CancerCare Manitoba
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Practice Guideline: **Disease Management**

Provincial Consensus on Diagnostic and Treatment Recommendations for the Management of Rectal Cancer

Effective Date: July 2015

CancerCare Manitoba
Disease Management – Rectal Cancer
Developed by: Surgical Oncology and Gastro-Intestinal DSG

Preface

At CancerCare Manitoba (CCMB) the Clinical Practice Guidelines Initiative (CPGI) seeks to improve patient outcomes in terms of survival and quality of life through the development, dissemination, implementation and evaluation of guidelines for the management of common clinical scenarios encountered by cancer patients throughout the province.

This practice guideline was created through the efforts of a large interdisciplinary group from CCMB in collaboration with community partners. Members of the CCMB Surgical Oncology Disease Site Group (DSG), Gastro-Intestinal DSG, Provincial Pharmacy Program, Department of Nursing, Department of Epidemiology, Department of Pathology and the Department of Surgery at the University of Manitoba, general surgeons from the community, oncologists from the Winnipeg Regional Health Authority (WRHA) Community Oncology Program and from Community Cancer Programs Network (CCPN) sites have participated in its development.

The Surgical Oncology and Gastro-Intestinal DSG will review and update this document every 5 years, unless emerging evidence from scientific research, or practice issues requiring urgent resolution dictate a need for immediate change in content.

Purpose

This document is intended as a guide to facilitate a common approach to the clinical management of rectal cancer.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, surgeons, nurses, radiation therapists, pharmacists, psychosocial oncology caregivers, and dieticians at CCMB and Community Oncology Program sites (CCPN sites, Uniting Primary Care and Oncology (UPCON) clinics and WRHA Community Oncology Program sites).

Disclaimer

This guideline document should be viewed as an evidence-based practice tool, and as such, it does not represent an exhaustive text on the subject of rectal cancer. Clinicians are advised to use it in their practice concomitantly with information from other evidence-based sources.

Use of this guideline in the clinical setting should not preclude use of the practitioner's independent clinical judgment, nor should it replace consultation with the appropriate oncology specialist when indicated (example: medical oncologist, radiation oncologist, family practitioner in oncology (FPO), nurse practitioner/clinical nurse specialist, pharmacist, psychosocial oncology professional and dietician).

It is the responsibility of the practitioner to develop an individualized disease or symptom management plan for each patient under his/her care, and ideally this should take place within the context of a multidisciplinary team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

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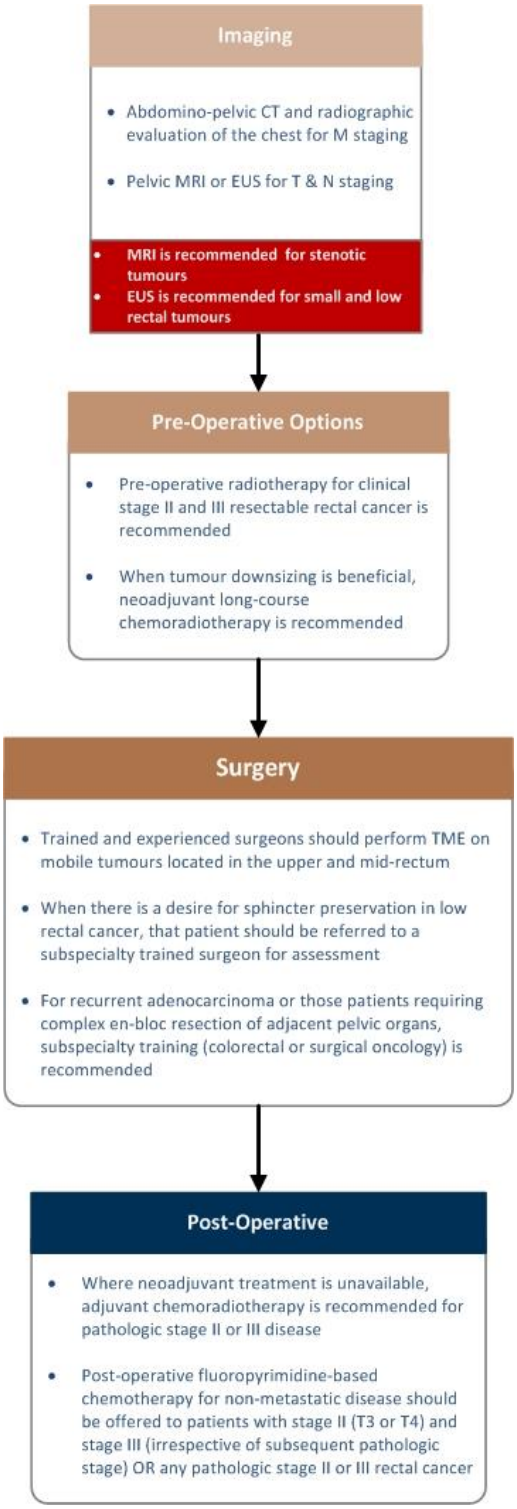

Guideline Recommendations

Imaging in Rectal Cancer Staging

1. All rectal cancer patients should undergo an abdomino-pelvic CT scan and radiographic evaluation of the chest for M staging. *Level of Evidence Ia*

2. Either pelvic MRI or EUS is required for T and N staging:

   - EUS is the recommended modality when available, within 10 business days, for small and low tumours.
   - Pelvic MRI would be the recommended modality for all stenotic tumours. *Level of Evidence III*

Chemotherapy for Rectal Cancer in Neoadjuvant Setting

1. Preoperative radiotherapy for clinical stage II and III resectable rectal cancer is recommended. *Level of Evidence Ia*

   - For tumours where downstaging would be beneficial*, neoadjuvant long-course chemoradiotherapy is recommended. *Level of Evidence Ib*
   - In all others, a strong recommendation of short-course radiation versus long-course chemoradiation cannot be made. Patient and tumour characteristics need to be taken into consideration. *Level of Evidence IV*

**NOTE: Beneficial is defined as the prevention of multi-visceral resections, sphincter preservation surgery and sterilization of radio margins.*

2. In the absence of neoadjuvant treatment, adjuvant chemoradiotherapy is recommended for pathologic stage II or III disease. *Level of Evidence Ib*

Adjuvant Chemotherapy

1. Post-operative fluoropyrimidine-based adjuvant chemotherapy for non-metastatic disease should be offered to patients with clinical stage II (T3 or T4) and stage III (irrespective of subsequent pathologic stage) OR any pathologic stage II or III rectal cancer. *Level of Evidence Ia*

Rectal Cancer Surgery

1. For mobile tumours located in the upper and mid-rectum, the surgeon must be trained and have experience in performing total mesorectal excision (TME). *Level of Evidence IV*
2. For recurrent rectal adenocarcinoma or those patients requiring complex en-bloc resection of adjacent pelvic organs, subspecialty training (colorectal or surgical oncology) is preferred. *Level of Evidence IV*
3. Where there is a desire for sphincter preservation in low rectal cancer, the patient should be referred to a subspecialty trained surgeon for assessment. *Level of Evidence IV*

CancerCare Manitoba

Disease Management Recommendations

Provincial Consensus on Diagnostic and Treatment Recommendations for the Management of Rectal Cancer

I. Introduction

In 2014, the Canadian Cancer Society estimated that 1 in 13 Canadian males and 1 in 16 Canadian females will be diagnosed with colorectal cancer in their lifetime.[1] Statistics show that rectal cancer is a significant cause of morbidity and mortality worldwide, accounting for 25% of all colorectal cancer cases, and has become one of the most frequently diagnosed cancers among men and women over the age of 65 in industrialized nations.[1-6] It is expected that in 2015 there will be approximately 25,100 new cases of colorectal cancer in Canada (14,000 men; 11,100 women) and that 9,300 people will die from rectal and colon cancer combined.[1] Compared to the high incidence rates in Europe, North America, Australia and Japan, rectal cancers are rare in developing countries.[6]

To ensure the best outcomes, management of patients with early stage (stage II and III) rectal cancer requires a multimodality approach involving Surgical, Radiation and Medical Oncology. Level I evidence supports the need for appropriate surgery (total mesorectal excision, TME), consolidated by perioperative radiotherapy.[7,8] This evidence is further supported by a 12-year follow-up of the TME trial.[9] Adjuvant chemotherapy has also been shown to provide benefit although the optimal use of chemotherapy is unclear.[10]

In 2005 CancerCare Manitoba convened a Rectal Cancer Consensus Conference to establish recommendations for management of early stage rectal cancer in Manitoba, Canada. CancerCare Manitoba serves the entire population of Manitoba, and offers the only radiation oncology facilities in the province. The Manitoba Cancer Registry (MCR) is housed within CancerCare Manitoba. Cancer is a reportable disease in Manitoba and as such the Registry collects data on all new cancer diagnoses. Since 2004 the MCR has assigned a collaborative stage to all submitted new cancer diagnoses. This serves as a useful resource for identifying subjects with early stage rectal cancer and reviewing the treatment they received.

The 2005 Rectal Cancer Consensus Conference generated 2 major recommendations:

1. Pre-operative Imaging
    - All patients with rectal cancer should have an abdominal CT scan pre-operatively as a screening tool to rule out metastatic disease.
    - All patients with rectal cancer should have a pelvic CT scan pre-operatively with a comment regarding the extent of the primary tumour and the status of the lymph nodes.
    - Unless the peri-rectal tissue or nodes are obviously involved on CT, all patients should proceed to endoscopic ultrasound (EUS). If an EUS is not available in a timely manner, pelvic magnetic resonance imaging (MRI) is an acceptable alternative.

- MRI should not be ordered routinely. MRI should be used when there are questions raised from the EUS or CT images, particularly when there are concerns with violation of the radial margin. MRI can be selectively used beyond that indication based on patient need and physician discretion.

2. Adjuvant Radiotherapy
    - No adjuvant radiotherapy is recommended for patients having:
        - Cancers with their lower edge above 15 cm from the anal verge.
        - Rectal cancers determined to be T1-2 N0 following pre-operative imaging or on final pathology.
    - Pre-operative long-course 25 x 2 Gy radiation with chemotherapy sensitization is recommended for all patients:
        - With T4 lesions or with tumour (primary or involved nodes) within 2 mm of radial margins on imaging.
        - With N1-2 disease on imaging.
        - In selective cases for sphincter preservation.
    - Pre-operative short-course 5 x 5 Gy radiation can be offered for all patients with T3 N0 based on pre-operative imaging.
    - Post-operative long-course 25 x 2 Gy radiation with chemotherapy sensitization is recommended for patients not radiated pre-operatively (due to under staging or patient refusal) who have:
        - T3-4 and/or N1-2 disease on final pathology.
        - Positive radial margins on final pathology.

Despite these recommendations, it was the perception of those focused on rectal cancer treatment that there remained considerable variation in the management of early stage rectal cancer patients in Manitoba. A decision was made to convene a second Rectal Cancer Consensus Conference to review any progress reported in the literature, to update practitioners involved in the care of these patients, and to consolidate the gains made from the initial conference.

To set the stage for the conference, data were presented on the management of rectal cancer patients prior to and following the initial consensus conference. These data are reported below in summary form.

Dr. Helewa and colleagues performed a retrospective audit of 370 patient records from 2004 to 2006 with stage I-III rectal cancer. [11] Of the 295 patients with clinical stage II or III disease, adjuvant or neoadjuvant radiotherapy was administered to 218 patients (73.9%). A total of 57 patients (19.3%) received neoadjuvant radiotherapy or chemoradiotherapy. There was a modest non-statistically significant trend towards an increase in the use of radiotherapy in each successive year.

A second audit was conducted in 2007 by Dr. Hunter et al (n = 90) in patients with clinical stage II and III rectal cancer.[12] That year was selected to ensure that there was adequate time for uptake of the recommendations from the 2005 Consensus Conference. With regard to the first set of recommendations above, 74 patients (82.2%) had pre-operative CT staging, and 47 patients (52.2%) had a pre-operative pelvic MRI or endorectal ultrasound. Relevant to adjuvant radiotherapy, a total of 61 patients (67.7%) were administered either adjuvant or neoadjuvant radiotherapy, of whom 30 patients (33.3%) had neoadjuvant radiotherapy or chemoradiotherapy.

Between the two studies, there was a clear increase in the use of neoadjuvant therapy, but little change in the overall use of radiotherapy. Only 38 patients (42.2%) were referred pre-operatively for consultation regarding the need for neoadjuvant therapy; there was a trend to improved survival in those referred pre-operatively, and a statistically significant improvement in survival in those receiving some form of peri-operative radiotherapy.

Despite the 2005 Provincial Consensus Conference involving all stakeholders, only one-half of stage II and III rectal cancer patients in Manitoba had been receiving appropriate pre-operative imaging investigations to adequately stage the primary tumour, and less than half had been referred pre-operatively for consideration of neoadjuvant therapy. Those whose treatment profile fits within the recommendations of the 2005 Consensus Meeting had better outcomes, but it was determined that Manitoba was still falling short of ensuring such optimal therapy for all of our patients. These results highlight the need for further education and integration of subspecialty services.

The recommendations from the 2011 Rectal Cancer Consensus Conference are contained in this document.

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11. Helewa R, Turner D, Wirtzfeld D, et al. Local recurrence of rectal cancer in Manitoba. Presented at the Provincial Consensus on Diagnostic and Treatment Recommendations for the Management of Rectal Cancer, April 2011.

12. Hunter W, Ahmed S, Nugent Z, et al. Stage II and III rectal cancer: Manitoba 2007. Presented at the Provincial Consensus on Diagnostic and Treatment Recommendations for the Management of Rectal Cancer, April 2011.

II. Scope of Guideline

Aim and Purpose

Development of this guideline was undertaken for the purpose of knowledge translation of the current standards in practice for treatment of rectal cancer in Manitoba. The overall aim of the developers is to improve the standard of care received by this patient population, through application of evidence-based interventions and promotion of best practices.

Clinical Questions

Is EUS or MRI more effective in the staging of suspected rectal cancer in adult patients?
For adult rectal cancer patients, what is the effectiveness of pre-operative radiotherapy or chemoradiotherapy versus post-operative chemoradiotherapy on tumour downstaging and local recurrence rates?
In adult patients with clinical stage II and III rectal cancer, what is the effectiveness of post-operative adjuvant chemotherapy on disease-free survival and local recurrence?
What is the relative effectiveness of conventional surgery versus TME surgery in adult rectal cancer patients in terms of local recurrence?

Development Panel

Development Panel

Oncology Subspecialties CancerCare Manitoba/University of Manitoba	2 Medical Oncologists, Gastrointestinal DSG 1 Radiation Oncologist, Gastrointestinal DSG 1 Surgical Oncologist, Gastrointestinal DSG 1 Surgical Oncology Fellow
Radiology/Imaging Health Sciences Centre/University of Manitoba	2 Radiologists
Quality, Patient Safety and Risk; Clinical Practice Guidelines Initiative CancerCare Manitoba	1 Quality/Guideline Development Professional
External Experts British Columbia Cancer Agency	1 Radiation Oncologist, 1 Surgical Oncologist
External Experts Cancer Care Nova Scotia	3 Surgeons, 1 Quality/Guideline Development Professional

Development Process

A multidisciplinary group of medical professionals participated in organizing a consensus conference with the goal of publishing the results of the meeting. Attendees included oncology experts and general practitioners from across the province as well as some external experts. Presentations were evidence-based recommendations based on the context of local practice. The guidelines were developed using a modified Delphi consensus method and the AGREE II tool *(see Section III Guideline Methodology for description).*

Patient Population and Healthcare Setting

The recommendations in this guideline are applicable to the care of adult (18 years or older) rectal cancer patients, male or female, who are receiving or will receive potential curative treatment. These recommendations are intended for use in both inpatient and outpatient settings.

End-Users

This guideline is written for use by clinicians providing care for the above mentioned patient population. Intended primarily for use by medical clinicians, the guideline may be of interest to trainees, physician extenders, allied healthcare staff, healthcare administrators, policy-makers and possibly members of the general public.

III. Guideline Methodology

A modified Delphi consensus method and the AGREE II tool were used to develop these guidelines.

Round 1

A chart audit was undertaken to ascertain practice patterns in Manitoba since the publishing of the 2007 guidelines. Based on the audit results, a working group identified key issues that needed to be addressed. The topics of focus were: the role of adjuvant chemotherapy, ideal pre-operative imaging for staging purposes, optimal pre-operative therapy (short-course radiotherapy versus long-course chemoradiotherapy) and clinical standards for rectal cancer surgery. Individuals from the region and other parts of the country (for impartiality) were invited to speak on these topics. Presenters were provided a template (to standardize the format for discussion), a list of guiding assumptions *(see Appendix III)*, a definition of consensus and a level of evidence scale *(see Appendix II)* to rank the evidence supporting their consensus statements. These individuals created consensus statements and learning objectives based on their presentations. Presenters were also required to provide the working group with their literature search, references and disclosure of conflicts of interest. Presenters did not confer prior to the conference.

Round 2

Participants at the consensus conference were medical professionals from the community, involved in the care of patients with rectal cancer. The meeting was attended by surgeons (general and oncology), radiation oncologists, medical oncologists, radiologists, nurses and general physicians, totalling 52 in attendance. A computerized audience response system was used to obtain basic demographics of the group, and to administer a pretest. The role of the pretest was to gauge the audience's pre-existing knowledge of the topics prior to presentation, as the conference's purpose was knowledge translation. The presentations and resulting question and discussion were audio recorded. The consensus statements were ranked and reviewed by all participants. Each individual was given a workbook in which to anonymously record ranking of the statements as well any commentary they wished to provide including any dissent. Participants were given three options for each statement "I support this statement", "I do not support this statement", or "I support this statement with modifications, as follows."

Round 3

After the presentations were completed, the participants were divided into 3 smaller groups *(see Appendix I)*. Composition of each group was representative of the larger group as a whole. A facilitator in each group was given a decision tree, and a recorder was assigned at each table. They were tasked with further discussion of the presenters statements and modification of statements (if necessary) to reach consensus.

Round 4

Participants reconvened into the larger group to share outcomes from small group discussions and re-rank

modified statements. The large group discussion was audio recorded. Final consensus was reached by a show of hands. The sixth item was tabled, to allow a thorough revision of statements based on suggestions stemming from the days discussion. Participant workbooks were collected at the end for review by the CPGI office and working group to confirm that consensus was reached.

2011 Provincial Rectal Cancer Consensus Meeting Attendees

Dr. S. Ahmed	Dr. R. Helewa	D. Moylneaux	Dr. J. Ross
Dr. A. Anozie	Dr. D. Hochman	Dr. W. Myers	Dr. R. Stimpson
Dr. B. Bashir	J. Ioculano	Dr. M. Nashed	Dr. Stoddart
Dr. S. Benjamin	Dr. D. Kinsley	E. Neufeld	Dr. S. Taira
Dr. P. Czaykowski	Dr. I. Kirkpatrick	Dr. J. Park	M. Wilfer
Dr. P. Daenick	Dr. A. Khan	Dr. S.V. Patel	Dr. D. Wirtzfeld
E. DeGrave	Dr. M. Kristjanson	Dr. D. Peterson	Dr. R. Wong
Dr. S. Garba	Dr. T. Lee	J. Petrella	Dr. C. Yaffe
Dr. C. Giacomantonio	S. McFall	Dr. P.T. Phang	Dr. B. Yip
Dr. N. Governo	Dr. McIntyre	Dr. J. Rauch	Dr. B. Zabolotny
Dr. R. Gupta	Dr. A. McKay	Dr. D.J. Reimer	Dr. M. Zaki
Dr. G. Harding	Dr. J. Momoh	Dr. J. Rivard	

Working Group Meetings

The working group developed this guideline in response to the consensus statements developed at the 2011 Provincial Rectal Cancer Consensus Meeting. The consensus statements formed the framework of the guideline and were integrated into the algorithm. Using the consensus statements for guidance, working group members drafted each of the guideline sections. Each section was reviewed by the working group and revised according to consensus decisions.

Internal and External Review

Internal and external peer reviews were pursued, the results of which are appended to this guideline. The internal review consists of revision by the working group. An external review was undertaken by two medical oncologists, a gastroenterologist and a surgical oncologist. All reviewers completed a full review of the guideline document and submitted a standardized practitioner feedback survey (adapted from Brouwers and colleagues).[1] Feedback was reviewed and discussed by the working group. Decisions to incorporate any changes into the guideline were consensus-based (acceptance, rejection or acceptance with modifications).

Maintenance

At CancerCare Manitoba clinical practice guidelines are considered 'living' documents which require ongoing evaluation, review and update. Re-evaluation of this guideline is planned for 2017. The working group will revise

and update the document as needed, with any critical new evidence brought forward before this scheduled review.

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IV. Imaging in Rectal Cancer Staging

Background

After diagnosis of rectal cancer has been made by endoscopy and biopsy, staging is vital for treatment considerations and prognosis. Assessment of local spread includes evaluation of tumour depth into the rectal wall, invasion of the mesorectal fascia, nodal status and involvement of surrounding pelvic and distant structures. The circumferential resection margin (CRM) is the shortest distance from the periphery of the tumour to the mesorectal fascia; it is a more powerful predictor of local recurrence than T staging and a strong prognostic factor.[1] Nodal status is another strong independent predictor of survival and local recurrence.

Endoscopic ultrasound (EUS) combines video endoscopy and ultrasound to give high resolution images of the GI tract, including intraluminal and extra-luminal structures. Individual layers of the GI tract are visible on EUS (mucosa, muscularis mucosa, submucosa, muscularis propria, subseros serosa). Magnetic Resonance Imaging (MRI) is capable of identifying atypical features of the tumour (mucinous, villous or fistulizing). Size and morphological criteria are used when evaluating lymph nodes on MRI.

Key Evidence

A study from the Mayo Clinic shows reduced recurrence rates in patients who received EUS (attributed to patients receiving neoadjuvant chemoradiation).[2] A meta-analysis comparing EUS versus MRI versus CT shows EUS outperforming for T1 staging with sensitivity of 94% and specificity of 86%.[3] EUS accuracy of N staging is not as remarkable: N0, 67%; N1, 78%. Lymph node staging is notoriously difficult with all imaging modalities. There is evidence showing 97% accuracy (29/30) in EUS identifying benign or low stage tumours that are eligible for trans-anal endoscopic micro-surgery (TEMS).[4] Short-comings of EUS include occasional over-staging of T2 lesions and under-staging of T3 lesions. Stenotic tumours are also difficult to assess with this modality.[5]

Advancements in MRI technology have provided reliable and accurate techniques to locally stage rectal cancer. Pelvic phased array coil has improved spatial resolution, signal to noise ratio, and a larger field of view; allowing visualization of the mesorectal fascia, pelvic sidewall lymph nodes, tumours at the rectosigmoid junction and stenotic rectal cancers.[1] MRI is the most accurate modality of measuring tumour invasion of the mesorectal fascia and the CRM (sensitivity 100%, specificity 88%).[6,7] These measures identify patients at high risk of incomplete resection, who will benefit from neoadjuvant chemoradiotherapy to downstage the tumour.[8] Morphological criteria have shown superior accuracy when evaluating nodal involvement with MRI. Nodes greater than 3 mm in maximum diameter can be assessed for irregular borders or heterogeneity (mixed signal intensity) with a sensitivity of 85% (95% confidence interval [CI], 74 to 92) and specificity 97% (95% CI, 95 to 99).[9]

Recommendations

1. All rectal cancer patients should undergo an abdomino-pelvic CT scan and radiographic evaluation of the chest for M staging. *Level of Evidence Ia*

2. Either pelvic MRI or EUS is required for T and N staging:

    - EUS is the recommended modality when available, within 10 business days, for small and low tumours.
    - Pelvic MRI would be the recommended modality for all stenotic tumours. *Level of Evidence III*

Clinical Considerations

For earlier stage tumours, EUS is the preferred imaging modality but requires availability of appropriate technology and operator expertise. In the absence of this, MRI is considered to be the most appropriate test.

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V. Neoadjuvant Chemoradiotherapy

Background

The addition of radiotherapy to surgical management of rectal cancer to improve local control is well established. Radiotherapy can be delivered in the neoadjuvant setting for increased local control with short-course 25 Gy radiation in 5 fractions with immediate surgery. Alternatively, cytoreductive or long-course 50.4 Gy radiation in 28 fractions with fluoropyrimidine-based chemotherapy 6-8 weeks prior to surgery can be used for increased local control, and increased complete (R0) resection (no gross or microscopic tumour) in appropriate cases. Neoadjuvant chemoradiotherapy (CRT) takes radiobiological advantage of better blood supply for increased tumour kill and increased normal tissue recovery, as well as increased patient tolerance and compliance.

Key Evidence

In a meta-analysis from the pre-TME era, local recurrence rate decreased from 22.2% to 12.5% for pre-operative radiotherapy versus 22.9% to 15.3% for post-operative radiotherapy versus surgery alone.[1] This data did not show an increase in R0 rates for neoadjuvant treatment however, a decrease in positive circumferential resection margins (CRM) from 13% to 4% has been seen comparing short-course neoadjuvant radiotherapy to cytoreductive neoadjuvant chemoradiotherapy.[2] This is significant since neither pre-operative nor post-operative radiotherapy can compensate for microscopically positive resection margins which lead to decreased local control.[3] Phang and colleagues have shown that locally advanced tumours threaten the CRM; T4 tumours and lower tumours with a thinner mesorectum have an increased risk of a positive CRM compared to high or mid-rectal tumours and tumours on MRI that are not encroaching on the CRM.[4] Several studies have confirmed that neoadjuvant cytoreductive chemoradiotherapy increases local control, increases R0 rates and has better tolerability and compliance than post-operative chemoradiotherapy.[2,5-7] Appropriate selection of patients is necessary however, because T2 patients do not benefit from short- or long-course treatment, but rectal dysfunction and decreased quality of life are significantly increased over surgery alone.[8,9]

Recommendations

1. Preoperative radiotherapy should be recommended for clinical stage II and III resectable rectal cancer. *Level of Evidence Ia*

    - For tumours where downstaging would be beneficial*, neoadjuvant long-course chemoradiotherapy is the treatment of choice. *Level of Evidence Ib*
    - In all others, a strong recommendation of short-course radiation versus long-course chemoradiation cannot be made. Patient and tumour characteristics need to be taken into consideration. *Level of Evidence IV*

**NOTE: Beneficial is defined as the prevention of multi-visceral resections, sphincter preservation surgery and sterilization of radio margins.*

2. In the absence of neoadjuvant treatment, adjuvant chemoradiotherapy is recommended for pathologic stage II or III disease. *Level of Evidence Ib*

Clinical Considerations

The most important aspect in considering neoadjuvant therapy is the clinical stage of the disease. Since neoadjuvant CRT results in pathological downstaging, the post-operative yTNM staging is not reliable for adjuvant chemotherapy decisions. Adjuvant chemotherapy should be offered to all patients with cT3 or N positive disease pre-operatively. There are considerations as to which chemotherapy regimen to pursue based on pathological response or lack of pathological response but systemic therapy should be offered as part of the management for all neoadjuvant CRT patients. For locally advanced disease that is clinically assessable as fixed, or on MRI as grossly extending into the mesorectal tissues, the choice of neoadjuvant CRT and subsequent addition of adjuvant chemotherapy falls into a favourable risk:benefit ratio.

For disease that may be only T2 but appears as minimal T3 on MRI due to inflammation or desmoid reaction, the long-term potential side-effects of radiotherapy are not as acceptable given a minimal benefit of radiotherapy or chemotherapy for T2 node negative disease. Post-operative pathology after CRT for these patients cannot distinguish the difference between no response in an initial cT2N0 to yT2N0 patient from a good pathological response in a cT3N+ to yT2N0 patient. Thus, MRI assessment becomes increasingly important to eliminate cT2N0 patients from overtreatment with radiotherapy pre-operatively. Review of the imaging by the surgeon with the radiologist is crucial, and the distance from the tumour to the potential CRM, the mesorectal fascia, in anterior, posterior and lateral directions should be as clearly described by the radiologist as possible in the report.

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VI. Adjuvant Chemotherapy

Background

Current literature largely considers colon cancer and rectal cancer to fall under one umbrella term - "colorectal carcinoma". This results in most of the rectal cancer chemotherapy data being extrapolated from studies of colon or colorectal cancer. Amongst this data is definitive evidence showing the benefit of adjuvant chemotherapy in colon cancer.

Key Evidence

In the pre-TME era the evidence is clear; adjuvant chemotherapy and chemoradiotherapy improves overall survival and recurrence free survival in stage II and III colorectal cancer.[1] Since the advent of TME, the results of clinical trials are highly variable, and therefore no unifying consensus exists between centres.[2-7] There does appear to be a modest benefit in disease free survival and local recurrence control for patients who receive adjuvant chemotherapy after TME. In a secondary analysis, one large European study indicated a survival benefit of adjuvant chemotherapy for patients who had significant downstaging from neoadjuvant therapy. [8] This was not seen in patients who did not experience downstaging prior to surgery.[8]

Recommendation

Post-operative fluoropyrimidine-based adjuvant chemotherapy for non-metastatic disease should be offered to patients with stage II (T3 or T4) and stage III (irrespective of subsequent pathologic stage) rectal cancer OR any pathologic stage II or III rectal cancer. *Level of Evidence Ia*

Clinical Considerations

Post-operative chemotherapy may be withheld in cases where post-operative recovery is prolonged and significant complications preclude safe administration within a reasonable period of time.

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VII. Rectal Cancer Surgery

Background

Several retrospective and prospective studies have shown improvement in local recurrence rates with application of TME surgery. A Dutch study comparing local recurrence rates in conventional surgery (16%) to TME surgery (9%) shows the impact of this technique.[1] Addition of pre-operative radiation has further improved these results (local recurrence rate of 11% in irradiated versus 27% with surgery alone).[2,3] Tumours in the distal third of the rectum require special attention as there is a higher rate of margin positivity following resection and increased risk of local recurrence.[4] A Glasgow study demonstrated that colorectal surgeons have better local and overall recurrence rates when compared with general surgeons.[5]

Key Evidence

TME surgery has greatly decreased local recurrence rates in rectal adenocarcinoma.[2,6] In the Dutch mesorectal trial, all surgeons were trained in the TME technique; the resultant overall local recurrence was 5.3% at 2 years.[7] The Stockholm and Norway studies showed that after a TME training session, local recurrence rates decreased by more than 50%.[8,9] A number of retrospective studies have concluded that high volume subspecialist surgeons should perform the surgery if the tumour is located in the distal third of the rectum, less than 2 cm from the sphincter complex, or in complex cases (i.e., locally recurrent adenocarcinoma, clinical fixation, invasion into adjacent pelvic organs).[10] When comparing high volume general surgeons (> 1 TME/month) to low volume (< 1 TME/month) there was a marked difference in local recurrence rates (4% versus 10%).[11] A similar phenomenon was seen when comparing hospital caseloads (> 30 cases/year versus < 10 cases/year) with local recurrence improving two-fold.[12]

Recommendations

1. For mobile tumours located in the upper and mid-rectum, the surgeon must be trained and have experience in performing total mesorectal excision (TME).
2. For recurrent rectal adenocarcinoma or those patients requiring complex en-bloc resection of adjacent pelvic organs, subspecialty training (colorectal or surgical oncology) is preferred.
3. Where there is a desire for sphincter preservation in low rectal cancer, the patient should be referred to a subspecialty trained surgeon for assessment.

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VIII. Implementation and Dissemination

The value of guidelines truly lies in their implementation and use. For that purpose, consideration was given to implementation tools during the planning of the consensus meeting, at the meeting, and during the drafting of this guideline document. Several tools emerged:

Local Consensus and Leader Support

As part of the knowledge translation approach, all physicians for whom these guidelines are applicable were invited to participate in the consensus meeting. There was an overwhelming response and a large attendance. An interdisciplinary contingent from Nova Scotia was in attendance and expressed interest in the consensus process utilized. Continuing Medical Education (CME) credits were offered.

Attendees from the meeting are expected to act as local opinion leaders disseminating and providing guidance to their colleagues on the recommendations developed at the consensus meeting.

CancerCare Resources

It was recognized during the meeting that resources would be needed to distribute these guidelines to the community. For that purpose, the guideline will be accessible online through the CancerCare Manitoba website. Online availability will be preceded by an e-blast notification with the website embedded. Announcement of the guideline and updates will be through established provincial communication channels; Community Oncology Program to CCPN rural sites, UPCON clinics and WRHA Community Oncology Program sites. This guideline will also be provided to partner organizations and guideline reviewers in other provinces. Use of the guideline in clinics will be through the online version.

Referring Checklist

For the purpose of streamlining and standardizing care it was suggested to develop an automatic checklist that would generate at the time of pathologic reporting. It would provide a clear identifier to where (if any) delays were occurring. This would be based on the existing Synoptic Surgical Reporting from the Canadian Partnership Against Cancer (CPAC).

TME Training Session

The initiative began at the meeting to institute a TME training session for all general surgeons who were interested in colorectal cancer surgery. The session was held on April 21, 2012 and was attended by more than 50 general surgeons from Manitoba, Saskatchewan and Northwest Ontario. The session included a series of didactic lectures and a structured cadaveric anatomy lab with mesorectal dissection.

Audit and Feedback

Adherence to these guidelines will be measured one year after publication. There will also be a measure of hard outcomes via chart audit in 5 years.

IX. Contact Physicians and Contributors

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Approved By

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X. Conflicts of Interest

In accordance with the CCMB policy no. 01.001, “Conflict of Interest”, the authors of this guideline declare that no commercial support was received for their presentations at the 2011 Provincial Rectal Cancer Consensus meeting or during development of this guideline.

XI. Appendices

Appendix I

Small Group Discussion Table

Statement		Group A	Group B	Group C
Acknowledging that EUS may be superior for small or low rectal cancers, all rectal cancer patients should undergo abdomino-pelvic CT for M staging and either pelvic MRI or EUS for T and N staging. Pelvic MRI would be the preferred modality for all stenotic tumours.	Support	17		15
	Do Not Support			
	Support with Modification		17	
	Modification	"abdomino-pelvic CT and radiographic evaluation of the chest"	"Acknowledging that EUS may be superior for small or low rectal cancers, all rectal cancer patients should undergo abdomino-pelvic and chest CT for M staging and either pelvic MRI or EUS for T and N staging. Pelvic MRI would be the preferred modality for all stenotictumours. The expectation would be for the EUS to be done on an expedited basis and MRI to be done within 10 business days."	

Small Group Discussion Table – cont'd

Statement		Group A	Group B	Group C
In patients with high risk clinical stage II (T3 or T4) and stage III rectal cancer that have neoadjuvant chemoradiotherapy, adjuvant chemotherapy should be offered for non-metastatic disease regardless of pathologic stage.	Support			15
	Do Not Support			
	Support with Modification	17	17	
	Modification	"After neoadjuvant therapy, patients with T4N0 (clin) and stage III rectal cancer (clinically) should be offered adjuvant chemo-XRT. T3N0 (clin) could be considered for adjuvant therapy"	"Fluoropyrimidine-based adjuvant chemotherapy"	

Small Group Discussion Table – cont'd

Statement		Group A	Group B	Group C
Preoperative radiotherapy should be strongly considered for clinical stage II and III resectable rectal cancer.	Support	17		13
	Do Not Support			
	Support with Modification		17	2
	Modification		"Preoperative radiotherapy is recommended for clinical stage II and III resectable rectal cancer	"Patients with clinical stage II or III resectable rectal cancer should be referred for consideration of neoadjuvant therapy (15)"

Small Group Discussion Table – cont'd

Statement		Group A	Group B	Group C
For tumours where downstaging would be beneficial, long-course chemoradiotherapy is the treatment of choice. *In all others a strong recommendation cannot be made, but patient characteristics need to be taken into consideration.*	Support	16		13
	Do Not Support	1		
	Support with Modification		17	1
	Modification		"For tumours where downstaging would be beneficial, neoadjuvant long-course chemoradiotherapy is the treatment of choice."	"For tumours where cytoreduction (i.e., locally advanced) would be beneficial, long-course chemoradiotherapy is the treatment of choice. In all others a strong recommendation cannot be made, but patient and tumour characteristics need to be taken into consideration"

Small Group Discussion Table – cont'd

Statement		Group A	Group B	Group C
The use of neoadjuvant chemoradiotherapy is the preferred treatment for appropriately staged and selected patients for increased local control.	Support			12
	Do Not Support			
	Support with Modification		17	3
	Modification	"this question answered previously"	"To improve local control, pre-operative radiotherapy is recommended (either as short-course or long- course chemoradiotherapy where clinically appropriate). In the absence of neoadjuvant treatment, adjuvant chemoradiotherapy is recommended for pathologic stage II or III disease."	"Delete this statement"

Small Group Discussion Table – cont'd

Statement		Group A	Group B	Group C
For mobile lesions in upper and mid-rectal location, the surgeon must be trained in, and have experience in performing TME.	Support	12		15
	Do Not Support	5		
	Support with Modification		17	
	Modification	"Considered replacing "must" with "should". Wording that is too strong may make it difficult for some surgeons to continue their practice, even though they are performing a technically correct TME (despite the fact they have not formally been trained). Furthermore, we worried that being too exclusive may, in fact work against the provision of ideal patient care. Strong wording can prove useful to direct funding in an attempt to standardize care. On the other hand, it could be used by administrators (with narrow viewpoints) to eliminate perfectly competent people from providing care. It is the latter point that concerned us with how strongly to word this statement."	"The surgical standard of care for rectal tumours is a properly performed meso-rectal excision (total or partial)."	

Small Group Discussion Table – cont'd

Statement		Group A	Group B	Group C
	Support	5		8
	Do Not Support	12	17	2
	Support with Modification	14		4
*For distally located rectal lesions: - with clinical fixation **or** -requiring en bloc resection of adjacent organ or anal sphincter **or** - whose which are recurrent cancers; subspecialty training (colorectal or surgical oncology) is preferred*	Modification	"Sub-specialty training (colorectal or surgical oncology) or demonstrated competency is preferred."		"For recurrent rectal cancer or those requiring complex en bloc resection of adjacent pelvic organ resection, subspecialty training (colorectal or surgical oncology) is preferred. Where there is a desire for sphincter preservation in a low rectal tumour, the patient should be referred to a subspecialty trained surgeon for assessment."

Appendix II

Levels of Evidence

Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed, quasi- experimental study
III	Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

British Committee for Standards in Haematology 2007 http://www.bcshguidelines.com

Appendix III

Guiding Assumptions

- Presenters' recommendations are based upon best available evidence from review of current published literature
- Presenters are unbiased in their presentation of the best available literature
- Participants will use the data to assess the validity and appropriateness of the consensus statement
- Participants will remain unbiased and attempt to make decisions based on the best available evidence as presented
- All consensus items will be reviewed prior to discussion of any particular items where consensus has not been reached
- Consensus will be reached as a product of the discussion groups, first individually and then as a consortium
- Consensus is defined as 'agreement of 75% of participants in attendance at the afternoon session'
- If any participant leaves the conference before the end of the day, it will be assumed that he/she is in agreement with all of the final consensus statements
- Participants are expected to act as local opinion leaders and provide guidance to their clinical peers concerning the consensus information generated by this conference

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