for the preoperative assessment of rectal cancer. The aim of this guideline is to assist in the local and metastatic staging of rectal cancer. Also, this guideline aims to set criteria for the appropriate MRI protocol as well as how MRI findings can guide patient management and whether a multidisciplinary cancer conference is appropriate or necessary.

METHODS

The evidence-based series (EBS) guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (9). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by four members of the PEBC Preoperative Assessment for Rectal Cancer Guideline Development Group and one methodologist (see Appendix 1).

The body of evidence in this review is primarily comprised of diagnostic and cohort studies. That evidence forms the basis of the recommendations developed by the Preoperative Assessment for Rectal Cancer Guideline Development Group and published in Section 1. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC and CCO's Surgical Oncology Program is editorially independent from the Ministry.

Literature Search Strategy

For each research question, a targeted environmental scan of international guideline developers and key organizations for evidence-based clinical practice guidelines was conducted (March 7, 2012) for documents about preoperative assessment of rectal cancer. A listing of the organizations that were examined is given in Appendix 2.

Following this search of other guidelines, the Preoperative Assessment for Rectal Cancer Guideline Development Group considered the evidence summaries from NICE 2011, NZGG 2011, Scottish Intercollegiate Guidelines Network (SIGN) 2011 and the PEBC 2006 guidelines were of high enough quality to adapt their recommendations for questions 1 and 2, and no further literature searches were conducted (10-13). For question 4, the Guideline Development Group chose to endorse the MRI criteria developed by CCO's Surgical Oncology Program and no further literature searches were performed (14).

For questions three, five, six and seven, MEDLINE (1946-April 25, 2013), EMBASE (1996-April 25, 2013), and the Cochrane Database of Systematic Reviews (2005- April 25, 2013) were searched using disease-specific terms and terms specific for each question. The search strategies can be found in Appendix 3.

Study Selection Criteria

For questions three, five and seven, all studies had to analyze quantitative data for at least 30 patients with rectal cancer and had to use histopathology as the reference standard. Also, studies that included phased-array body coil and at least 1.0 Tesla MRI were included. Studies that included only patients with rectosigmoid cancers were also excluded.

For question three, a literature search for all studies that compared at least two different protocols of MRI [e.g., MRI with or without contrast (gadolinium, rectal contrast), MRI with or without diffusion weighted imaging, ultrasmall superparamagnetic iron oxide contrast agent (USPIO) enhanced versus not, two reviewers versus one reviewer, experienced

versus inexperienced reviewers] on the same sample was conducted. The studies needed to report diagnostic measures such as sensitivity, specificity, positive or negative predictive values or inter-rater reliability. Also, meta-analyses that reported subgroup analyses on any of these protocols were included. Studies that combined the results of patients who received neoadjuvant therapy with those that did not receive neoadjuvant therapy or did not report the treatments of the patients were excluded.

For question five, a search for randomized-controlled trials (RCTs) or comparative studies that included outcomes for patients who were selected for neoadjuvant therapy prior to surgery or surgery alone based on MRI criteria was conducted.

For question six, studies that compared the impact of having a MCC versus not having an MCC on any patient outcome were included. Studies were excluded if they assessed multidisciplinary programs that included more than just meetings (for example, changes in surgical techniques were also included in the program).

For question seven, any RCT, prospective or retrospective study that associated the results of MRI following neoadjuvant therapy with any patient outcome such as recurrence or survival was included. Studies that reported surrogate endpoints such as positive CRM rates were excluded.

Publications in a language other than English were not eligible because of lack of funding for translation. Non-systematic reviews, abstracts, case studies, letters, editorials, and commentaries were excluded.

Quality Appraisal of Evidence-Based Guidelines

The Appraisal of Guidelines Research and Evaluation (AGREE II) scores were taken from the Standards and Guidelines Evidence Inventory of Cancer Guidelines developed by the Canadian Partnership Against Cancer if available (15,16). Only clinical practice guidelines in which the objective of the guideline was specifically described and the document included a review of the evidence were evaluated using the AGREE II tool (15,16). Systematic reviews and meta-analyses were assessed for quality using the 'assessment of multiple systematic reviews' or 'AMSTAR' tool (17).

Guideline Selection for Adaptation

The Guideline Development Group included guidelines that met a minimum criteria of 50% on the rigour of development scale of the AGREE II tool and were not more than three years old (2009) (15,16). The AGREE II tool assesses the quality of guidelines (15,16). The rigour of development scale assesses the methodological quality of the guideline and, from a methodological perspective, is considered one of the more important domains. However, for research questions where no guidelines were found that met these minimum criteria, the Guideline Development Group included recommendations from Canadian guidelines, as their recommendations would be more relevant. These guidelines are described in Section 2, below. The process of adapting the recommendations is described in Section 3.

RESULTS

Literature Search Results

Of 2,271 articles identified in the literature search, 51 were deemed relevant for full article review. Of these, 22 articles met the inclusion criteria and were retained (18-39). In addition, four guidelines were included from the environmental scan and, from the reference lists, three primary studies and two systematic reviews were included (10-13,40-44). The reasons for exclusion can be found in Figure 1.

Study Design and Quality

Guidelines and Reviews

Although the NICE 2011 guideline encompassed all colorectal cancer, this guideline did provide evidence unique to rectal cancer for local staging (10). There was a clear link from the evidence to the recommendations for local staging of rectal cancer. For metastatic detection, the evidence was weak for rectal cancer, because most of the studies included patients with colorectal cancers, not solely rectal cancer.

The NGZZ 2011 guideline provided an excellent systematic review of the literature that was highly relevant to the second research question (11). Like the NICE 2011 guideline, there was a clear link between the evidence and their recommendations.

The PEBC 2006 guideline is older than the other guidelines but was chosen for its Canadian relevance and because it addresses research question seven, unlike the other guidelines (13). Like the NICE guideline, this guideline included all colorectal cancers. There was limited evidence from studies that included only rectal cancer patients in their systematic review.

The SIGN 2011 systematic review was not as extensive as the NICE 2011 and NZGG 2011 systematic reviews (12). Also, the justification linking the evidence to their recommendations was not as clearly written.

The quality of the guidelines from NICE 2011, NZGG 2011, the SIGN 2011 and the PEBC 2006 was assessed with the AGREE II instrument (Table 1) (10-13,15,16).

Table 1. Results of AGREE II Tool quality rating of evidence-based guidelines.

Guideline	AGREE II Domain Scores					
	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigour of Development (%)	Clarity and Presentation (%)	Applicability (%)	Editorial Independence (%)
NICE 2011 (10)	83.3	86.1	88.5	83.3	70.8	75.0
NZGG 2011 (11)	69.4	75.0	62.5	77.8	60.4	66.7
PEBC 2006 (13)	85.6	54.4	73.8	78.9	39.2	60.0
SIGN 2011 (12)	88.9	88.9	63.5	94.4	58.3	29.2

Abbreviations: NICE, National Institute for Health and Clinical Excellence; NZGG, New Zealand Guidelines Group; PEBC, Program in Evidence-Based Care; SIGN, Scottish Intercollegiate Guidelines Network.

Most of the scores were above 60%, including all of the rigour-of-development domains, suggesting that the evidence reviewed and recommendations developed were performed adequately. Only the PEBC 2006 document had two scores below 60% for stakeholder involvement and applicability. The recommendations for consideration from these guidelines can be found in Appendix 4.

Table 2 shows how the systematic reviews scored on each of the 11 AMSTAR items. Two of the reviews only searched one database (41,42), three did not provide information about the authors' conflict of interest (19,41,42), and none of them assessed the likelihood of publication bias (19,21,29,41,42). Kwok et al (2000) did not specifically state how the pooled estimates of diagnostic accuracy were calculated (41). Four of the reviews had high overall scores except for Lahaye et al (2005). Lahaye et al (2005) did not provide detail on the characteristics of the studies besides the sample sizes and did not assess the quality of the studies (42).

Table 2. Evaluation of included publications using AMSTAR.

ITEM	Al-Sukhni et al. 2012 (19)	Bipat et al. 2004 (21)	Kwok et al. 2000 (41)	Lahaye et al. 2005 (42)	Purkayastha et al. 2007 (29)
1. Was an 'a priori' design provided?	Y	Y	Y	Y	Y
2. Was there duplicate study selection and data extraction?	Y	Y	Y	Y	Y
3. Was a comprehensive literature search performed?	Y	Y	N	N	Y
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Y	Y	Y	Y	Y
5. Was a list of studies (included and excluded) provided?	Y	Y	Y	Y	Y
6. Were the characteristics of the included studies provided?	Y	Y	Y	N	Y
7. Was the scientific quality of the included studies assessed and documented?	Y	Y	Y	N	Y
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	Y	Y	N	Y
9. Were the methods used to combine the findings of the studies appropriate?	Y	Y	N	Y	Y
10. Was the likelihood of publication bias assessed?	N	N	N	N	N
11. Was the conflict of interest stated?	N	Y	N	N	Y
TOTAL AMSTAR POINTS	9	10	7	5	10

Abbreviations: N, no; NA, not applicable; Y, yes.

Primary Studies

Based on the Cochrane Collaboration method for assessing the methodological quality of diagnostic studies, using a modified QUADAS tool, several factors affected the quality of the included diagnostic studies for research question three (45). The details of these factors can be found in the Table 3. Most of the studies were retrospective, and some studies did not recruit consecutive patients. However, most of the readers were blinded to the other reader's assessment, if applicable, or were blinded to other clinical data.

For research questions five to seven, there were several issues with the quality of these cohort studies according to the Newcastle-Ottawa quality assessment scale (46). The details of these factors can be found in evidence Tables 4 through 6. Some of these studies did not do regression analysis or did not control for confounding variables, some were not blinded to the clinical or pathological data, and some did not report the length of follow-up.

Table 3 Study characteristics of included articles for the research question about the optimal MRI protocol to locally stage rectal cancer.

Study	Retro/Pro	Sample Size, Consecutive, Treatment	Comparison	Blinded to Index / Standard	Type of MRI	Missing/ Uninterpretable Data Explained	Withdrawals Explained	Results
Wong 2010 (35)	Retro	50 without neoadj tx, T1:2, T2:14, T3:31, T4:2	Phased-array vs. endorectal plus phased-array	Yes	1.5T	No	No	T staging: with endorectal coil - accuracy 77% (11/13), sensitivity 100%, specificity 86%, PPV 83%, NPV 100%; without endorectal coil - accuracy 68% (25/37), sensitivity 88%, specificity 60%, PPV 83%, NPV 69%
Kim 2010 (24)	Retro	109 consecutive without neoadj tx, T1:13, T2:26, T3:63, T4:7	2D T2-weighted vs. 3D T2-weighted	Yes	3.0T	None missing	No withdrawals	T staging: No difference in k values between 2D and 3D-weighted images for reviewer 1 (p=.465) or reviewer 2 (p=.402); agreement between reviewer 1 versus 2 for 2D k=0.50, for 3D k=0.52; N staging: No difference in k values between 2D and 3D-weighted images for reviewer 1 (p=.427) or reviewer 2 (p=.666); agreement between reviewer 1 versus 2 for 2D k=0.44, for 3D k=0.69; mean score for tumoural conspicuity higher for 2D than 3D (p=0.001);

Study	Retro/Pro	Sample Size, Consecutive, Treatment	Comparison	Blinded to Index / Standard	Type of MRI	Missing/ Uninterpretable Data Explained	Withdrawals Explained	Results
								no difference in overall image quality on basis of artifact degree between 2D & 3D (p=.189)
Jao 2010 (23)	Retro	88 consecutive (37 no neoadj tx, 26 with long-course neoadj tx, 19 with short-course neoadj tx had preop MRI), T1:12, T2:24, T3:42, T4:10	T2-weighted vs. gadolinium-enhanced T1-weighted vs. both	Yes	1.5T	Yes	No withdrawals	T staging: No difference in Az values between MRI techniques for each reviewer (p>0.05); interobserver agreement - T2WI k=0.75, T1 + Gd k=0.56, combined k=0.57; subgroup analysis Az values not significant and showed k values ranging from 0.40-0.89; N staging: No difference in Az values between MRI techniques for each reviewer (p>0.05); interobserver agreement - T2WI k=0.32, T1 + Gd k=0.30, combined k=0.29; subgroup analysis Az values not significant and showed k values ranging from 0.08-0.44
Vliegen 2005 (34)	Retro	83 consecutive (27 with and 56 without neoadj tx)	T2-weighted vs. gadolinium-enhanced T1-weighted vs. both	Yes	1.5T	None missing	No withdrawals	No difference between T2 MRI and gadolinium T1 MRI for patients with or without neoadj tx for invasion of mesorectal fascia, only difference

Study	Retro/Pro	Sample Size, Consecutive, Treatment	Comparison	Blinded to Index / Standard	Type of MRI	Missing/ Uninterpretable Data Explained	Withdrawals Explained	Results
								between Az values of T2 MRI and gadolinium T1 MRI in group of patients with neoadj tx for observer 2 ($p<0.05$)
Tamakawa 2010 (33)	Retro	58 consecutive without neoadj tx, T1:13, T2:13, T3:32, T4:0	T2-weighted vs. gadolinium-enhanced T2-weighted (combined)	Yes	1.5T	None missing	Yes	T staging overall: no difference between techniques, T2WI $k=0.34$, combined $k=0.43$; T1 limited to mucosa/submucosal layer: no difference in Az values between techniques, T2WI $k=0.62$, combined $k=0.57$; T2 limited to muscularis propria: significant difference in Az values between techniques (observer 1 $p=0.0002$, observer 2 $p=0.248$), T2WI $k=0.06$, combined $k=0.31$; T3 mesorectal fat extension: significant difference in Az values between techniques (observer 1 $p=0.0007$, observer 2 $p=0.001$), T2WI $k=0.44$, combined $k=0.48$
Lambregts 2011 (26)	Pros	68 consecutive (group 1: 26 surgery only / short-course	Standard MRI vs. gadofosveset MRI	yes	1.5T	None missing	Yes	N staging: Group 1: per lesion AUC better on gadofosveset MRI (reader 1 $p<0.001$, reader 2 $p=0.54$), per

Study	Retro/Pro	Sample Size, Consecutive, Treatment	Comparison	Blinded to Index / Standard	Type of MRI	Missing/ Uninterpretable Data Explained	Withdrawals Explained	Results
		tx; group 2: 42 MRI restaged after long-course neoadj tx)						patient AUC better on gadofosveset MRI (reader 1 p=0.005, reader 2 p=0.6), interobserver agreement standard MRI k=0.60, gadofosveset MRI k=0.42; Group 2: per lesion AUC better on gadofosveset MRI (reader 1 p=0.01, reader 2 p=0.04), per patient AUC not different on gadofosveset MRI (reader 1 p=0.54, reader 2 p=0.06), interobserver agreement standard MRI k=0.78, gadofosveset MRI k=0.78
Kim 2004 (25)	Pros	62 consecutive without neoadj tx, T1:5, T2:13, T3:41, T4:3	Warm water distention vs not	Yes	1.5T	None missing	Yes	Presence of outer wall penetration: mean accuracy for 3 reviewers better with distended than nondistended images (p<0.05), interobserver agreement distended mean k=0.78 nondistended mean k=0.64; no difference for presence of regional lymph node metastasis,

Study	Retro/Pro	Sample Size, Consecutive, Treatment	Comparison	Blinded to Index / Standard	Type of MRI	Missing/ Uninterpretable Data Explained	Withdrawals Explained	Results
								interobserver agreement distended mean $k=0.67$ nondistended mean $k=0.61$
Rafaelsen 2008 (30)	Retro	59 consecutive without neoadj tx, T1:11, T2:31, T3:82, T4:10	Inexperienced (0 yrs) vs experienced (>10 yrs) radiologist	Yes	1.5T	No	No	T staging: difference between readers in sensitivities ($p<0.05$), specificities ($p<0.05$), and accuracies ($p<0.01$); N-staging: no overall differences

Abbreviations: AUC or Az, area under the curve; k, kappa; MRI, magnetic resonance imaging; neoadj, neoadjuvant; NPR, negative predictive value; PPV, positive predictive value; pros, prospective; retro, retrospective; tx, treatment; vs., versus.

Table 4 Study characteristics of included articles for the research question about the optimal MRI criteria to select patients for neoadjuvant therapy.

Study	Retro/Pro	Sample Size, Consecutive, Treatment	MRI Criteria	Blinded to Index / Standard	Type of MRI	Missing/ Uninterpretable Data Explained	Follow-up	Results
Taylor 2011 (47)	Pros subgroup analysis	122 consecutive with good prognosis	Good prognosis: >1 mm predicted CRM, extramural depth of invasion into the mesorectal fascia < 5 mm, no extramural venous invasion	Yes	1.0/1.5T As per Mercury protocol; high resolution T2 weighted; perpendicular to axis of tumour	Subgroup analysis	Median f/u 61.5 months	All tumours: 3.3% local recurrence, overall survival at 5 years 68.2% (95%CI 60.3%-77.0%) disease-free survival 84.7% (95%CI 76.0%-90.4%); T3 stage tumours: 1.7% local recurrence, overall survival at 5 years 67.9% (95%CI 53.9%-78.5%), disease-free survival 81% (95%CI 66.1%-89.8%)
Strassburg 2011 (48)	Pros	230: 96 neo-adj tx, 134 surgery	For low rectal cancers all cT3 and cT4 tumours; for upper third of rectal cancer at hospital's discretion; for middle third of rectal cancer only if CRM \leq 1 mm	No	1.0/1.5T	yes	Interim analysis	Positive CRM Both groups: 13/230 (5.7%); Primary surgery 2/134 (1.5%); PreCRT 11/96 (11%)

Abbreviations: adj, adjuvant; CRM, circumferential resection margin; f/u, follow-up; mm, millimetre; MRI, magnetic resonance imaging; pros, prospective; retro, retrospective; tx, treatment.

Table 5 Study characteristics of included articles for the research question about the role of multidisciplinary cancer conferences.

Study	Retro/Pro	Sample Size, Consecutive, Type of Cancer & treatment, Setting	MCC Described	Blinded	Confounding variables	MRI?	Outcome (f/u?)	Results
Abraham 2006 (18)	Retro	73 with stage II/III rectal or rectosigmoid cancer, USA	NR	NR	Age, marital status, tumour board	NR	Regression comparing received recommended tx vs. not	S (p=0.02)
Augestad 2010 (20)	Retro	123 surgeon survey, USA, Australia, Europe	NR	No	Not included	35%	Preoperative decision making (bivariate analysis)	With MCC: more likely to receive neoadj tx (RR=5.67, p=0.03), better pathology report quality (RR=4.85, p=0.01), more new chemotherapy regimen if there are liver metastases (RR=6.41, p=0.02), more one-stage surgery when there are liver metastases (RR=0.25), p=0.02)

Burton 2006 (22)	Retro	298 consecutive primary rectal cancer (62 MCC-, 116 MCC+, both surgery alone tx), UK	Specialist surgeons, clinical and medical oncologists, radiologists, histopathologists, specialist nurses	NR	Not relevant	100%	Positive CRM rate	S (p<0.001))
Keating 2012 (38)	Retro	1389 rectal cancer from Veteran Affairs, survey data, USA	Mainly medical oncologists, pathologists, surgeons, radiation oncologists, radiologists	NR	Adjusted for patient age, sex, race/ethnicity, marital status, quartiles of the proportion with a college degree in zip code of residence, history of previous cancer, Charlson comorbidity score, year of diagnosis, tumour grade, veteran integrated service network	NR	3-year (all cause) survival	No MCC 52.5%, general MCC 56.2%, colorectal cancer-specific MCC 54.6%, p=0.37
Levine 2012 (36)	Retro	25 MCC+, 85 MCC-, USA	Colorectal surgeons, radiation and medical oncologists, radiologists, pathologists, clinical trials coordinators, physicians-in-training, nurse navigator	NR	Not included	NR	Compare proportion receiving neoadjuvant therapy between MCC+ and MCC- groups	76% MCC+ vs. 20% MCC-, p<0.0001
MacDermid	Retro	85 MCC-, 40	Colorectal	NR	NR	NR	Compare	32.5% MCC+

2009 (43)		MCC+ rectal cancer	surgeons, radiologist with interest in MRI, pathologist, colorectal clinical oncologist and nurse specialists, audit clerk				proportion receiving neoadjuvant therapy between MCC+ and MCC- groups	vs. 24.4% MCC-, p=0.462
Palmer 2011 (27)	Retro	303 locally advanced rectal cancer (44 MCC+, 44 MCC-), Sweden	At least a CRC surgeon, an oncologist, a radiologist and a pathologist	NR	Age, gender, tumour level, hospital level (university/other) and time period	More than 90%	Overall survival or cancer-specific survival, f/u at least 4 years	NS
Swellengrebel 2011 (32)	Retro	210 cT2-4, N0-2 rectal cancer (114 MCC+, 94 MCC-), Netherlands	Consulting oncologic surgeon, radiation oncologist, medical oncologist, treating specialist, radiologist, pathologist, specialized nurse	NR	Not relevant	(91% MCC+, 73% MCC-)	Positive CRM rate	NS
Wille-Jorgensen 2012 (37)	Retro	344 MCC+, 467 MCC-	Surgeons, oncologists, radiologists, pathologists, clinical physiologists	NR	NR	NR	Cumulative distant metastases, local recurrence and overall survival, f/u at least 5 years	NS for local recurrence and overall survival, S (p <0.001) for distant metastases

Abbreviations: CRM, circumferential resection margin; f/u, follow-up; MCC, multidisciplinary cancer conference; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; pros, prospective; retro, retrospective; S, significant; tx, treatment; UK, United Kingdom; USA, United States of America; vs., versus.

Table 6 Study characteristics of included articles for the research question about the role of restaging MRI after neoadjuvant therapy.

Study	Retro/Pro	Sample size, Consecutive, Type of Cancer & Treatment, Setting	MRI Criteria	Blinded	Confounding Variables	Outcome (f/u?)	Results
Nougaret 2012 (39)	Retro	51 consecutive locally advanced low or midrectal cancer with neoadj tx and surgery	Tumour volume reduction (threshold 70%), tumour regression grade (TRG)	Yes	Tumour reduction volume, downstaging, extramural spread, histological TRG and CRM	DFS, mean f/u 52 mths	multivariate analysis significant for DFS: tumour volume reduction
Patel 2011 (28)	Pros	111 consecutive with neoadj tx	Tumour regression grade (TRG) or circumferential resection margin (CRM) or nodal status or tumour stage	Yes	Age, sex, height of tumour from anal verge, type of preoperative treatment, type of operation	Overall survival (OS), disease-free survival (DFS), local recurrence (LR); 5 year f/u	TRG significant for OS & DFS; CRM significant for LR; nodal status significant for OS and DFS
Shihab 2011 (31)	Pros (same trial as Patel 2011 but different subset)	36 with low rectal tumours treated with neoadj tx	TRG or margin involvement	Yes	MRI low rectal stage, tumour position, MRI-predicted margin involvement and MRI-measured TRG, pathological CRM	LR, distant recurrence, and survival	High-grade TRG associated with decreased distant recurrence rates and improved survival

					involvement, pathological T- and N-stage and operation performed		
Yeo 2012 (44)	Retro	430 with locally advanced rectal cancer, no distant metastases, no other malignancy concurrent or within 5 yrs, received neoadj, surgery and adj tx	Tumour volume, tumour volume reduction rate (TVRR - threshold 45%)	NR	Age, gender, CEA, distance to distal end of tumour from anal verge, histologic grade, neoadj tx, surgery type, adj tx, ypT and ypN classifications, downstaging, TVRR, histological CRM	DFS, OS, median f/u 60 mths	Significant on multivariate analysis for DFS: TVRR, CRM, ypT classification, ypN classification; for OS: TVRR, CRM, ypN classification

Abbreviations: adj, adjuvant; f/u, follow-up; MRI, magnetic resonance imaging; neoadj, neoadjuvant; pros, prospective; retro, retrospective; tx, treatment; yrs, years.

Outcomes of Systematic Review

1. What investigations (chest X-ray or CT thorax/abdomen/pelvis, colonoscopy, serum carcinoembryonic antigen) should be performed to assess for distant metastases and synchronous lesions in patients with rectal cancer?

Two systematic reviews from NICE 2011 and the PEBC 2006 guidelines examined this question; however, only one of the 26 included studies by Choi et al (2010) was performed in patients with rectal cancer (10,13,40). Choi et al's (2010) prospective comparative study with patients with T3/T4 mid or lower rectal cancer, included in the NICE 2011 review, suggested that CT may be more sensitive than chest X-ray in detecting lung metastases. Nine unequivocal metastases among 103 (8.7%) patients with rectal cancer were found with CT and only five (5%) of these showed metastases with X-ray (40). However, not all patients were followed, and CT was used as the reference standard. Thirty-seven of 40 patients with indeterminate CT results were followed. Four of these patients (10.8%) showed changes that were metastatic.

2. What imaging investigations (MRI pelvis, EUS, TRUS, CT pelvis) should be performed for local staging of rectal cancer?

Four systematic reviews from NICE 2011, NZGG 2011, SIGN 2011 and the PEBC 2006 guidelines were found that addressed this question (10-13). The reviews had similar conclusions. All reviews were limited by lack of high-quality studies that were mainly case series without comparable control groups.

Depth of tumour invasion (T-category)

Two systematic reviews, included in the guidelines, suggested that EUS may be better at predicting the depth of tumour invasion than MRI or CT (21,41). Bipat et al (2004) found that EUS was more specific [86% (95%CI, 80%-90%)] than MRI [69% (95%CI, 52%-82%)] ($p=.02$) in detecting muscularis propria invasion, with more overstaging with T1 tumours on MRI (21). Also, EUS was more sensitive [90% (95%CI, 88%-92%)] than MRI [82% (95%CI, 74%-87%)] ($p=.003$) or CT [79% (95%CI, 74%-84%)] ($p<.001$) in detecting perirectal tissue invasion, with more understaging of T3 (or higher) tumours with CT and MRI. Kwok et al (2000) also found that EUS had higher sensitivity, specificity and accuracy than MRI in detecting muscularis propria invasion, when data were grouped as T1 and non-T1 tumours (41).

Predicted CRM involvement

Two systematic reviews included in the NZGG 2011 guideline as well as evidence from the MERCURY study group (2006) included in the NICE 2011 guideline, suggest that MRI is the best modality to predict CRM involvement (29,42,49). However, neither of these systematic reviews compared MRI to other imaging modalities in predicting CRM involvement. Lahaye et al (2005) found a summary ROC sensitivity of ~80% and a false-positive rate of ~20% (42). Purkayastha et al (2007) found a pooled sensitivity of 94% and specificity of 85% (29). The MERCURY study group (2006) found a wide range of sensitivities (42%-94%) and high specificities (73%-98%) and accuracies (77%-91%) depending on the patients' treatment profiles (49).

Lymph node involvement (N-category)

Three systematic reviews, with at least one of these reviews included in each of the guidelines, suggested that all modalities are moderate at assessing nodal involvement

(21,41,42). Bipat et al (2004) found that estimates for nodal involvement using EUS, CT or MRI were similar (21). Also, Lahaye et al (2005) found no significant difference in summary ROCs between EUS, CT and MRI when predicting nodal status (42). Likewise, Kwok et al (2000) found comparable results between EUS and MRI in detecting nodal metastases (41).

3. What MRI protocol has been shown to have the best accuracy to locally stage rectal cancer?

Four studies compared the diagnostic accuracy of gadolinium-enhanced images to unenhanced images (21,23,33,34). One study found no difference in the area under the curve for nodal staging, and two papers found no difference in the area under the curve for tumour staging (23,34). In the meta-analysis by Bipat et al (2004), subgroup analysis for perirectal tissue invasion showed no difference between unenhanced MRI versus gadolinium-enhanced MRI (21). Likewise, Tamakawa (2010) found no difference in the accuracy of tumour staging; however, they did find a difference for T3 tumours where fewer tumours were understaged with the addition of the gadolinium-enhanced T1-weighted images (33).

Rafaelsen et al (2008) compared the accuracy of an experienced reader to an inexperienced reader to determine the T and N category of rectal cancer in patients who had not received chemoradiotherapy prior to surgery (30). Eighty-four percent of the tumours were T2 or T3. The experienced reader had higher overall sensitivity and specificity with pathology for T staging compared to that of the inexperienced reader. The accuracy for T-category among the 64 patients with tumours 3 mm or less from the mesorectal fascia was higher with the experienced reader compared to the inexperienced reader. The determination for N category was not different between the readers. In the meta-analysis by Al-Sukhni et al (2012), covariate analysis showed that studies that used a consensus approach to assess T category had higher sensitivity and diagnostic odds ratio than did those in which images were reviewed independently (19). Likewise, in subgroup analysis, Purkayastha et al (2006) found that studies that used two or more interpreters had a higher sensitivity, specificity and AUC for the prediction of CRM than did the overall results (29).

Four other articles were also included, each examining a different variable of MRI (24-26,35). In a Chinese population of patients with rectal cancer who had not received neoadjuvant therapy, the diagnostic accuracy to detect mesorectal tumour involvement appeared to increase with the use of endorectal coils; however, the sample size was small and did not reach statistical significance (35).

In a Korean study, Kim et al (2010) compared two-dimensional (2D) to three-dimensional (3D) T2-weighted 3T-MRI in patients with rectal cancer that had not received neoadjuvant therapy (24). There were no significant differences between these two techniques in T or N category assessment or overall image quality (as determined by degree of artifact), but tumoural conspicuity based on an arbitrary scale was better for 2D than for 3D T2-weighted imaging.

Lambregts et al (2011) found that for patients with rectal cancer who did not receive long-course neoadjuvant therapy, the area under the curve for nodal staging was better on a per-lesion or per-patient basis with gadofosveset-enhanced MRI compared to standard MRI (26).

Kim et al (2004) found that distending the rectum using warm water resulted in greater accuracy in determining the presence of penetration beyond the muscularis propria, but there was no difference in determining the presence of regional lymph node metastasis (25).

4. What MRI criteria are necessary to locally stage rectal cancer preoperatively?

The Guideline Development Group chose to endorse CCO's MRI synoptic report, which uses multidisciplinary consensus and evidence; therefore, a systematic review of the literature was not performed (14).

5. Which MRI criteria should be used to select patients for neoadjuvant therapy?

There have been no published RCTs that have solely used MRI criteria to stage patients to determine eligibility for neoadjuvant therapy. There were two prospective, non-randomized cohort studies that used MRI criteria to select patients for neoadjuvant treatment. Taylor et al (2011) reported outcomes for a subgroup of patients from the MERCURY group with a good prognosis, defined on MRI as: (i) predicted CRM of >1 mm, absence of extramural venous invasion (EMVI) and extramural depth of invasion into the mesorectal fascia (EMD) of less than 5 mm (47). This subgroup of patients was treated with surgery alone and was found to have favourable 5-year local recurrence rates (3.3%), overall survival (68.2%, 95%CI 60.3%-77.0%) and disease-free survival (84.7%, 95%CI 76.0%-90.4%) rates.

Strassburg et al (2011) reported interim results of patients treated with chemoradiotherapy based on a MRI-predicted CRM of ≤ 1 mm (48). Overall, the results showed a positive CRM rate of 5.7% (13/230) in all patients, 1.5% (2/134) in patients having surgery alone and 11% (11/96) in patients receiving preoperative chemoradiation.

These studies suggest that using an MRI-predicted CRM <1 mm may be useful in selecting patients for neoadjuvant chemoradiotherapy. However, higher level evidence, ideally from RCTs, is needed to support this conclusion.

6. Does a pretreatment discussion at multidisciplinary cancer conference (MCC) improve patient outcome for patients with rectal cancer?

Two studies examined the effect of having an MCC discussion on the surrogate endpoint of positive CRM rate (22,32). One study found no difference in positive CRM rates between patients discussed at an MCC versus those that were not (32). However, the proportion of patients with advanced disease (at least T3 and/or node positive) was higher in patients discussed at MCC compared to those patients that were not discussed at an MCC. Another study did find that CRM-positive rates were significantly lower for those patients discussed at an MCC compared to those patients not discussed (22).

Three studies looked at the effect of having an MCC on patient outcomes, and none of them found a significant effect on survival (27,37,38). Wille-Jorgensen et al (2012) found that distant metastases were found in the MCC group more often compared to the pre-MCC group during the follow-up period, but there was no difference in cumulative local recurrence or overall survival (37). Keating et al (2013) surveyed Veteran Affairs Medical Centers and found that three-year survival in rectal cancer patients was not associated with the presence of an MCC (38). Using multivariate analysis, Palmer et al (2011) found no significant difference for overall survival and cancer-specific survival between patients that had an MCC discussion versus those that did not (27). However, all of these patients received appropriate preoperative staging. Patients that received inappropriate preoperative staging were separated into a third group regardless of whether they received an MCC. It is unknown what the impact of an MCC versus no MCC would have

been if all appropriate and inappropriate preoperative staged patients were not separated.

Four studies reported that patients were more likely to receive appropriate therapy if they had an MCC discussion (18,20,36,43). Rectal cancer patients presented at an MCC were more likely to receive appropriate therapy as described in the National Cancer Institute Physician Data Query (18). Also, a survey of international colorectal surgeons found that patients who had a threatened CRM were more likely to receive neoadjuvant treatment if they were discussed at an MCC (20). They were also more likely to have higher pathology-report quality, and receive a new chemotherapy regimen or one-stage surgery if there were liver metastases. As well, two studies found that patients were more likely to receive neoadjuvant therapy if their cases were reviewed at an MCC compared to cases that were not reviewed at an MCC (36,43).

7. Does a restaging MRI after neoadjuvant therapy improve patient outcomes for patients with rectal cancer?

The PEBC 2006 guideline reviewed the role of CT, MRI or ultrasound to assess tumour response in patients undergoing chemotherapy or radiotherapy (13). There was no strong evidence to support a role for repeat-staging imaging investigations, and recommendations were based on expert opinion.

Four studies that have been included since the PEBC 2006 guideline examined the association between MRI assessment after neoadjuvant therapy and patient outcomes (28,31,39,44). Patel et al (2011) used data from the MERCURY study to investigate the relationship between post-neoadjuvant therapy MRI assessment of tumour stage, nodal status, CRM and tumour regression grade (TRG) with OS, DFS and LR (28). Using multivariable analysis, controlling for age, sex, distance of tumour from anal verge, type of preoperative treatment, and type of operation, they found that MRI-assessed TRG was a significant predictor of OS and DFS, MRI-predicted CRM involvement significantly predicted for LR, and nodal status predicted OS and DFS.

Likewise, another study used data from the MERCURY group to examine the prognostic accuracy of MRI margin involvement and MRI TRG in patients with low rectal tumours (31). They found that poor TRG was a significant predictor of poor OS and distant recurrence.

Nougaret et al (2012) found that tumour reduction volume using a cut-off of 70% was a significant predictor of DFS with multivariate analysis in patients with locally advanced low or mid-rectal tumours (39). Similarly, Yeo et al (2012) found that in multivariate analysis, tumour reduction volume using a cut-off of 45% was a significant predictor of DFS and OS in patients with locally advanced rectal cancer (44).

These studies suggest there may be a relationship between some MRI-based tumour descriptors post-neoadjuvant therapy and patient outcomes. However, whether treatment strategies should be changed based on these MRI criteria has not been assessed in other prospective studies.

DISCUSSION

For preoperative assessment of rectal cancer, accurate staging is critical to determine appropriate management strategies. From the systematic reviews in the included guidelines, MRI is currently the best studied and most accurate modality to predict CRM involvement, and EUS is the best modality to distinguish between T1 and T2 tumours (29,42,49,50). The evidence from the guidelines to assess for distant metastasis in patients with rectal cancer is weak, and therefore, any recommendations would need to be based on consensus (10,13).

There were few comparative studies assessing different technical MRI parameters. Most of these studies examined gadolinium-enhanced images to unenhanced images, but the results were conflicting, and no definite conclusions could be drawn (21,23,33,34). There is some evidence from two meta-analyses to suggest that consensus evaluation is more accurate than independent evaluation in the local staging of rectal cancer (19,29). If feasible, consensus assessment may be a valuable approach to assessment.

While there is randomized controlled evidence showing that preoperative chemoradiation decreases the risk of local recurrence, these RCTs did not use MRI to preoperatively stage patients. Therefore, there is currently no RCT evidence to support the specific MRI criteria that are required to appropriately select patients for preoperative chemoradiation (51,52). Therefore, no conclusions can be made as to which MRI criteria are required to appropriately select patients for preoperative chemoradiation.

There is insufficient evidence to suggest that an MCC discussion of rectal cancer patients improves patient outcomes. There has been some evidence to suggest that patients discussed at an MCC have more appropriate therapy (18,20,36,43). However, the effect of MCC discussion on local recurrence rate or survival is unclear.

The evidence to support restaging MRI following neoadjuvant therapy is also insufficient. There were no studies that examined the effect of MRI findings on a change in patient management or patient outcomes. There were four studies that suggested that certain MRI criteria were predictive of local recurrence and survival; however, whether patients should have another MRI following preoperative therapy to affect change in treatment decisions has not been examined (28,31,39,44).

With the increasing use of MRI in the assessment of rectal cancer patients, more research to investigate the benefits of restaging MRI will be necessary before routine use of restaging MRI can be recommended.

CONCLUSIONS

The diagnostic evidence for local staging of rectal cancer has been extensively investigated and suggests that MRI should be the primary imaging modality, with EUS preferred in cases of early-stage rectal cancer (29,42,49,50). However, studies are needed to assess the accuracy of CT pelvis compared to MRI pelvis in predicting CRM involvement and the accuracy of CT chest in detecting lung metastases. Also, the evidence for determining the best technical MRI protocol and which pre- and post-therapy MRI criteria should be used to assist in patient management is weak and needs further evaluation.

CONFLICT OF INTEREST

The conflict of interest details are shown at the end of Section 3.

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A complete list of the members of the Preoperative Assessment for Rectal Cancer Expert Panel and the Working Group, with their affiliations and conflict of interest information, is provided in Section 2, Appendix 1.

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Appendix 1. Members of the Rectal Cancer Referral Working Group and Expert Panel.

Preoperative Assessment for Rectal Cancer Working Group	
Erin Kennedy General Surgeon Mount Sinai Hospital Toronto, ON	Blair MacDonald Diagnostic Radiologist Ottawa Hospital Ottawa, ON
Shun Wong Radiation Oncologist Sunnybrook Health Sciences Centre Toronto, ON	Robin McLeod General Surgeon Mount Sinai Hospital Toronto, ON
Emily Vella Research Coordinator Program in Evidence-Based Care, Cancer Care Ontario, Hamilton, ON	Amber Hunter Manager Surgical Oncology Program, Cancer Care Ontario, Toronto, ON
Yasmin Sallay Project Coordinator Surgical Oncology Program, Cancer Care Ontario, Toronto, ON	
Preoperative Assessment for Rectal Cancer Expert Panel	
Dr. Belal Ahmed Radiation Oncologist London Health Sciences Centre London, ON	Dr. Brigitte Ala Radiologist Hotel Dieu Grace Hospital Windsor, ON
Dr. Michael Anderson General Surgeon Royal Victoria Hospital Barrie, ON	Dr. Christine Brezden-Masley Medical Oncologist St. Michael's Hospital Toronto, ON
Dr. Robert El-Maraghi Medical Oncologist Royal Victoria Hospital Barrie, ON	Dr. Stanley Feinberg Surgeon North York General Hospital, Toronto, ON
Dr. Mark Fruitman Radiologist St. Joseph's Health Centre Toronto, ON	Dr. Susan Hegge General Surgeon North Bay Regional Health Centre North Bay, ON
Dr. Wayne Kendal Radiation Oncologist The Ottawa Hospital Ottawa, ON	Dr. Richard Kirsch Pathologist Mount Sinai Hospital Toronto, ON
Dr. Enoch Lai Radiologist North York General Hospital Toronto, ON	Dr. Mehran Midia Radiologist Hamilton Health Sciences Centre Hamilton, ON
Dr. Laurent Milot Radiologist Sunnybrook Health Sciences Centre Toronto, ON	Dr. Anat Ravid General Surgeon Hotel Dieu Grace Hospital Windsor, ON
Dr. Dolores Sicheri Medical Oncologist	Dr. Marko Simunovic General Surgeon

Thunder Bay Regional Health Sciences Centre Thunder Bay, ON	Hamilton Health Sciences Centre Hamilton, ON
Dr. Peter Stotland General Surgeon North York General Hospital Toronto, ON	Dr. Raimond Wong Radiation Oncologist Hamilton Health Sciences Centre Hamilton, ON
Dr. Louis Wu Radiologist Oshawa General Hospital Oshawa, ON	
Preoperative Assessment for Rectal Cancer Targeted Peer Reviewers	
Carl Brown Specialist in General and Colorectal Surgery St. Paul's Hospital Vancouver, BC	Tim Durrant Diagnostic Radiologist Halton Healthcare Services Oakville, ON
Barbara Fisher Radiation Oncologist London Health Sciences Centre London, ON	

Appendix 2. List of Sites Searched for the Targeted Environmental Scan

CMA Infobase

[National Guideline Clearing House](#)

Standards and Guideline Evidence (SAGE) database

NICE (UK) - [NICE Guidance](#)

SIGN (UK) - [SIGN Guidelines](#)

ASCO (US) - [ASCO Guidelines](#)

National Health and Medical Research Council (Aus) - [Cancer Guidelines](#)

New Zealand Guidelines Group - [Guidelines](#)

ARCHIVED

Appendix 3. Literature Search Strategies

MEDLINE for Research Questions Three and Five

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
<1946 to Present> Search Strategy:

- 1 exp magnetic resonance imaging/ (267132)
- 2 nmr imaging.mp. (1164)
- 3 zeugmatograph*.mp. (36)
- 4 mr tomograph*.mp. (487)
- 5 nmr tomograph*.mp. (199)
- 6 proton spin* tomograph*.mp. (38)
- 7 magneti#ation transfer contrast imag*.mp. (24)
- 8 (mri adj2 scan*).mp. (10469)
- 9 chemical shift* imag*.mp. (742)
- 10 (magnetic resonance adj2 imag*).mp. (289631)
- 11 (MR adj2 imag*).mp. (39668)
- 12 (NMR adj2 imag*).mp. (1553)
- 13 (diffusion weighted adj2 imag*).mp. (4863)
- 14 (T1-weighted adj2 imag*).mp. (6364)
- 15 (T2-weighted adj2 imag*).mp. (9824)
- 16 mri.mp. (115213)
- 17 dwi.mp. (3166)
- 18 dwi.tw. (3166)
- 19 magnetic resonance spectroscop*.mp. (124954)
- 20 MRS.tw. (9974)
- 21 (dynamic contrast-enhanc* adj2 (imag* or MR or MRI)).mp. (1518)
- 22 "3.0 tesla".mp. (427)
- 23 rectal coil*.mp. (13)
- 24 (endorectal adj2 coil*).mp. (328)
- 25 (endo-rectal adj2 coil*).mp. (6)
- 26 gadolidium.mp. (4)
- 27 gadolinium.mp. (21613)
- 28 or/1-27 (447133)
- 29 exp rectal neoplasms/ (34832)
- 30 (Adenocarcinom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (1881)
- 31 (Cancer: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (15067)
- 32 (Carcin: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (5512)
- 33 (Neoplas: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (31549)
- 34 (Tumor: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (2396)
- 35 (Tumour: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (774)
- 36 (Adenom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (622)

37 (Malignan: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (444)
 38 or/29-37 (41140)
 39 Neoplasm Staging/ (105613)
 40 (stage or stages or staged or staging).mp. (708817)
 41 (restage or re-stage or restages or re-stages or restaged or re-staged or restaging or re-
 staging).mp. (1767)
 42 (duke or dukes).mp. (6739)
 43 ajcc.mp. (1555)
 44 tumor?r-node?-metastasis.mp. (1124)
 45 tnm.mp. (8562)
 46 circumferential resection margin?.mp. (305)
 47 mesorectal fascia.mp. (79)
 48 meso-rectal fascia.mp. (0)
 49 radial resection margin?.mp. (14)
 50 resection margin?.mp. (3327)
 51 or/39-50 (715888)
 52 28 and 38 and 51 (762)
 53 (20101: or 2011: or 2012:).ed. (1582396)
 54 52 and 53 (123)

EMBASE for Research Questions Three and Five

Database: Embase <1996 to 2012 Week 22>

Search Strategy:

1 exp nuclear magnetic resonance imaging/ (381500)
 2 nmr imaging.mp. (390)
 3 zeugmatograph*.mp. (5)
 4 mr tomograph*.mp. (291)
 5 nmr tomograph*.mp. (26)
 6 proton spin* tomograph*.mp. (4)
 7 magneti#ation transfer contrast imag*.mp. (16)
 8 (mri adj2 scan*).mp. (13687)
 9 chemical shift* imag*.mp. (710)
 10 (magnetic resonance adj2 imag*).mp. (375373)
 11 (MR adj2 imag*).mp. (38691)
 12 (NMR adj2 imag*).mp. (555)
 13 (diffusion weighted adj2 imag*).mp. (15196)
 14 (T1-weighted adj2 imag*).mp. (6094)
 15 (T2-weighted adj2 imag*).mp. (9514)
 16 mri.mp. (152665)
 17 dwi.tw. (4832)
 18 magnetic resonance spectroscop*.mp. (71813)
 19 MRS.tw. (12462)
 20 (dynamic contrast-enhanc* adj2 (imag* or MR or MRI)).mp. (1965)
 21 "3.0 tesla".mp. (684)
 22 rectal coil*.mp. (12)
 23 (endo-rectal adj2 coil*).mp. (6)
 24 (endorectal adj2 coil*).mp. (389)

25 gadolidium.mp. (6)
 26 gadolinium.mp. (33571)
 27 or/1-26 (487182)
 28 exp rectum cancer/ (76949)
 29 (Adenocarcinom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (3083)
 30 (Cancer: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (25655)
 31 (Carcin: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (8100)
 32 (Neoplas: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (2304)
 33 (Tumor: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (12324)
 34 (Tumour: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (738)
 35 (Adenom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (2092)
 36 (Malignan: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (1011)
 37 or/28-36 (91030)
 38 cancer classification/ or cancer grading/ or cancer staging/ (156798)
 39 (stage or stages or staged or staging).mp. (618508)
 40 (restage or re-stage or restages or re-stages or restaged or re-staged or restaging or re-staging).mp. (2396)
 41 (duke or dukes).mp. (6053)
 42 ajcc.mp. (2390)
 43 tumo?r-node?-metastasis.mp. (1233)
 44 tnm.mp. (9793)
 45 circumferential resection margin?.mp. (445)
 46 mesorectal fascia.mp. (136)
 47 meso-rectal fascia.mp. (0)
 48 radial resection margin?.mp. (30)
 49 resection margin?.mp. (4043)
 50 or/38-49 (654881)
 51 di.fs. (1623322)
 52 predict*.tw. (761962)
 53 specificity.tw. (230713)
 54 or/51-53 (2402648)
 55 "sensitivity and specificity"/ (161713)
 56 exp diagnostic error/ or false negative result/ or false positive result/ (37889)
 57 di.fs. (1623322)
 58 sensitivity.tw. (385782)
 59 (predictive adj4 value*).mp. (70396)
 60 distinguish*.tw. (127561)
 61 differentiat*.tw. (369722)
 62 enhancement*.tw. (109387)
 63 identif*.tw. (1543845)
 64 detect*.tw. (1189086)
 65 diagnos*.tw. (1245444)

66 accura*.tw. (360437)
 67 comparison.tw. (501504)
 68 or/55-67 (5097744)
 69 54 or 68 (5464482)
 70 27 and 37 and 50 (1847)
 71 69 and 70 (1559)
 72 (2010: or 2011: or 2012:).ew. (2494793)
 73 71 and 72 (377)

Cochrane Controlled Trials for Research Questions Three and Five

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2012> Search Strategy:

1 exp magnetic resonance imaging/ (3883)
 2 nmr imaging.mp. (9)
 3 zeugmatograph*.mp. (0)
 4 mr tomograph*.mp. (11)
 5 nmr tomograph*.mp. (2)
 6 proton spin* tomograph*.mp. (1)
 7 magneti#ation transfer contrast imag*.mp. (0)
 8 (mri adj2 scan*).mp. (324)
 9 chemical shift* imag*.mp. (12)
 10 (magnetic resonance adj2 imag*).mp. (4791)
 11 (MR adj2 imag*).mp. (635)
 12 (NMR adj2 imag*).mp. (12)
 13 (diffusion weighted adj2 imag*).mp. (71)
 14 (T1-weighted adj2 imag*).mp. (96)
 15 (T2-weighted adj2 imag*).mp. (115)
 16 mri.mp. (2523)
 17 dwi.mp. (96)
 18 dwi.tw. (96)
 19 magnetic resonance spectroscop*.mp. (510)
 20 MRS.tw. (351)
 21 (dynamic contrast-enhanc* adj2 (imag* or MR or MRI)).mp. (31)
 22 "3.0 tesla".mp. (7)
 23 rectal coil*.mp. (0)
 24 (endorectal adj2 coil*).mp. (6)
 25 (endo-rectal adj2 coil*).mp. (0)
 26 gadolidium.mp. (0)
 27 gadolinium.mp. (624)
 28 or/1-27 (6302)
 29 exp rectal neoplasms/ (925)
 30 (Adenocarcinom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (263)
 31 (Cancer: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (845)
 32 (Carcin: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (339)

- 33 (Neoplas: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (962)
- 34 (Tumor: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (104)
- 35 (Tumour: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (30)
- 36 (Adenom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (103)
- 37 (Malignan: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (13)
- 38 or/29-37 (1610)
- 39 Neoplasm Staging/ (3798)
- 40 (stage or stages or staged or staging).mp. (24727)
- 41 (restage or re-stage or restages or re-stages or restaged or re-staged or restaging or re-staging).mp. (72)
- 42 (duke or dukes).mp. (452)
- 43 ajcc.mp. (53)
- 44 tumo?r-node?-metastasis.mp. (24)
- 45 tnm.mp. (214)
- 46 circumferential resection margin?.mp. (18)
- 47 mesorectal fascia.mp. (1)
- 48 meso-rectal fascia.mp. (0)
- 49 radial resection margin?.mp. (1)
- 50 resection margin?.mp. (86)
- 51 or/39-50 (25084)
- 52 28 and 38 and 51 (19)
- 53 limit 52 to medline records (16)
- 54 52 not 53 (3)
- 55 limit 54 to yr="2010 -Current" (0)

Cochrane Systematic Reviews for Research Questions Three and Five

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 2012>
Search Strategy:

-
- 1 magnetic resonance imag*.mp. (319)
 - 2 nmr imaging.mp. (1)
 - 3 zeugmatograph*.mp. (0)
 - 4 mr tomograph*.mp. (0)
 - 5 nmr tomograph*.mp. (0)
 - 6 proton spin* tomograph*.mp. (0)
 - 7 magneti#ation transfer contrast imag*.mp. (0)
 - 8 (mri adj2 scan*).mp. (93)
 - 9 chemical shift* imag*.mp. (0)
 - 10 (magnetic resonance adj2 imag*).mp. (325)
 - 11 (MR adj2 imag*).mp. (21)
 - 12 (NMR adj2 imag*).mp. (1)
 - 13 (diffusion weighted adj2 imag*).mp. (5)
 - 14 (T1-weighted adj2 imag*).mp. (3)
 - 15 (T2-weighted adj2 imag*).mp. (5)

16 mri.mp. (331)
 17 dwi.mp. (9)
 18 dwi.tw. (9)
 19 magnetic resonance spectroscop*.mp. (18)
 20 MRS.tw. (270)
 21 (dynamic contrast-enhanc* adj2 (imag* or MR or MRI)).mp. (0)
 22 "3.0 tesla".mp. (0)
 23 rectal coil*.mp. (0)
 24 (endorectal adj2 coil*).mp. (0)
 25 (endo-rectal adj2 coil*).mp. (0)
 26 gadolidium.mp. (0)
 27 gadolinium.mp. (24)
 28 or/1-27 (669)
 29 rectal neoplas*.mp. (28)
 30 (Adenocarcinom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (8)
 31 (Cancer: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (68)
 32 (Carcin: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (25)
 33 (Neoplas: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (67)
 34 (Tumor: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (13)
 35 (Tumour: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (19)
 36 (Adenom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (11)
 37 (Malignan: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (9)
 38 or/29-37 (102)
 39 Neoplas* Staging*.mp. (20)
 40 (stage or stages or staged or staging).mp. (3502)
 41 (restage or re-stage or restages or re-stages or restaged or re-staged or restaging or re-
 staging).mp. (9)
 42 (duke or dukes).mp. (74)
 43 ajcc.mp. (18)
 44 tumo?r-node?-metastasis.mp. (9)
 45 tnm.mp. (66)
 46 circumferential resection margin?.mp. (3)
 47 mesorectal fascia.mp. (0)
 48 meso-rectal fascia.mp. (0)
 49 radial resection margin?.mp. (0)
 50 resection margin?.mp. (21)
 51 or/39-50 (3533)
 52 28 and 38 and 51 (15)
 53 limit 52 to last 2 years (9)

MEDLINE for Research Questions Six

MEDLINE(R) <1946 to Present> Search Strategy:

- 1 exp rectal neoplasms/ (35006)
- 2 (Adenocarcinom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (1899)
- 3 (Cancer: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (15236)
- 4 (Carcin: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (5537)
- 5 (Neoplas: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (31695)
- 6 (Tumor: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (2440)
- 7 (Tumour: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (779)
- 8 (Adenom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (624)
- 9 (Malignan: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (447)
- 10 or/1-9 (41425)
- 11 tumo\$r board\$.mp. (225)
- 12 multidisciplinary conference\$.mp. (79)
- 13 multidisciplinary clinic\$.mp. (569)
- 14 multidisciplinary team\$.mp. (6869)
- 15 (morbidity and mortality conference\$).mp. (156)
- 16 multidisciplinary cancer.mp. (147)
- 17 or/11-16 (7979)
- 18 10 and 17 (84)

EMBASE for Research Questions Six
Database: Embase <1996 to 2012 Week 30>
Search Strategy:

- 1 exp rectum cancer/ (78603)
- 2 (Adenocarcinom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (3135)
- 3 (Cancer: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (26112)
- 4 (Carcin: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (8231)
- 5 (Neoplas: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (2388)
- 6 (Tumor: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (12535)
- 7 (Tumour: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (747)
- 8 (Adenom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (2152)
- 9 (Malignan: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (1025)

- 10 or/1-9 (92927)
- 11 tumo\$r board\$.mp. (307)
- 12 multidisciplinary conference\$.mp. (95)
- 13 multidisciplinary clinic\$.mp. (737)
- 14 multidisciplinary team\$.mp. (9322)
- 15 (morbidity and mortality conference\$).mp. (151)
- 16 multidisciplinary cancer.mp. (175)
- 17 or/11-16 (10682)
- 18 10 and 17 (268)

Cochrane Systematic Reviews for Research Questions Six

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 2012>
Search Strategy:

-
- 1 [exp rectum cancer/] (0)
 - 2 (Adenocarcinom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (8)
 - 3 (Cancer: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (69)
 - 4 (Carcin: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (25)
 - 5 (Neoplas: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (68)
 - 6 (Tumor: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (13)
 - 7 (Tumour: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (19)
 - 8 (Adenom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (11)
 - 9 (Malignan: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp. (9)
 - 10 or/1-9 (104)
 - 11 tumo\$r board\$.mp. (0)
 - 12 multidisciplinary conference\$.mp. (1)
 - 13 multidisciplinary clinic\$.mp. (9)
 - 14 multidisciplinary team\$.mp. (112)
 - 15 (morbidity and mortality conference\$).mp. (0)
 - 16 multidisciplinary cancer.mp. (0)
 - 17 or/11-16 (119)
 - 18 10 and 17 (3)

MEDLINE for Research Questions Seven

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
<1946 to Present> Search Strategy:

-
- 1 exp magnetic resonance imaging/ (267132)
 - 2 nmr imaging.mp. (1164)
 - 3 zeugmatograph*.mp. (36)

4 mr tomograph*.mp. (487)
 5 nmr tomograph*.mp. (199)
 6 proton spin* tomograph*.mp. (38)
 7 magneti#ation transfer contrast imag*.mp. (24)
 8 (mri adj2 scan*).mp. (10469)
 9 chemical shift* imag*.mp. (742)
 10 (magnetic resonance adj2 imag*).mp. (289631)
 11 (MR adj2 imag*).mp. (39668)
 12 (NMR adj2 imag*).mp. (1553)
 13 (diffusion weighted adj2 imag*).mp. (4863)
 14 (T1-weighted adj2 imag*).mp. (6364)
 15 (T2-weighted adj2 imag*).mp. (9824)
 16 mri.mp. (115213)
 17 dwi.mp. (3166)
 18 dwi.tw. (3166)
 19 magnetic resonance spectroscop*.mp. (124954)
 20 MRS.tw. (9974)
 21 (dynamic contrast-enhanc* adj2 (imag* or MR or MRI)).mp. (1518)
 22 "3.0 tesla".mp. (427)
 23 rectal coil*.mp. (13)
 24 (endorectal adj2 coil*).mp. (328)
 25 (endo-rectal adj2 coil*).mp. (6)
 26 gadolidium.mp. (4)
 27 gadolinium.mp. (21613)
 28 ((uspio or "ultrasmall superparamagnetic iron oxide") adj5 (imag* or MRI or MR)).mp.
 (236)
 29 USPIO-enhanc*.mp. (105)
 30 (((T2-weight* adj5 spin-echo) or (T1-weight* adj5 gradient-echo) or T2*-weight*) adj10
 (imag* or MR or MRI)).mp.
 (15566)
 31 ((surface adj3 coil) and (MR or MRI or imag*)).mp. (1303)
 32 gadofosveset*.mp. (172)
 33 or/1-32 (447170)
 34 exp Neoadjuvant Therapy/ (8342)
 35 ((neo-adjuvant or neoadjuvant) adj3 therapy).mp. (10404)
 36 ((neo-adjuvant or neoadjuvant) adj3 treatment).mp. (1919)
 37 "neoadjuvant therapy".mp. (9593)
 38 "induction chemotherapy".mp. (4784)
 39 "pre-operative therapy".mp. (42)
 40 "preoperative therapy".mp. (660)
 41 ("pre-operative care" or "preoperative care").mp. (47663)
 42 ("pre-operative chemotherapy" or "preoperative chemotherapy").mp. (2689)
 43 exp combined modality therapy/ (183066)
 44 (chemoradiotherapy or CRT).mp. (12652)
 45 (chemoradiation or chemoradiotherapy).mp. (10967)
 46 (post-chemoradiotherapy or "post chemoradiotherapy").mp. (23)
 47 "concomitant chemotherapy".mp. (688)
 48 radiochemotherapy.mp. (2178)
 49 ((pre-operative or preoperative) adj5 (chemotherapy or radiotherapy or radiation or
 chemoradiotherapy or

radiochemotherapy or radio-chemo-thermotherapy)).mp. (8057)
 50 or/34-49 (243447)
 51 neoplasm staging/ (105613)
 52 (stage or stages or staged or staging).mp. (708817)
 53 (restage or re-stage or restages or restaged or re-staged or restaging or re-staging).mp.
 (1763)
 54 (duke or dukes).mp. (6739)
 55 ajcc.mp. (1555)
 56 tumo?r-node?-metastasis.mp. (1124)
 57 tnm.mp. (8562)
 58 circumferential resection margin?.mp. (305)
 59 mesorectal fascia.mp. (79)
 60 meso-rectal fascia.mp. (0)
 61 radial resection margin?.mp. (14)
 62 resection margin?.mp. (3327)
 63 circumferential margin?.mp. (186)
 64 (downstage or downstages or downstaged or downstaging or T-downstaging or N-
 downstaging).mp. (1595)
 65 or/51-64 (716388)
 66 exp rectal neoplasms/ (34832)
 67 (adenocarcinom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (1881)
 68 (cancer: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (15067)
 69 (Carcin: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (5512)
 70 (Neoplas: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (31549)
 71 (Tumor: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (2396)
 72 (Tumour: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (774)
 73 (Adenom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (622)
 74 (Malignan: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or
 rectosigmoid*)).mp. (444)
 75 or/66-74 (41140)
 76 exp "Sensitivity and Specificity"/ (358725)
 77 exp Diagnostic Errors/ (86371)
 78 apparent diffusion co-efficient.mp. (7)
 79 "receiver operating characteristic".mp. (20642)
 80 "curve analysis".mp. (5815)
 81 (PPV or "positive predictive value").mp. (25187)
 82 (NPV or "negative predictive value").mp. (18816)
 83 "diagnostic performance".mp. (4389)
 84 specificity.mp. (744713)
 85 "accuracy of imaging technique".mp. (19)
 86 "observer variation".mp. (28156)
 87 "predict* pathologic* tumo?r".mp. (14)
 88 (predict* or detect* or discriminat*).mp. (2280706)

89 (SI or "signal intensity").mp. (52058)
 90 evaluation studies.pt. (166294)
 91 (evaluation adj1 (study or studies)).mp. (287931)
 92 validation studies.pt. (56068)
 93 (validation adj1 (study or studies)).mp. (61614)
 94 likelihood functions/ (14585)
 95 (likelihood: or likelihood ratio:).mp. (78302)
 96 di.fs. (1805461)
 97 sensitivity.tw. (463629)
 98 (predictive adj4 value*).tw. (59157)
 99 distinguish*.tw. (165871)
 100 differentiat*.tw. (445353)
 101 enhancement.tw. (136429)
 102 identif*.tw. (1615425)
 103 detect*.tw. (1430567)
 104 diagnos*.tw. (1449441)
 105 accura*.tw. (403104)
 106 comparison.tw. (639156)
 107 or/76-106 (7041167)
 108 33 and 50 and 65 and 75 and 107 (358)
 109 (20101: or 2011: or 2012:).ed. (1582396)
 110 108 and 109 (64)

EMBASE for Research Questions Seven

1. exp nuclear magnetic resonance imaging/
 2. nmr imaging.mp.
 3. zeugmatograph*.mp.
 4. mr tomograph*.mp.
 5. nmr tomograph*.mp.
 6. proton spin* tomograph*.mp.
 7. magneti#ation transfer contrast imag*.mp.
 8. (mri adj2 scan*).mp.
 9. chemical shift* imag*.mp.
 10. (magnetic resonance adj2 imag*).mp.
 11. (MR adj2 imag*).mp.
 12. (NMR adj2 imag*).mp.
 13. (diffusion weighted adj2 imag*).mp.
 14. (T1-weighted adj2 imag*).mp.
 15. (T2-weighted adj2 imag*).mp.
 16. mri.mp.
 17. dwi.tw.
 18. magnetic resonance spectroscop*.mp.
 19. MRS.tw.
 20. (dynamic contrast-enhanc* adj2 (imag* or MR or MRI)).mp.
 21. "3.0 tesla".mp.
 22. rectal coil*.mp.
 23. (endorectal adj2 coil*).mp.
 24. (endo-rectal adj2 coil*).mp.
 25. gadolidium.mp.

26. gadofosveset*.mp.
27. gadolinium.mp.
28. ((uspio or "ultrasmall superparamagnetic iron oxide") adj5 (imag* or MRI or MR)).mp.
29. USPIO-enhanc*.mp.
30. (((T2-weight* adj5 spin-echo) or (T1-weight* adj5 gradient-echo) or T2*-weight*) adj10 (imag* or MR or MRI)).mp.
31. ((surface adj3 coil) and (MR or MRI or imag*)).mp.
32. or/1-31
33. cancer classification/ or cancer grading/ or cancer staging/
34. (stage or stages or staged or staging).mp.
35. (restage or re-stage or restages or restaged or re-staged or restaging or re-staging).mp.
36. du.mp.
37. (duke or dukes).mp.
38. ajcc.mp.
39. tumo?r-node?-metastasis.mp.
40. tnm.mp.
41. circumferential margin?.mp.
42. circumferential resection margin?.mp.
43. mesorectal fascia.mp.
44. meso-rectal fascia.mp.
45. radial resection margin?.mp.
46. resection margin?.mp.
47. or/33-36
48. exp "Sensitivity and Specificity"/
49. exp Diagnostic Errors/
50. apparent diffusion co-efficient.mp.
51. "receiver operating characteristic*".mp.
52. "curve analysis".mp.
53. (PPV or "positive predictive value").mp.
54. (NPV or "negative predictive value").mp.
55. "diagnostic performance".mp.
56. "accuracy of imaging technique*".mp.
57. "observer variation".mp.
58. exp false negative result/ or false positive result/
59. "diagnostic performance".mp.
60. accuracy.mp.
61. sensitivity.mp.
62. specificity.mp.
63. "predict* pathologic* tumo?r".mp.
64. (SI or "signal intensity").mp.
65. di.fs.
66. distinguish*.tw.
67. sensitivity.tw.
68. differentiate*.tw.
69. enhancement*.tw.
70. predict*.tw.
71. specificity.tw.
72. detect*.tw.
73. discriminat*.tw.
74. identif*.tw.

75. diagnos*.tw.
76. accura*.tw.
77. comparison*.tw.
78. (predict* adj4 value*).mp.
79. or/48-78
80. neoadjuvant*.mp.
81. "induction chemotherapy".mp.
82. ("preoperative therapy" or "pre-operative therapy").mp.
83. ("preoperative care" or "pre-operative care").mp.
84. ("pre-operative chemotherapy" or "preoperative chemotherapy").mp.
85. exp multimodality cancer therapy/
86. cancer chemotherapy/ or exp cancer adjuvant therapy/ or exp cancer combination chemotherapy/
87. exp radiotherapy/
88. "combined modality therapy".mp.
89. (chemoradiotherapy or CRT).mp.
90. (chemoradiation or chemoradiotherapy).mp.
91. (post-chemoradiotherapy or "post chemoradiotherapy").mp.
92. "concomitant chemotherapy".mp.
93. radiochemotherapy.mp.
94. ((pre-operative or preoperative) adj5 (chemotherapy or radiotherapy or chemotherapy or radiotherapy or radiation or chemoradiotherapy or radiochemotherapy or radio-chemo-thermotherapy)).mp.
95. or/80-94
96. exp rectum cancer/
97. (adenocarcinom: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp.
98. (cancer: adj3 (rect: or mesrectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp.
99. (carcin: adj3 (rec: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp.
100. (neoplas: adj3 (rect: or mesrectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp.
101. (tumor: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp.
102. (tumour: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp.
103. (adenom: adj3 (rect: or mesorectal* or endorectal* or extraesorectal* or rectosigmoid*)).mp.
104. (malignan: adj3 (rect: or mesorectal* or endorectal* or extramesorectal* or rectosigmoid*)).mp.
105. or/97-104
106. 32 and 47 and 79 and 95 and 105
107. (2011: or 2012:).ew.
108. 106 and 107

Appendix 4 Recommendations to Consider from Other Guidelines

1. What investigations are necessary to assess for distant metastases and synchronous lesions (e.g., rectal and secum)? OR 2. What pretreatment investigations need to be completed for local staging of rectal cancer?			
SIGN 2011	NICE 2011	New Zealand Guideline 2011	PEBC 2006
All patients with colorectal cancer should be staged by contrast enhanced CT of the chest, abdomen and pelvis unless the use of intravenous iodinated contrast is contraindicated. Complete colonic examination by colonoscopy, CT colonography or barium enema should be carried out, ideally preoperatively, in patients with colorectal cancer.	Offer contrast enhanced CT of the chest, abdomen and pelvis, to estimate the stage of disease, to all patients diagnosed with colorectal cancer unless it is contraindicated. If intracranial disease is suspected, offer contrast-enhanced MRI of the brain. Do not offer imaging of the head, neck and limbs unless involvement of these sites is suspected clinically.	Preoperative assessment for rectal cancer should include clinical examination, complete blood count, liver and renal function tests, carcinoembryonic antigen (CEA), chest X-ray and contrast-enhanced CT of the abdomen / pelvis / liver	Prior to surgery patients with rectal cancer should have full staging including adequate images of the chest (i.e., an X-ray), abdomen and pelvis. CT or MRI scanning of the abdomen is recommended over ultrasound for detecting liver metastases.
MRI of the rectum is recommended for local staging of patients with rectal cancer. Endoluminal US can be used in a complementary role with MRI in staging patients with early rectal cancer.	Offer magnetic resonance imaging (MRI) to assess the risk of local recurrence, determined by anticipated resection margin, tumour and lymph node staging, to all patients with rectal cancer unless it is contraindicated.	Offer endorectal ultrasound to patients with rectal cancer if MRI shows disease amenable to local excision or if MRI is contraindicated. Preoperative assessments for rectal cancer should include MRI for identifying circumferential resection margin (CRM) involvement and local staging	CT or MRI of the pelvis should be done to assess mesorectal margin status. If T and N category determinations will drive decisions on the use of neoadjuvant therapy, transrectal ultrasound or MRI with endorectal coil is recommended. Operator skill is more likely to

		Preoperative assessment of possible T1 rectal cancers may include endorectal ultrasound (EUS) for local staging, as an alternative to MRI of the pelvis Endorectal ultrasound should not be used as the sole assessment to predict CRM involvement in people with rectal cancer	influence the accuracy of transrectal ultrasound versus MRI with endorectal coil. It is likely that advances in technology will demonstrate similar staging accuracy for routine MRI versus MRI with endorectal coil.
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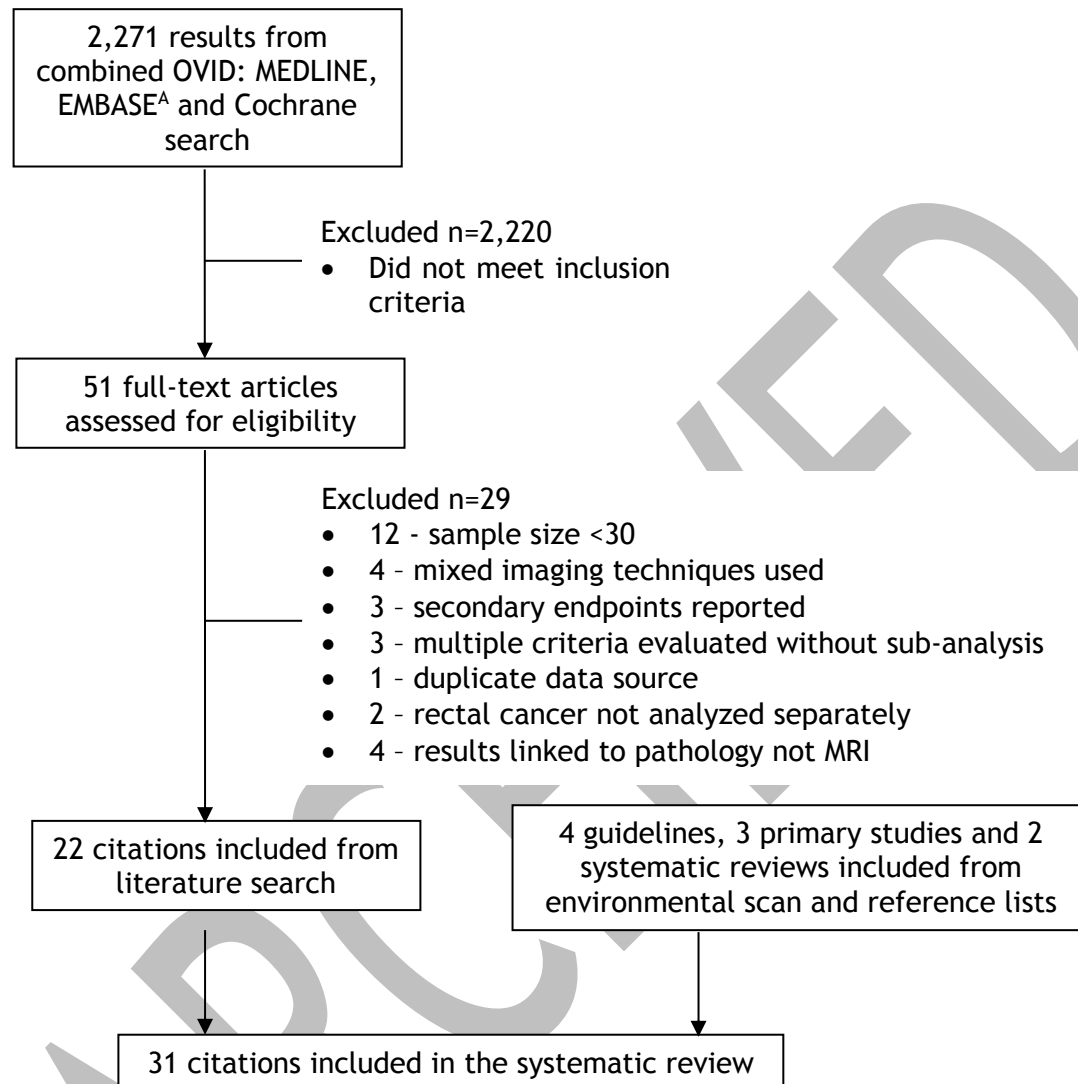
National Institute for Health and Clinical Excellence. Colorectal cancer: the diagnosis and management of colorectal cancer [Internet]. London: National Institute for Health and Clinical Excellence (NICE); 2011 [cited 2011 Oct 24]. Available from <http://publications.nice.org.uk/colorectal-cancer-cg131>.

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Simunovic M, Stewart L, Zwaal C, Johnston M, and the Diagnostic Imaging Guidelines Panel. Cross-Sectional Imaging in Colorectal Cancer [Internet]. Toronto, ON: Program in Evidence-Based Care, Cancer Care Ontario; 2006 [cited 2011 Oct 24]. Available from <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2566>.

Figure 1: Flow diagram of results from literature search strategies



^A Online search strategy available in Appendix 3

Abbreviations: EMBASE, Excerpta Medica; MEDLINE, Medical Literature Analysis and Retrieval System Online

Evidence-Based Series #17-8: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO) Optimization of Preoperative Assessment in Patients Diagnosed with Rectal Cancer:

Development Methods, Recommendations Development and External Review Process

*E. Kennedy, E. Vella, D. B. MacDonald, S. Wong, R. McLeod, and the Preoperative Assessment
for Rectal Cancer Guideline Development Group*

Report Date: January 20, 2014

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations.* Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.

- *Section 3: EBS Development Methods and External Review Process.* Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Preoperative Assessment for Rectal Cancer Guideline Development Group of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on preoperative assessment of rectal cancer, developed through review of the evidentiary base, evidence synthesis, an adaptation of existing guidelines, consensus of the Preoperative Assessment for Rectal Cancer Guideline Development Group, and input from external review participants in Ontario.

Development of the Recommendations

For research questions one and two, the recommendations from NZGG 2011, NICE 2011, PEBC 2006 and SIGN 2011 guidelines were considered during the development of the recommendations (see Section 2, Appendix 4) (3-6). The Working Group (Section 2, Appendix 1) held a teleconference to develop the recommendations through informal consensus. Each of the recommendations in Section 2, Appendix 4 was discussed taking into consideration any evidence found in the guidelines. For research question four, the Working Group chose to endorse CCO's MRI synoptic report developed by the Surgical Oncology Program (7). For research questions three and five through seven, the Working Group considered the evidence from the systematic review to develop recommendations during the teleconference. The Working Group believed the likelihood of harm of any of the imaging modalities or of a multidisciplinary cancer conference discussion was minimal and was outweighed by the potential benefits to the patients. The recommendations were written and approved by all members during the meeting. The Preoperative Assessment for Rectal Cancer Expert Panel (Section 2, Appendix 1) reviewed and approved the guideline as well.

Expert Panel (EP) Review and Approval

The draft guideline was presented to the Preoperative Assessment for Rectal Cancer EP on February 1, 2013 and discussed at an in-person meeting with the EP and the Working Group on February 11, 2013. For recommendation one, while the EP preferred CT chest over chest X-ray, they believed the choice of CT chest or chest X-ray should be left to the discretion of the institution. Although CT chest is more sensitive than chest X-ray, it is not very specific, and therefore, results in more indeterminate lung nodules. The EP also believed that CEA should be assessed preoperatively to ensure that CEA levels decreased postoperatively. Furthermore, in response to the comments from the EP the following qualifying statements were added to recommendation one:

- The choice of CT chest or chest X-ray should be consistent with the modality used for postoperative surveillance. If CT chest is used for postoperative surveillance, then CT chest should be done preoperatively at the same time as the CT abdomen and pelvis. If chest X-ray is used for postoperative surveillance, then CT chest is recommended only if abnormalities requiring further investigation were found on chest X-ray.
- When CT chest is performed in combination with CT abdomen and pelvis, intravenous contrast is recommended. However, when CT chest is the sole investigation, intravenous contrast is not indicated.
- If the use of intravenous contrast is contraindicated, abdominal MRI or ultrasound may be used to supplement CT findings to further assess for liver metastasis.

- Colonoscopy is preferred, but CT colonography can be used to complete the assessment when the colonoscopy is incomplete. If not completed preoperatively, a complete colonoscopy should be assessed postoperatively

For recommendation two, the EP was concerned about the lack of evidence to determine whether CT is at least as good as MRI at predicting the CRM preoperatively. Therefore, this concern was addressed in the justification section. Also, the EP notes that MRI does not assess regional disease at the level of the mesenteric artery. In response to the comments from the EP, the following qualifying statements were added to recommendation two:

- For upper rectal cancers, defined as 10 to 15 cm above the anal verge, in which the mesorectal fascia is not threatened, MRI may not provide significantly more information than CT of the pelvis.
- MRI is for local staging only and does not adequately assess regional disease at the level of the inferior mesenteric artery; therefore, CT should be used to assess for distant metastases and regional lymph node involvement along the inferior mesenteric artery.

For recommendation six, the EP believed that an MCC may not always be available, and therefore, the following qualifying statement was added:

- Alternately, the case could be the subject of a collaborative discussion, which would include assessment at a multidisciplinary clinic or a documented discussion with the appropriate clinicians.

After these and other more minor modifications were made, the draft document was recirculated to the Expert Panel for approval before external review.

Following external review (see below), on December 3, 2013 by email, the EP considered a final draft of the document, and formally approved the document by vote. Of the 19 members of the EP, 15 members cast votes and 4 abstained, for a total of 79% response. Of those that cast votes, 15 approved the document (100%).

Report Approval Panel Review and Approval

The purpose of the Report Approval Panel (RAP) review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For each document, three RAP members review the document: the Director and two others. RAP members must not have had any involvement in the development of the guideline prior to Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

In July 2013, the RAP reviewed this document. The RAP approved the document on July 10, 2013. Key issues raised by the Report Approval Panel included the following:

Perhaps the recommendations can be listed on one page so they stand out more.

- The recommendations were placed into shaded tables so they would be more apparent. Please label your tables more clearly.
- Labels for the tables were stated more clearly.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of

specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the Preoperative Assessment for Rectal Cancer Guideline Development Group circulated the draft document with recommendations modified as noted under Internal Review, above, to external review participants for review and feedback.

Methods

Targeted Peer Review: During the guideline development process, five targeted peer reviewers from Ontario and British Columbia considered to be clinical and/or methodological experts on the topic were identified by the Preoperative Assessment for Rectal Cancer Guideline Development Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on September 13, 2013. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Preoperative Assessment for Rectal Cancer Guideline Development Group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Surgeons, medical oncologists, radiologists, radiation oncologists and pathologists in Ontario from the Surgical Oncology Program database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on September 5, 2013. The consultation period ended on October 17, 2013. The Preoperative Assessment for Rectal Cancer Guideline Development Group reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Reviewer Ratings (N=3)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	2	1
2. Rate the guideline presentation.	0	0	0	1	2
3. Rate the guideline recommendations.	0	0	0	3	0
4. Rate the completeness of reporting.	0	0	0	2	1

5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	1	1
6. Rate the overall quality of the guideline report.	0	0	0	2	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	0	2	1
8. I would recommend this guideline for use in practice.	0	0	0	2	1

9. What are the barriers or enablers to the implementation of this guideline report?

One reviewer stated that the only barrier might be access to MRI. However, a provincial strategy to prioritize rectal cancer patients' access to MRI should coincide with the introduction of this guideline.

Table 2. Summary of written comment by targeted peer reviewers and modifications/actions taken.

<i>Summary of Written Comment</i>	<i>Modifications/Actions/Comments</i>
1. Since guidelines are described as evidence-based, I question the recommendation for all patients with rectal cancer to be presented at an MDT discussion since the evidence doesn't prove that this affects the survival or recurrence rate of patients. This appropriateness of decision-making is subjective and suggests that some patients might benefit.	The Working Group wanted to be consistent with CCO's MCC standard document. Also, there is emerging evidence that MCCs lead to a change in management in patients with rectal cancer (8,9). Therefore, the Working Group decided not to change this recommendation.

Professional Consultation: Forty-eight responses were received. Key results of the feedback survey are summarized in Table 3.

Table 3. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	2(4)	30(63)	16(33)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	1(2)	0	2(4)	17(36)	28(58)
3. I would recommend this guideline for use in practice.	0	0	1(2)	18(38)	29(60)

4. What are the barriers or enablers to the implementation of this guideline report?

One reviewer mentioned that since gadolinium was not recommended as a mandatory component of the MRI protocol, this will obviously take less time and be less costly.

Several reviewers suggested that timely access to MRI or ultrasound would be a barrier for this guideline. Furthermore, several reviewers were concerned that an MCC would be difficult to implement for all patients with rectal cancer.

Table 4. Summary of Written Comments by professional consultants and Modifications/Actions Taken.

<i>Summary of Written Comments</i>	<i>Modifications/Actions/Comments</i>
1. The guideline does not define a "rectal cancer."	A definition of rectal cancer was added. This was taken from the PEBC guideline "Optimization of Surgical and Pathological Quality Performance in Radical Surgery for Colon and Rectal Cancer: Margins and Lymph Nodes" (10).
2. The imaging component is highly prescriptive and directed specifically at the surgeon-radiologist interface. Regrouping the recommendations into radiology/treatment/MCC would make it a more practical document. Some of the recommendations are not clear, e.g., "There is insufficient evidence to support the routine use of restaging MRI" is a qualifier, not a recommendation; "RECOMMENDATION 5 Current practice is to offer preoperative therapy" needs to be worded as a proper recommendation.	The Working Group believed that the management of rectal cancer at all levels involves multidisciplinary input and, therefore, kept the existing grouping of recommendations. Recommendation 5 and 7 were reworded as recommendations rather than qualifiers.
3. Does the CCO have timeline targets set for time from diagnosis to 1) completion of preoperative imaging workup, 2) presentation at tumour board, 3) initiation of treatment, 4) other targets?	The Working Group considered this to be outside the scope of this guideline but CCO does have targets for some wait times and works with regions to achieve optimal results.
4. Does not address issues of perforation or obstruction at presentation.	A qualifying statement for recommendation 1 was added "This recommendation applies to patients undergoing elective treatment only (i.e., does not include patients with obstruction or perforation)."
5. Advise recommending CT chest only rather than CXR. Leaving it as one or the other leads to uncertainty/inconsistency/perception of varied practice by patients/practitioners. CT chest should be standard and takes no more time with little radiation concern.	After considering the comments from several reviewers as well as feedback from the Expert Panel, the Working Group chose to recommend CT rather than X-ray. A rationale was provided under key evidence/justification.
6. CEA should read serum CEA just to clarify we are not talking about IHC	'Serum' was added.
7. If there's going to be a pelvic MRI, does the pelvic CT add anything?	Yes, the pelvic CT adds to the continuity and baseline for follow-up, and the pelvic MRI and CT can provide complementary evaluation of the peritoneal space. We also state in the Qualifiers that MRI does not adequately assess regional disease at the level of inferior mesenteric artery or distant disease, and CT abdomen/pelvis should be used.
8. Specify what 'High resolution' MR means. (i.e., 3 mm or less)	A qualifying statement was added "A high-resolution MRI meets the specifications outlined by the MERCURY Group Protocol and is shown in Appendix 1."
9. Under Qualifying Statement for Recommendation 6, you may wish to add medical oncologists and	Medical Oncologists and pathologists were added.

pathologists as they would typically be part of an MCC.	
10. The guideline does not address the role of CT scan post-neoadjuvant treatment. I agree with post-neoadjuvant MRI. However, in some patients, systemic disease progresses while on treatment. It does open the question of systemic treatment versus surgery.	There is no evidence to support the use of CT chest/abdominal/pelvis post-neoadjuvant treatment. However, restaging CT may be appropriate in cases where there is concern about systemic disease progression, on a per patient basis.
11. The wording in Future Research could be improved. For example - "MRI protocols, including diffusion weighted imaging, etc...". It is not clear why a study of the diagnostic accuracy of CT and MRI in predicting the distance to MRF should be restricted to tumours above the peritoneal reflection - is this issue not relevant for all rectal cancers?	For tumours below the peritoneal reflection, MRI may be better than CT in predicting the distance to the MRF.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Preoperative Assessment for Rectal Cancer Expert Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Preoperative Assessment for Rectal Cancer Guideline Development Group members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Four Working Group members did not declare conflicts. Dr. Kennedy reported that she was involved in the development and pilot testing of an MRI synoptic report for rectal cancer from 2009 to 2011. She was also a principal investigator for the Cancer Services Innovations Partnership.

For the Expert Panel, eighteen members did not declare conflicts. Dr. Wu stated that he received more than \$5000 in a single year as a speaker for Bayer Canada.

No conflict of interest was declared by the Targeted Peer Reviewers.

The COIs declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.

UPDATING

This document will be reviewed in three years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

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