Study Protocol

Background

The standard treatment of rectal cancer is shown below in Figure 1. Patients with early or Stage I rectal cancer proceed to surgery alone and patients with locally advanced rectal cancer or Stage II and III rectal cancer receive chemotherapy and radiotherapy before surgery (preCRT) and chemotherapy following surgery.

Figure 1. Standard Treatment of Rectal Cancer

EARLY RECTAL CANCER		LOCALLY ADVANCED RECTAL CANCER
Stage 1 = T1 or T2; N0		Stage II = T3 or T4; N0 Stage III = Any T; N1 or N2
↓		↓
Surgery		PreCRT (5 weeks)
		↓
		Surgery
		↓
		Chemotherapy (4 months)

This recommendation for pre-operative chemoradiotherapy is based on several, well designed randomized controlled trials (RCTs) that have shown preCRT significantly reduces the risk of local recurrence (LR) from 15% to 7.5% at 2 years [1-6]. Unfortunately, while preCRT reduces the risk of LR, it does not improve survival and leads to significantly poorer bowel and sexual function and increases the risk of developing second malignancies compared to surgery alone [7-10]. Follow up from two RCTs have reported that compared to non-irradiated patients, irradiated patients have significantly increased bowel incontinence and use of pads that impacts ability to perform daily activities and participate in social activities [7,8]. Furthermore, irradiated patients report increased problems with sexual function resulting in decreased sexual activity compared to non-irradiated patients [7, 8, 10]. More recently, long term RCT data has shown an increased risk of second malignancies in irradiated patients and an increased risk of hip fracture [9, 11]. Lastly, there is an increasing body of evidence showing that the majority of patients seem willing to accept an increased risk of LR to avoiding preCRT and achieve improved bowel and sexual function [12, 13]. Therefore, it is essential that new approaches to reduce the number of patients receiving preCRT are evaluated in order to improve the long term functional results and overall quality of life for rectal cancer patients and survivors.

Currently magnetic resonance imaging (MRI) is used to pre-operatively stage rectal cancer as early or locally advanced based on T-category and N-category. However, two recent, non-randomized, prospective cohort studies (UK and Germany) have used MRI to assess the circumferential resection margin (CRM) to stage rectal cancers as early or advanced and guide treatment [14, 15]. In these studies, patients with a MRI predicted CRM of > 1 mm were staged as early rectal cancer and were treated with primary surgery and patients with a MRI predicted CRM of $\leq$ 1 mm were staged as advanced rectal cancer and treated with preCRT. Using this new MRI criteria to stage rectal cancer, the proportion of patients classified as advanced decreased from 85% to 62% (n=84 patients) and 79% to 34% (n=81 patients) in the UK and German studies, respectively, compared to standard MRI criteria using T-category and N-category. Therefore, using this new MRI criteria 30% fewer patients received preCRT compared to standard MRI criteria. The results of these studies showed very favourable clinical outcomes with low rates of positive CRMs (3.3% [4/122] and 6.0% [11/181]) and LR (3.3% [4/122]). Therefore, the results of these studies are extremely important since they show that use of this new MRI criteria leads to similar clinical outcomes as the standard MRI criteria while significantly reducing the number of patients who require preCRT. Therefore, use of new MRI criteria to stage rectal cancer has significant potential to improve bowel and sexual function in our rectal cancer patients as well as decrease the risk of second malignancies and hip fracture following treatment.

While an RCT would be most appropriate to answer this question, there is significant concern as to the feasibility of this since a minimum sample size of 1000 patients would be required and would require an international effort to complete recruitment within a reasonable time period (i.e., 2 years). Furthermore, the minimum cost of an international trial such as this would be at least $1M/year and it is unlikely that funding agencies would be willing to fund such a project based on the results of two small, prospective, cohort studies. Recently, our group has conducted a survey of colorectal surgeons across Canada that indicated that evaluation of the use of this new MRI criteria to stage rectal cancer patients is an important clinical question and indicated they would consider adopting this approach into their clinical practice provided that it was safe for use in the Canadian context as there are significant variations in both the use and quality of MRI reporting, receipt of preCRT, surgical technique and pathologic assessment across jurisdictions.

Therefore, the specific aim of this proposal is:

1. To conduct a Phase II (prospective cohort) study to assess the safety of new MRI criteria to pre-operatively stage rectal cancer across Canada

Work to Date

Our team organized an investigator's meeting on June 28, 2013 that was attended by 34 colorectal surgeons, radiation oncologists, radiologists, medical oncologists and pathologists from centres across Canada. At the meeting, the study protocol was reviewed and based on feedback from this group, refinements to the study protocol were

made. At the meeting, all of the investigators confirmed their intention to participate in this study.

Study Overview

The overall aim of this study is to evaluate the safety of new MRI criteria (predicted CRM instead of T-category and N-category) to pre-operatively stage rectal cancer as early or advanced and use these results to guide treatment. While the treatment for both early and advanced rectal cancer will be the exact same as the current standard of care, the new MRI criteria will likely lead to a significant proportion of rectal cancers being re-classified from advanced tumours (based on standard MRI criteria) to early tumours (based on new MRI criteria) and therefore these patients will undergo primary surgery and preCRT will be deferred. The safety of this new MRI criteria will be evaluated by assessing the positive CRM rate in the group of patients re-classified from advanced to early rectal cancer who undergo primary surgery (i.e. preCRT is deferred) to determine if this approach is safe. The positive CRM rate is a well-established and accepted surrogate measure of local recurrence and the new MRI criteria will be considered safe if a positive CRM rate of less than 5% is achieved. This is lower than reported positive CRM rates of 10% reported in previous RCTs. A Safety Monitoring Committee will assess the positive CRM rate every 25 patients accrued and the study will be stopped if the positive CRM rate is over 10% at any interim analysis.

Methods

Start-Up Period (0-3 months)
Research Ethics Board approval and data sharing agreements will initially be obtained at Mount Sinai Hospital (lead site for the study) followed by each of the participating sites during the three month start-up period. During this time, radiology, surgery and pathology webinars will be conducted with participating physicians to review the study protocol and data collection processes for each discipline.

Patient sample and Recruitment (3-21 months)
Newly diagnosed rectal cancer patients attending surgical clinics at participating centres will be invited to participate in the study.

The *inclusion criteria* for the study are:
1. Diagnosis of rectal cancer (0-15 cm from the anal verge) on endoscopy and/or proximal extent of tumour at or below the sacral promontory on CT and/or MRI
2. Meets all MRI criteria for “good prognosis” rectal tumours as defined by the study protocol
3. No metastatic disease
4. 18 years or older
5. Able to provide written consent

The *exclusion criteria* for the study are:
1. Planned abdomino-perineal resection (APR) based on pre-treatment assessment

2. Planned local excision based on pre-treatment assessment
3. T1/early T2 tumour on MRI (and/or TRUS)
4. Suspicious extramesorectal lymph nodes on MRI
5. Unable to undergo MRI due to claustrophobia, metal fragments, implanted metal devices or contrast allergy
6. Metastatic disease (including extramesorectal lymph nodes, carcinomatosis, liver, lung)
7. Pregnancy
8. Inflammatory bowel disease
9. Previous pelvic radiation
10. More than one primary tumour
11. Unfit for surgery

Clinical Assessment

The initial assessment will be performed by participating surgeons at each centre. The surgeon will be responsible for facilitating the standard pre-operative assessment that includes: (i) clinical and endoscopic examination of the primary tumour, (ii) CT chest, abdomen and pelvis, (iii) pelvic MRI and (iv) presentation of cases at multidisciplinary cancer conference (MCC).

At the MCC, all potentially eligible rectal cancer cases will be reviewed. All patients staged as locally advanced with standard MRI criteria will be re-staged with the new MRI criteria. Patients in this group that are re-staged as early tumours using the new MRI criteria (based on consensus between the surgeon, radiologist and radiation oncologist) and meeting the inclusion and exclusion criteria will be invited to participate in the study (Figure 2). This group of patients will proceed to primary surgery (i.e., preCRT will be deferred). The surgeon will be responsible for informing eligible patients about the study and will arrange for informed consent to be obtained on-site by a research coordinator or clinic nurse not involved in the patient's circle of care.

Figure 2 Standard and Proposed MRI Criteria for Early Rectal Cancer

MRI Criteria for Early Rectal Cancer	**Standard**	**Proposed Study**
Predicted CRM	Not assessed	> 1 mm (non-threatened)
T-category	T1 or T2	T1, T2 or early T3 with < 5 mm extramural depth of invasion into the mesorectal fascia
N-category	N0	N0, N1 or N2
Extramural venous invasion	Not assessed	Absent or equivocal

Radiologic Assessment

Each MRI will be reported according to the standard protocol at each institution. At minimum, the MRI protocol must include high resolution, axial oblique T2 weighted images. The MRI report must include: (i) distance to the mesorectal fascia (predicted CRM), (ii) T-category including extramural depth of invasion into the mesorectum (EMD) for all tumours T3 or greater, (iii) N-category and (iv) presence or absence of extramural venous invasion (EMVI). If there is any uncertainty regarding these MRI criteria, the reporting radiologist will be instructed to have a second radiologist at their centre review the image to achieve consensus. If consensus is not achieved and/or uncertainty still exists after review by the second radiologist, the reporting radiologist will be asked to contact Dr. Laurent Milot for central review. The MRI reports will be reviewed by the central study office (SS, EK) to ensure that all of these MRI criteria are reported and in the case of missing data, the treating surgeon and reporting radiologist will be contacted. Participating centres and radiologists will be encouraged to use a synoptic MRI template that has been pilot tested and is currently being used in Ontario, however this is not mandatory for participation in the study [16]. Prior to the start of the study, a Radiology Webinar will be organized to review definitions and interpretation of MRI criteria and educational materials will be provided. In addition, Radiology Training sets for predicted CRM and EMVI will be developed and be required to be successfully completed by participating radiologists.

Surgical Assessment

The surgical procedure will be left to the discretion of the surgeon and will involve a partial mesorectal excision for upper rectal cancers (above the anterior peritoneal reflection) and total mesorectal excision for mid and low rectal cancers (below the anterior peritoneal reflection)[17]. To be eligible for the study, surgeons must have completed colorectal or surgical oncology fellowship training in Canada or the United States. All fresh TME specimens will be photographed and grossly evaluated by the pathologist to assess the quality of the TME. Any surgeon with 2 incomplete TME specimens will be required to undergo peer review. Surgery should occur as soon as possible from the time of decision for surgery. Participating surgeons will also be required to attend the Pathology Webinar in which the protocol for gross evaluation of the TME specimen will be reviewed and discussed. Participating surgeons will be provided with education materials and log book to record their cases included in the study. Participating surgeons will be encouraged to present cases with positive CRM or incomplete TME at MCC for feedback and audit from the site group. Surgeons will also be encouraged to use a synoptic OR template that has been pilot tested and is currently being used in British Columbia, however this is not mandatory for participation in this study [18].

Pathologic Assessment

Each surgical specimen will be processed and reported according the standard protocol at each institution. At minimum, this must include both macroscopic (quality of the TME) and microscopic assessment (including T-category, EMD, EMVI and N-category) as described by Quirke [19]. Photographs of the gross specimen and serial section are required. If there is any uncertainty about any of these criteria, the reporting pathologist will be instructed to have this reviewed by a second pathologist at their centre to achieve

consensus. However, if consensus is not achieved or uncertainty still exists after review by the second pathologist, the reporting pathologist will be asked to contact Dr. Richard Kirsch for central review. The pathology reports will be reviewed by the central study office (SS, EK) to ensure that all of the required criteria have been reported and in the case of missing data the treating surgeon/reporting pathologist will be contacted. Prior the start of the study, a Pathology Webinar to review the Quirke method will be organized. At the webinar, there will be a review of definitions and interpretation of the reported criteria with particular attention to the assessment of the quality of the TME and EMVI. Educational materials will be provided and a Pathology Training set will be developed and will be required to be successfully completed by participating pathologists. Participating pathologists will be encourages to use the College of American Pathologists (CAP) checklist for their reports since this is currently used across North America, however this is not mandatory for participation in the study [20].

Follow up

The post-operative treatment for the patients will be the standard treatment recommended for all patients who undergo primary surgery. It is expected (based on pre-operative MRI) that the majority of patients will have a negative CRM and no lymph node involvement and, therefore, will not require any further treatment. These patients will be placed in a surveillance program as per institutional protocols. Approximately 20% of patients will have a negative CRM and positive lymph nodes and will be recommended to have chemotherapy. The chemotherapy regimen will be as per the standard of care at each institution. Less than 10% of patients are expected to have a positive CRM (with either positive or negative lymph nodes) and will be recommended to have post-operative chemoradiotherapy. The post-operative chemoradiation will be as per the standard of care at each institution.

Data Collection

Participating surgeons will be required to FAX a de-identified copy of the MRI report, operative report and pathology report for each participant to the central study office at Mount Sinai Hospital (Toronto, Ontario) for data abstraction and data entry. The study coordinator at the central office will send regular reminders and updates to all participating physicians and will ensure data collection is complete for each patient. A stand alone FAX will be kept in the study coordinator's locked office and will be used only for the purposes of this study.

Outcomes and Data Analysis (21-24 months)

The primary outcome for the study is the positive CRM rate. A positive margin will be defined as any macroscopic or microscopic tumour, tumour nodule or lymph node located within 1 mm of the CRM on final pathologic assessment.

We expect to have 30 high volume surgeons participate in this study and on average will see a minimum of 10 rectal cancer patients over the 18 month time period. Therefore, a minimum of 300 potentially eligible patients will be assessed and based on the UK and German studies, it is estimated that 30% (n=90) will be re-staged from advanced to early

rectal cancer using the new MRI criteria and will be eligible to participate in the study. Assuming an 80% participation rate, it is expected that 75 patients will be recruited over the study period.

For this study, a positive CRM rate of 5% or less will be considered acceptable and based on a sample size of 75, a 95% CI of +/-5% around a point estimate of 5% will be achieved.

A Safety Monitoring Committee will be organized and will consist of a statistician, one colorectal surgeon, pathologist and radiologist (who are not participating in the study). The study will be stopped if a positive CRM of >10% is reported at any interim assessment which will occur after every 25 patients accrued in the study.

Descriptive statistics will be used to report: (i) positive CRM rate, (ii) MRI findings (T-category, N-category, predicted CRM, EMVI) and (iii) final pathology (quality of the TME, CRM, T-category, N-category and EMVI). Regression analysis will be performed to assess if any clinical variables are predictive of positive CRM.

The feasibility of the study will be evaluated by assessing (i) the number of eligible patients across Canada over the study period and (ii) the proportion of eligible patients who participate in the study over the study period. Furthermore, a survey of participating surgeons will be conducted to assess facilitators and barriers to use of the new MRI criteria.

Relevance

It is expected that the results of this study will show that this new MRI criteria will be safe (i.e., positive margin rate less than 5%) and feasible for physicians to implement into their clinical practice. Therefore, this study has significant potential to change the current management of rectal cancer in Canada and result in improved quality of life for rectal cancer patients and survivors while reducing overall health care costs. These results would provide the necessary data to determine if an international RCT to address this question would be feasible based on sample size, recruitment and cost. Lastly, standardization of pre-operative MRI imaging, surgical and pathological assessment across centres of excellence in Canada will be important for reporting long term outcomes for this study (i.e., 2 year survival, local recurrence rates, quality of life), improving the quality of patient care across Canada and facilitating participation in future clinical trials on both a national and international level.

Project Team

Our proposed study brings together a group of experienced clinicians and scientists who are considered opinion leaders in North America and have the necessary trial experience and leadership skills to ensure that this project is successfully completed. The central study office and research coordinator for the study will be located at the Zane Cohen Digestive Disease Research Centre, a state of the art research facility affiliated with Mount Sinai Hospital.

Reference List

1. Tjandra JJ, Kilkenny JW, Buie WD, et al. Practice parameters for the management of rectal cancer (revised). *Dis Colon Rectum.* Mar 2005;48(3):411-423.
2. Wong R, Berry S, Spithoff K, Simunovic M, Chan K, Agboola O, Dingle B, Rumble RB. *Preoperative or postoperative therapy for the management of patients with Stage II of Stage III rectal cancer: guideline recommendations.* Toronto, ON: Cancer Care Ontario. Program in Evidence-Based Care; 2008.
3. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* Oct 21 2004;351(17):1731-1740.
4. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med.* Aug 30 2001;345(9):638-646.
5. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet.* Mar 7 2009;373(9666):811-820.
6. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg.* Oct 2006;93(10):1215-1223.
7. Marijnen CA, van de Velde CJ, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol.* Mar 20 2005;23(9):1847-1858.
8. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. *J Clin Oncol.* Sep 1 2005;23(25):6199-6206.
9. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Occurrence of second cancers in patients treated with radiotherapy for rectal cancer. *J Clin Oncol.* Sep 1 2005;23(25):6126-6131.
10. Stephens RJ, Thompson LC, Quirke P, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. *J Clin Oncol.* Sep 20 2010;28(27):4233-4239.
11. Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA. Risk of pelvic fractures in older women following pelvic irradiation. *JAMA.* Nov 23 2005;294(20):2587-2593.
12. Kennedy ED, Schmocker S, Victor C, et al. Do patients consider preoperative chemoradiation for primary rectal cancer worthwhile? *Cancer.* Jan 10 2011.

13. Harrison JD, Solomon MJ, Young JM, et al. Patient and physician preferences for surgical and adjuvant treatment options for rectal cancer. *Arch Surg.* Apr 2008;143(4):389-394.
14. Taylor FG, Quirke P, Heald RJ, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. *Ann Surg.* Apr 2011;253(4):711-719.
15. Strassburg J, Ruppert R, Ptok H, et al. MRI-based indications for neoadjuvant radiochemotherapy in rectal carcinoma: Interim results of a prospective multicenter observational study. *Annals of Surgical Oncology.* 2011;18(10):2790-2799.
16. Al-Sukhni E, Milot L, Fruitman M, Brown G, Schmocker S, Kennedy ED. User's guide for the synoptic MRI report for rectal cancer and the synoptic report MRI template for rectal cancer. Available from: https://www.cancercare.on.ca/cms/one.aspx?portalId=1377&pageId=80771.
17. Smith AJ, Driman DK, Spithoff K, et al. Guideline for optimization of colorectal cancer surgery and pathology. *J Surg Oncol.* Jan 1 2010;101(1):5-12.
18. BC Cancer Agency. Rectal Cancer Surgery Checklist (rectal cancer synoptic operative report template). Available from: http://www.bccancer.bc.ca/NR/rdonlyres/8D745DCB-5819-4706-8DBF-D077D1BB06CC/56772/RectalCancerChecklistsmall.pdf.
19. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet.* Mar 7 2009;373(9666):821-828.
20. College of American Pathologists - Cancer Protocols and Checklists. Colon and Rectum. Available from: http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=/portlets/contentViewer/show&_windowLabel=cntvwrPtlt&cntvwrPtlt{actionForm.contentReference}=committees/cancer/cancer_protocols/protocols_index.html&_pageLabel=cntvwr.