Cancer Care Nova Scotia

Clinical Standards for the Treatment of Rectal Cancer in Nova Scotia

nova scotia health authority

Endorsed by CCNS Clinical Standards Oversight Committee: May, 2016
Approved by NSHA VP Integrated Health Services, Program of Care 1 and Senior Leadership Team: June, 2016

Table of Contents

Introduction

In 2011, Cancer Care Nova Scotia (CCNS) began the development of clinical standards for rectal cancer as a result of concerns, identified through a chart review, that there were unacceptable variations in care and outcomes for rectal cancer patients across Nova Scotia.

A Working Group was established with members from across the province representing the key disciplines involved in rectal cancer treatment and a patient. The Working Group began meeting in January 2012. See Appendix 7 for a description of the development process and Appendix 9 for a list of Working Group members.

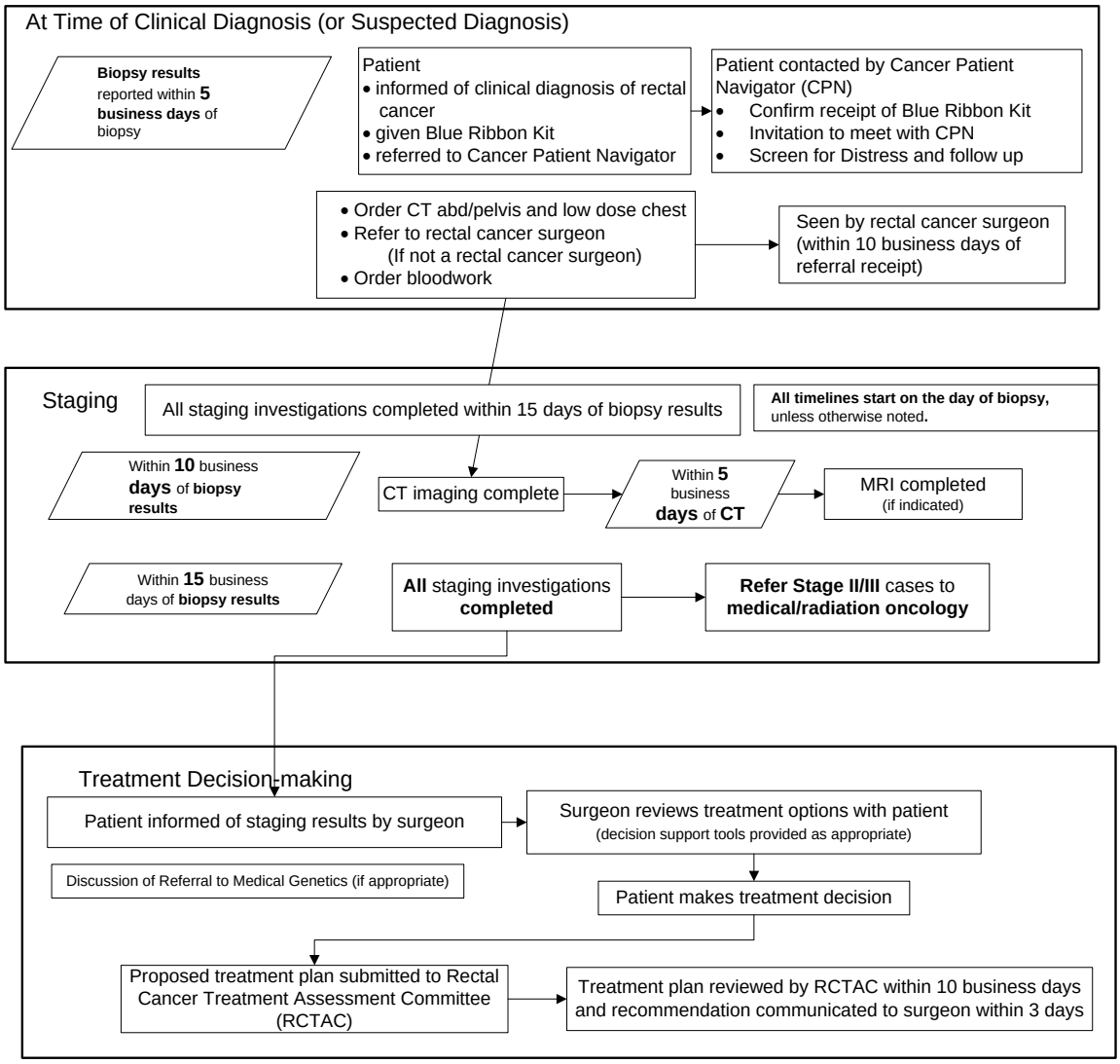
The purpose of the Nova Scotia Rectal Cancer Treatment Standards is to define the standards that must be met by physicians, other members of the interdisciplinary care team and healthcare facilities that treat patients with rectal cancer. This will ensure that all patients receive consistent, high quality care regardless of where they live in the province. This document addresses all aspects of rectal cancer care from diagnosis to survivorship and/or palliation.

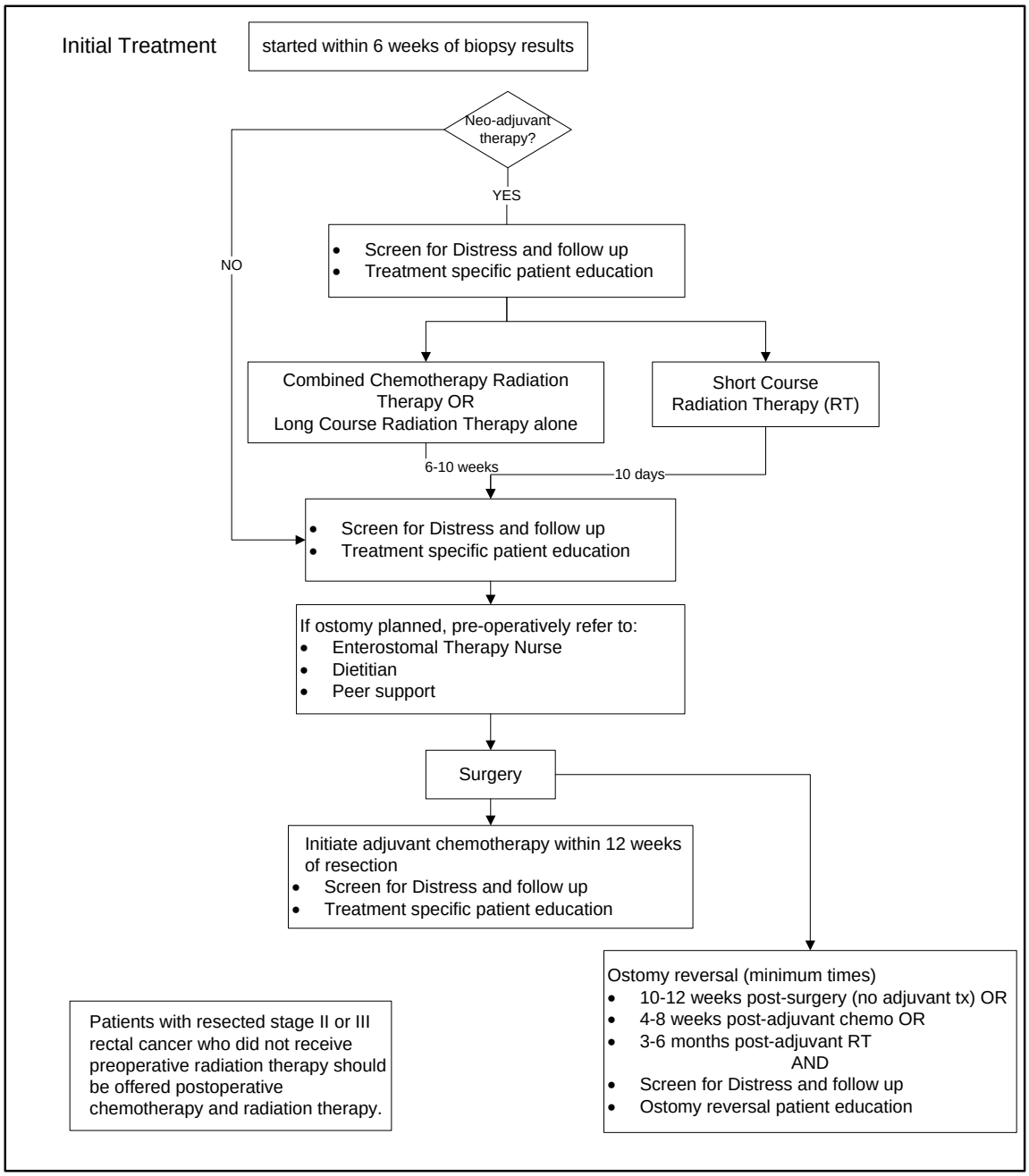
The recommendations have been written for health care providers in Nova Scotia based on current evidence, best practice and the Nova Scotia context. The Working Group adopted and/or adapted recommendations from guidelines as appropriate for the Nova Scotia context. References are provided at the end of this document. Where issues of importance in Nova Scotia were not addressed by the references, the Working Group provided expert opinion. Unless otherwise specified, the recommendations were based on Working Group consensus.

A list of the source guidelines and the abbreviations used in this document can be found in Appendix 1.

CCNS will work collaboratively with the NSHA to develop implementation plans and priorities to support the achievement of these standards.

Overview of Initial Rectal Cancer Treatment




Initial Treatment
started within 6 weeks of biopsy results
Neo-adjuvant therapy?
YES
NO
Screen for Distress and follow up
Treatment specific patient education
Combined Chemotherapy Radiation Therapy OR Long Course Radiation Therapy alone
Short Course Radiation Therapy (RT)
6-10 weeks
10 days
Screen for Distress and follow up
Treatment specific patient education
If ostomy planned, pre-operatively refer to:
Enterostomal Therapy Nurse
Dietitian
Peer support
Surgery
Initiate adjuvant chemotherapy within 12 weeks of resection
Screen for Distress and follow up
Treatment specific patient education
Ostomy reversal (minimum times)
10-12 weeks post-surgery (no adjuvant tx) OR
4-8 weeks post-adjuvant chemo OR
3-6 months post-adjuvant RT
AND
Screen for Distress and follow up
Ostomy reversal patient education
Patients with resected stage II or III rectal cancer who did not receive preoperative radiation therapy should be offered postoperative chemotherapy and radiation therapy.

Overview of Rectal Cancer Treatment Timelines

The recommendations in this section have been taken from the other sections in the document and collected here to provide an overview of appropriate time frames for the various aspects of rectal cancer treatment.

Standards:

Application

These wait-time standards apply to all specialists involved in the diagnosis and treatment of rectal cancer.

Overall Timeline

The treatment plan (i.e. the first treatment (surgery conducted or chemotherapy and/or radiation therapy started)) should be initiated within 6 weeks of the date of biopsy. If there is a delay past 6 weeks, the reason will be documented.

(CCNS Working Group consensus)

Pre-treatment Investigations
(Recommendation 1 from Pre-treatment Investigations for Clinical Staging)

All timelines start on the date of biopsy.

At the time of Diagnosis
(from *Guidelines for the Investigation of Patients with Symptoms Suggestive of Colorectal Cancer*)

The endoscopist diagnosing the cancer will **immediately**:

- inform the patient and family of the probable diagnosis, next steps and timelines
- refer to Cancer Patient Navigator
- order CT (abdomen/pelvis and low-dose chest)
    - The endoscopist will preferably contact the radiologist directly to inform them of the case when ordering the imaging.
- order blood work (see Pre-treatment Staging Investigations for details)

If the endoscopist is not a rectal cancer surgeon[1], a referral to a rectal cancer surgeon should be sent within one day of the clinical diagnosis being made. **The rectal cancer surgeon must see the patient within 10 business days of receiving the referral.** The referring endoscopist should confirm with the receiving surgeon that the referral has been received and that the patient can be seen urgently.

It is important to organize tests and referrals concurrently for maximum efficiency of time and to streamline the decision to treat.(CCNS Working Group consensus)

[1] **Definition:** The Rectal Cancer Surgeon is a surgeon who meets the established criteria for rectal cancer surgery in Nova Scotia. See Rectal Cancer Surgeon section for details.

Timeline for Completion of Investigations and Related Referrals
(from Pre-Treatment Staging Investigations)

- CT imaging should be completed within 2 weeks (10 business days) of the date of biopsy to ensure that the appropriate information is available to make timely pre-treatment management recommendations to the Rectal Cancer Treatment Assessment Committee.

- Pelvic MRI, if required (as determined by the radiologist), to be completed within 5 business days of the CT.

- All other pre-treatment staging investigations (blood work, colonoscopy) should be completed within 3 weeks (15 business days) of the clinical diagnosis.

- Biopsy reporting must be complete within 5 days of the biopsy being taken.

- Pre-operative referrals to Medical/Radiation Oncology will be made when the pathological diagnosis is confirmed. The referral can be made while other investigation results are pending.

- ORs will be booked and other necessary pre-operative arrangements made when the surgeon makes the decision to operate.

(CCNS Working Group consensus)

The NSHA Zones are encouraged to develop protocols to expedite requisitions for suspected rectal cancer.

Rectal Cancer Treatment Assessment Committee (RCTAC)
(from Recommendation 1 RCTAC)

The RCTAC will review the proposed treatment plan within 10 business days of receipt and communicate its decision to the referring surgeon within 3 days of the RCTAC meeting.

(CCNS Working Group consensus)

Treatment Plan Initiation

The treatment plan (i.e. the first treatment; surgery conducted or chemotherapy and/or radiation therapy started) should be initiated within 6 weeks of the clinical diagnosis. If there is a delay past six weeks, the reason will be documented.

Neo-adjuvant Therapy
(Recommendation 1 from Neo-Adjuvant Therapy)

Neo-adjuvant therapy should begin within 6 weeks of the biopsy date.

(CCNS Working Group consensus)

No Neo-Adjuvant Therapy
(Recommendation 2.1 from Surgery)

Surgery should be ideally performed within 6 weeks from the biopsy date of clinical diagnosis if no neo-adjuvant therapy is to be undertaken.

(CCNS Working Group consensus)

Timing of Surgery Following Neo-Adjuvant Therapy
(Recommendation 2.2 from Surgery)

Curative surgery 6-10 weeks following the completion of neo-adjuvant long course chemoradiotherapy.

The exception is the use of short-course radiotherapy where, in relatively healthy patients, surgery can occur immediately after radiotherapy, and ideally within 10 days of the initiation of radiotherapy (CCO).

Adjuvant Therapy

Adjuvant therapy should be started within 12 weeks of resection. If a post-operative complication precludes this, adjuvant chemotherapy can still be offered at the discretion of the treating physician.

See appropriate sections in Appendix 1 for evidence sources.

1.0 The Rectal Cancer Surgeon

Rationale:

The delivery of high quality rectal cancer care requires the involvement and coordination of a variety of health care disciplines. The rectal cancer surgeon is uniquely positioned to serve as the coordinator of this care as he/she is actively involved in all aspects of the rectal cancer patient's treatment (i.e. diagnosis, active treatment, and long-term surveillance).

Standards:

1.1 Surgeons treating rectal cancer should have experience and training with Total Mesorectal Excision (TME) surgery, maintain satisfactory experience in the surgical management of rectal cancer and refer all patients to the Rectal Cancer Treatment Assessment Committee for review of treatment plan.

For transparency and quality assurance, there will be a process for assessment and monitoring the quality of TME surgery and reporting of surgical outcomes.

1.2 It is the role of the rectal cancer surgeon to inform the patient about his/her disease, prognosis and treatment options.

1.3 The rectal cancer surgeon is responsible for ensuring the following occurs:

- pre-treatment investigations,
- development of the initial treatment plan,
- referral to key professionals such as;
    - Cancer Patient Navigator
    - Pre-admission clinic
    - Enterostomal Therapy Nurse
    - Psychosocial Oncology Specialist when needed
    - Dietitian
- referral to Rectal Cancer Treatment Assessment Committee
- referral to Medical and Radiation Oncology (when appropriate)
- long-term surveillance
- investigation and management of abnormal findings or possible cancer recurrence
- communication with the primary care provider

2.0 Pre-Treatment Investigations for Clinical Staging of Rectal Cancer

Rationale:

Pre-treatment staging of rectal cancer is critical for optimum treatment by identifying characteristics that influence the treatment strategy in order to maximize survival and quality of life for the patient. The implications of either under-staging or over-staging rectal cancer can be substantial.

These investigations will be used to direct decisions regarding choice of primary treatment, including surgical intent (curative or palliative) and whether to recommend neo-adjuvant therapy. Staging information will be provided to the Nova Scotia Rectal Cancer Treatment Assessment Committee for review and discussion of the patient's condition and treatment options proposed by the surgeon and to make recommendations that will achieve optimal patient outcomes.

Standards:

2.1 Timeline for Completion of Investigations and Related Referrals
See clinical pathway for rectal cancer patients.

These wait-time standards apply to all specialists involved in the diagnosis of rectal cancer.

All timelines start on the date of biopsy.

a) When the diagnosis is made by an endoscopist who does not treat rectal cancer, a referral to a rectal cancer surgeon should be sent within 1 day of the biopsy date. The rectal cancer surgeon must see the patient within ten (10) business days of receiving the referral. The referring physician should confirm with the receiving surgeon that the referral has been received and that the patient can be seen urgently.

b) Biopsy results should be transcribed and reported within one (1) week (five (5) business days) of biopsy.

c) CT imaging should be completed within two (2) weeks (ten (10) business days) of the biopsy date to ensure that the appropriate information is available to make timely pre-treatment management recommendations to the Rectal Cancer Treatment Assessment Committee. MRI, if required, is to be completed within five (5) business days of the CT. All endoscopsists will preferably contact the radiologist directly to inform them of the case when ordering the imaging.

d) All other pre-treatment staging investigations (bloodwork, colonoscopy) should be completed within three (3) weeks (15 business days) of the biopsy date.

NSHA Zones are encouraged to develop protocols to expedite requisitions for suspected rectal cancer.

Rationale:

Keeping wait times as short as possible to address patient anxiety is a reasonable objective. The Working Group recognizes that these are tight timelines. We believe that the system is capable of meeting these timelines if appropriately challenged and organized. Achieving these wait times requires coordination, communication and collaboration by all specialists, both urban and rural. It is important to organize tests and referrals concurrently for maximum efficiency of time and streamline the decision to treat:

- Gastroenterologists (or other non-rectal cancer surgeons) who diagnosis rectal cancer will immediately order CT and MRI while also referring to the surgeon.
- ORs will be booked and other necessary pre-operative arrangements made when the surgeon makes the decision to operate
- Referrals to Medical/Radiation Oncology will be made when the pathological diagnosis is confirmed. The referral can be made while other investigation results are pending.

2.2 Pathology Review of Biopsy and Histological Diagnosis

All suspected rectal cancers will be biopsied and a definitive histopathologic diagnosis obtained prior to initiation of treatment. (BCSON, NCCN)

2.3 Colonoscopy (pre- or post-op)

a) In a non-obstructed patient, complete imaging of the colon should be obtained pre-operatively: either full colonoscopy or with CT colonography (where complete colonoscopy is not possible).
b) In an obstructed patient, post-op colonoscopy will be performed as soon as safe following completion of therapy (chemotherapy and closure of ileostomy).

(CCNS Working Group consensus informed by AHS (early), BCSON, BCCA, CACC (early), NCCN, SIGN)

2.4 Blood Work

- CEA,
- CBC with differential,
- liver (total bilirubin, alkaline phosphatase, ALT, LDH, INR) and renal function tests

Pre-operative baseline CEA is important to determine if the patient's tumour is a CEA producing tumour. This provides context for interpreting the post-operative CEAs that will be done to monitor for either a future disease recurrence or a new primary colorectal cancer for those patients who have been treated with curative intent.

(AHS (early), NCCN, NZ)

2.5 Imaging
(See Appendix 2 for specifics regarding requisitions, protocols and reporting expectations)

- Intravenous (IV) contrast enhanced CT scan of abdomen and pelvis.
  *Staging CT must precede MRI.
- Rectal cancer patients requiring MRI should have pelvic phased-array MRI for identification of circumferential resection margin (CRM) and tumour local staging. Radiologists will expedite MRI booking based on CT results (see Appendix 2 for radiology reporting requirements).
- When available, endorectal ultrasonography may be complementary to MRI in some T1/2 patients to enhance pre-operative determination of T-stage.
- A low-dose CT scan of the chest should be performed at the same time as the CT abdomen/pelvis (to exclude distant metastases and to provide a baseline for surveillance)

  There is a paucity of data assessing the optimal chest staging strategy for patients presenting with rectal cancer. The CCNS Working Group discussed in detail the benefits and harms, and a vote was taken on the final recommendation.

FDG-PET
A routine PET scan is not indicated for pre-op staging baseline in the absence of synchronous metastatic disease.

(NCCN)

2.6 Evaluation and Documentation of Tumour Height Pre-operative assessment of tumour height (location in the rectum) is essential for determining the management of rectal cancer. This information is needed to guide the use of neo-adjuvant chemotherapy/radiation and determine the type of surgery that will be performed (radical vs. local excision, sphincter-preserving vs. APR).

All patients should undergo pre-operative digital rectal examination, and endoscopic evaluation of the rectum with a rigid and/or flexible scope (AHS (early), BCSON, BCCA, NCCN, CCO).

The following information must be recorded by the operating surgeon and communicated to the RCTAC:

i. Is the tumour palpable? (Yes/ No)

ii. For tumours that are palpable on rectal exam:
- Does the tumour invade the anal sphincter? (Yes/ No)
  - If it does NOT invade the anal sphincter, what is the distance from the top of the anorectal ring to the lower edge of the tumour on rectal exam?
- Location of the tumour (anterior/posterior), mobile vs. fixed

- What is the height (in cm) of the lower margin of the tumour from the anal verge? (document type of scope used)

iii. For tumours that are not palpable on rectal exam:

- What is the height (in cm) of the lower margin of the tumour form the anal verge? (document type of scope used)

iv. Where is the tumour located relative to the rectal folds?

The surgical treatment plan should be based on the original tumour height, radial location and extent (i.e. pre-treatment extent of disease will determine extent of surgical resection). Such details should be documented in the surgeon's pre-operative report and this should be communicated to the Rectal Cancer Treatment Assessment Committee.

2.7 Communication of Stage to Patient

Patients and their families will be informed of their suspected pre-treatment cancer stage based on pre-treatment staging investigations.

Potential inaccuracies of pre-operative testing on tumour staging should be discussed with patients to allow them to make informed decisions (CCO).

3.0 Rectal Cancer Treatment Assessment Committee

Definition:

A provincial treatment planning forum in which a team of surgeons reviews and discusses the proposed surgical treatment plan for every patient with newly diagnosed and recurrent rectal cancer.

The Rectal Cancer Treatment Assessment Committee (RCTAC) is not the same as and should not be confused with the Multidisciplinary Case Conference (e.g. GI Cancer Site Team) or the Interprofessional Care Team. See Appendix 3 for an explanation of the difference between the Rectal Cancer Treatment Assessment Committee, Multidisciplinary Case Conference and Interprofessional Care Teams.

Rationale:

The management of rectal cancer is complex and an appropriate treatment plan is essential to ensure that patients have optimal oncologic and functional outcomes. Previous research has suggested that discussion of rectal cancer patients by a multidisciplinary tumour board (MTDB) is associated with improved outcomes. Although cases presented at MDTB tend to be more complex, a pre-treatment discussion of all rectal cancer cases may be beneficial and has been advocated by others (Swellengrebel).

Such an approach would be very relevant for surgical planning to ensure that patients are appropriately offered sphincter-preserving surgery and extended resections (pelvic exenteration) in cases of locally advanced disease. A second benefit of a single Rectal Cancer Treatment Assessment Committee is the ability to identify all newly diagnosed rectal cancer patients and prospectively track key quality benchmarks.

It would not be feasible for the Gastro-intestinal (GI) Cancer Site Team (CST) to review every patient with rectal cancer in Nova Scotia. However, given the geography and rectal cancer incidence rates in Nova Scotia, a single provincial Rectal Cancer Treatment Assessment Committee is a realistic means of assessing the treatment plan for every patient with rectal cancer. The RCTAC will consist of three surgeons on a rotating basis with access to radiology and radiation oncology for consultation when necessary.

The RCTAC will review the endoscopy findings, diagnostic imaging and treatment plan for each patient with newly diagnosed and recurrent rectal cancer. Review by the RCTAC will be required before the patient can undergo surgery. Information will be submitted electronically, in a standardized manner using a web-based platform for the RCTAC members to review. Complex rectal cancer cases (i.e. those involving metastatic disease) will be referred for Multidisciplinary Case Conference for review by the RCTAC.

See Appendix 1 for additional sources of evidence.

Standards:

3.1 All patients in Nova Scotia with newly diagnosed and recurrent rectal cancer who have potentially curable disease will be referred to the Rectal Cancer Treatment Assessment Committee by their surgeon prior to any definitive treatment. Patients whose proposed treatment plan includes neo-adjuvant therapy will be referred by their surgeon concurrently to the cancer centre to prevent delays.
(CCNS Working Group consensus informed by NZ)

The Rectal Cancer Treatment Assessment Committee will review the referring surgeon's proposed treatment plan and communicate its recommendations (i.e. the proposed treatment plan is accepted, the treatment plan is modified, a new treatment plan is proposed) to the referring surgeon, the patient's primary care provider and the recommendation will be clearly documented in the medical record. It is the responsibility of the referring surgeon to inform the patient of the RCTAC recommendations. (CCNS Working Group consensus informed by Department of Health & Human Services, Melbourne)

A treatment plan will be accepted if all three members of the RCTAC agree.

The referring physician is not obliged to follow the recommendation but should document reasons for choosing another approach (including patient decision). If the patient refuses the RCTAC's plan, this refusal should be documented and signed by the patient.

3.2 The Rectal Cancer Treatment Assessment Committee consists of:

- 2 Colorectal surgeons or surgical oncologists
- 1 Community general surgeon

The RCTAC will have ready access to a radiologist experienced in MRI and a radiation oncologist for their expertise and opinion when deemed necessary by the RCTAC. The RCTAC may also refer the case for multidisciplinary case conferencing.

The RCTAC quorum will be two (2) surgeons.

Any surgeon with the appropriate experience in Nova Scotia can be a member of the RCTAC. Radiation oncologists and radiologists may also be members of the RCTAC.

Membership will be on a rotating basis.

3.3 The RCTAC will review the proposed treatment plan within ten (10) business days of receipt and communicate its decision to the referring surgeon within three (3) days of the RCTAC meeting. The RCTAC will meet at least twice a month.

3.4 All cases reviewed by the RCTAC will be entered into a database for quality assurance purposes.

4.0 Multidisciplinary Case Conference (MCC)

Definition:

The Multidisciplinary Cancer Conference (MCC) is a regularly scheduled multidisciplinary forum where complex and/or metastatic rectal cancer cases are discussed prospectively and recommendations made for best management. The ultimate treatment decision is made by the patient in consultation with his/her physicians. The MCC is not the same as and should not be confused with the Rectal Cancer Treatment Assessment Committee (RCTAC) or the Interprofessional Care Team. There is a wider scope of participation and goals than in the RCTAC. The Interprofessional Care Team consists of all the health professionals involved in the patient's care and may cross NSHA Zone boundaries. See Appendix 3 an explanation of the difference between the Rectal Cancer Treatment Assessment Committee, Multidisciplinary Case Conference and Interprofessional Care Teams.

Rationale:

There is evidence that multidisciplinary consultation, clinics and multidisciplinary cancer conferences improves cancer outcomes. Various organizations (Commission on Cancer (US)) and jurisdictions (Cancer Care Ontario) have set expectations for multidisciplinary case conferences.

While the Gastro-intestinal (GI) Cancer Site Team (based at the QEII) provides a multidisciplinary case conference forum for rectal (and other GI cancers) in Nova Scotia, this does not preclude other centres from establishing their own MCCs for rectal cancer.

Limited evidence indicates that the formation of an MCC and adherence to treatment standards may increase survival for patients with **colon** cancer. Whether the existence of an MCC affects the outcomes for **rectal** cancer patients is unclear (NZ). See Appendix 3 for a summary of the evidence of the role of multidisciplinary team discussion in rectal cancer treatment.

See Appendix 1 for additional sources of evidence.

Standards:

4. 1 Any physician or surgeon in Nova Scotia with a complex or metastatic rectal cancer patient who would benefit from a multidisciplinary discussion has access to a Multidisciplinary Case Conference (i.e. GI Cancer Site Team).

The team's recommendation will be provided in writing to the referring physician/surgeon, the patient's primary care provider and be clearly documented in the medical record. It is the responsibility of the physician who brings the case to the MCC to inform the patient of the recommendations.

The referring physician is not obliged to follow the recommendation but should document reasons for choosing another approach (including patient decision). If the patient refuses the MCC plan, this refusal should be documented and signed by the patient.

4.2 The MCC will consist of health professionals with expertise/ interest in GI cancers including but not limited to:

- Surgical oncologists
- Colorectal surgeons
- General surgeons
- Medical oncologists
- Radiation oncologists
- Pathologists
- Radiologists
- Pharmacists
- Clinical nurse specialists
- Nurse practitioners
- Nurses
- ETN
- Psychosocial health specialists
- Dietitians

Health professionals involved in rectal cancer should actively participate in multidisciplinary discussions. (NZ)

5.0 Interprofessional Care Team

Definition:

The Interprofessional Care Team is the group of professionals from diverse disciplines who provide comprehensive assessment, consultation and treatment to a rectal cancer patient and may include specialist physicians, nurses, primary care practitioners, pharmacists, psychosocial specialists and palliative care staff, with the aim of using their skills and knowledge to conduct a comprehensive multidimensional assessment and plan to maintain the best physical, mental, emotional, functional and social status of the patient (i.e. a wider scope of participation and goals than those of the MCC) (NZ). Members of the Interprofessional Care Team may come from different organizations or facilities. See Appendix 3 for an explanation of the difference between the Rectal Cancer Treatment Assessment Committee, Multidisciplinary Case Conference and Interprofessional Care Teams.

Rationale:

Cancer care generally, and rectal cancer care specifically, requires the skills and knowledge of medical and other health professionals from a variety of disciplines including surgery, medical and radiation oncology, pathology, diagnostic imaging, nursing, pharmacy, enterostomal therapy, dietitians, and psychosocial health professions.

Most guidelines are in agreement that a multidisciplinary team approach is necessary for treating and managing people with colorectal cancer. Recommendations from these guidelines focus on prompt, appropriate and seamless care (NZ).

It is common for rectal cancer patients to be seen by many health professionals within and across multiple health services and across different settings. Lack of coordination and communication can lead to fragmented assessment and care as well as duplication of tests at various settings. Nova Scotia rectal cancer survivors and their families stressed the importance of good communication between health care providers.

See Appendix 1 for additional sources of evidence**.**

Standards:

5.1 An Interprofessional Care Team including all relevant medical specialties and health care professions is required to define and provide the optimal care for a patient with rectal cancer. The Interprofessional Care Team is built around the patient's unique needs and is community-based.

5.2 The plan of care will be communicated to all members of the Interprofessional Care Team.

6.0 Psychosocial Health Services and Supportive Care Recommendations

Definition:

Psychosocial health services are psychological, social and spiritual care services and interventions that enable patients, their families, and health care providers to optimize biomedical health care and to manage the psychological/behavioural, social and spiritual aspects of illness and its consequences so as to promote better health (adapted from Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs[2], pgs 359-360).

Psychosocial health services include:

> **Supportive care** services address a range of needs, including informational and counselling needs related to the management of symptoms and specific practical or functional issues. A variety of disciplines may be involved in provision of supportive care, such as nursing, medicine, nutrition and rehabilitation services. Supportive Care services address unmet needs of persons with cancer who require information, education, support, financial advice, or other practical advice.
>
> **Psychosocial oncology** (PSO) is a specialty in cancer care concerned with understanding and treating the social, psychological, emotional, spiritual, quality-of-life and functional [practical] aspects of cancer, from prevention through bereavement.

The key principles of psychosocial health services and supportive care are:

1. Person/Family centred care
2. Access to services
3. Ethical practice
4. Respect for culture/diversity
5. Interprofessional collaboration
6. Evidence-based care (Canadian Association of Psychosocial Oncology)

There are five aspects of supportive care relevant to rectal cancer patients addressed in this document:

- coordination of support
- communication and information provision
- screening and management of distress symptoms including sexual dysfunction, incontinence, and financial concerns
- access to enterostomal therapy nurses and dietitians
- patient involvement in decision making.

[2] Adler NE, Page AE, editors. Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs. National Academies Press; 2008 Mar 19.

Rationale:

CCNS is adopting the Canadian Association of Psychosocial Oncology (CAPO) *Standards of Psychosocial Health Services for Persons with Cancer and their Families.* These standards will apply to all cancer patients. This section puts the CAPO standards into the context of care for rectal cancer patients in Nova Scotia.

Receiving a diagnosis of rectal cancer and facing both emotionally and physically demanding treatment options are significant and life changing events for most people. Rectal cancer treatment can result in poor body image, low self-esteem, sexual dysfunction, bowel issues, flatus, and odor that can interfere with quality of life during treatment and into survivorship. Patients who have stomas report particular difficulty in social functioning (i.e. problems with work, frequency of social contacts, quality of relationships) and diet as well as problems with management of the stoma such as leakage and odor. The cost of stoma supplies can be a financial burden to many stoma patients.

Feedback received from Nova Scotia rectal cancer survivors and their families during the review of the draft standard re-affirmed the importance of psychosocial health services including financial support and assistance with insurance issues. They noted the specific and unique need for support while living with an ostomy, and at the time of ostomy-reversal.

The Working Group feels strongly that psychosocial health services are important and recommends that psychosocial interventions should be a standard of care to address emotional adjustment, functional status, knowledge of disease, treatments and disease related symptoms and overall (including financial) quality of life. There should be an integrated and coordinated system that involves the patient and their family, support agencies, interprofessional collaboration amongst health professionals and encompasses both the hospital and the community.

See Appendix 1 for additional sources of evidence.

Standards:

6.1 Access to Psychosocial Health Services

6.1.1 **Persons affected by rectal cancer will receive psychosocial health services that meet their needs and are respectful of, and attend to, their cultural and linguistic diversity, health literacy, gender and sexual orientation** (Canadian Association of Psychosocial Oncology). Nova Scotia rectal cancer patient survivors added that services need to be respectful of and meet the needs of **age, location and (dis)abilities**. Language and literacy includes American Sign Language (ASL) and Braille.

6.1.2 **Persons affected by rectal cancer will be made aware of the different psychosocial and supportive care resources available to them and their families**. Information on how to access these resources is also important. Throughout the cancer continuum, particularly during critical transition points, a discussion will take place about common psychosocial changes that can be expected during this phase. The

concerns of the persons affected by cancer will be acknowledged and discussed throughout their treatment.

Psychosocial health services may include peer or professional led support groups, psycho-education, individual/couple/family counseling or psychotherapy, sexual counseling, psychotropic medication and rehabilitation services (Canadian Association of Psychosocial Oncology).

6.2 Referral to Cancer Patient Navigator

Rectal cancer patients will be referred at the time of clinical diagnosis to a Cancer Patient Navigator or a designated health professional who can provide navigation functions.
(CCNS Guidelines for the Investigation of Patients with Symptoms Suggestive of Colorectal Cancer)

The Cancer Patient Navigator (CPN) is uniquely positioned to support cancer patients and their families throughout the continuum of care. Proactive interventions by navigators improve patient outcomes by coordinating care, providing psychosocial support, making appropriate referrals, and providing and reinforcing patient education.

6.3 Screening for Distress

All rectal cancer patients will be offered screening for and management of distress shortly after diagnosis and at key transition points (e.g. initiation of neo-adjuvant therapy, pre-operatively, adjuvant therapy, end of treatment) (Howes).

Screening for distress, which is the routine and systematic approach to quickly identifying psychosocial health care needs, helps to identify people who are at risk of psychological, physical or social distress. This screening provides the opportunity for further assessment that is specific to the patient's needs and recognizes the individual factors that may place them at increased risk of distress. A detailed assessment helps to identify those patients who require more specific one-to-one intervention and and/or referral to a psychosocial oncology specialist.

6. 4 Financial Concerns

6.4.1 All patients will be informed of financial assistance programs for which they may be eligible.

6.4.2 Patients with financial concerns identified as a result of screening for distress or through other channels will be referred to appropriate resources (e.g. BTO program, Medication Resource Specialist).

Rationale:

Rectal cancer patients may face significant financial pressure as a result of their diagnosis and treatment including costs for ostomy supplies, medications and transportation to and from appointments. The Working Group believes all rectal cancer

patients should have access to financial support as needed. Nova Scotia rectal cancer patients emphasized the impact the diagnosis of rectal cancer has on family finances and the resulting stress.

6.5 Rectal Cancer Patient Education

6.5.1 Patient education will be conducted in accordance with the CCNS Education Standards for Adults Affected by Cancer (Murray).

6.5.2 Standardized rectal cancer patient education resources will be available across the province. These will address preventable harms, treatment effects and how to manage them. Education may be provided through a variety of means including one-to one, group teaching, written and/or electronic resources as appropriate for the patient.

Topics will include but not be limited to:

- Rectal cancer
- Surgical management
- Pre-treatment care (e.g., dental care)
- Pre- and post-op stoma care and Lower Anterior Resection Syndrome (LARS)
- Diet and nutrition
- Tools for making treatment decisions
- Sexual health

6.5.3 Education will be provided at appropriate times based on the treatment plan and starting at the time of diagnosis. Patients should be informed about the possible impact (physical, emotional, sexual, and relational) of treatment before the initiation of any treatment modality, during treatment and after treatment.

If barriers exist that limit understanding (e.g. literacy, language), these need to be recognized and responded to in order to ensure understanding of their condition and potential risks and benefits of treatment options.

6.5.4 Education will be tailored to patients' desired level of involvement.
Education will be individualized based on treatment choices and tailored to abilities, literacy and patient's preferred level of involvement.

Rectal cancer patients are key players in the management of their disease and should receive information tailored to their desired level of involvement in decision making about their cancer management and understanding of their illness.

Healthcare professionals should respect patients' wishes to be involved when making plans about their own management (SIGN).

Patients should be offered the amount of information that is appropriate to their wishes in a way which is sensitive, understandable and accurate (SIGN).

When patients are unable to actively participate in their own care, or have legally designated substitute decision-makers, the substitute decision-maker and/or other care givers will be provided with education.

6.5.5 Pelvic and Sexual Health

6.5.5 a) During pre-treatment visits for pelvic surgery or pelvic radiation, all patients will receive:

- education on the impact of acute and late effects of pelvic radiation and pelvic surgery on pelvic, genito-urinary, sexual health, and fertility
- information on common changes of genito-urinary function, sexual functioning, intimate relationships, body image and fertility
- specific information on how to minimize harms

Education will be individualized based on treatment choices.

6.5.5 b) All patients will be asked about any changes related to genito-urinary function, sexual functioning, intimate relationships, body image and fertility throughout treatment and recovery. The importance of talking to a health professional soon after a change has been experienced will be emphasized. Patients will be given the opportunity to talk with an appropriately trained health professional regarding pelvic and sexual health throughout treatment and during follow-up care.

6.5.5 c) All women will be informed about the side effect of vaginal stenosis post-pelvic radiation, and recommendations for prevention as per the Guidelines on Vaginal Dilation after Pelvic Radiotherapy (International Guidelines Group).

6.5.5 d) Men who have post-treatment concerns about sexual functioning will be referred to urology.

Rationale:

Clear and effective communication of information can improve wellbeing and quality of life (NICE).

Scheer reported a study of 30 rectal cancer patients interviewed at the first post-operative visit.

- None perceived having a choice of surgical options,
- 47% could not recall a pre-operative discussion of risks to bowel function,
- 47% could not recall a pre-operative discussion of risks to sexual function, and
- 57% could not recall a pre-operative discussion of risks to urinary function.

6.6 Nutrition

6.6.1 All rectal cancer patients will be assessed by a Registered Dietitian during the post-operative period and have ongoing assessment and management as necessary that continues into the outpatient setting.

6.6.2 All rectal cancer patients undergoing neo-adjuvant and adjuvant therapy will be referred for a nutrition assessment by a Registered Dietitian at the commencement of treatment and following chemotherapy and/or radiation therapy.

6.6.3 All rectal cancer patients presenting with partial obstruction will be referred to a Registered Dietitian for guidance on low-fibre/low residue or liquid diets.

6.7 Survivorship Care Planning

6.7.1 All rectal cancer patients will be given the opportunity to attend a group teaching session to help prepare for transition from active treatment to survivorship. This may include opportunities for online support groups.

6.7.2 Rectal cancer patients will be given disease-specific survivorship care plans (CAPO).

In addition to surveillance for rectal cancer, fit patients should be offered age and gender appropriate screenings for other cancers and diseases.

Rectal cancer patients should receive counselling about maintaining healthy body weight, having a physically active lifestyle and eating a healthy diet (Meyerhardt, Earle).

7.0 Clinical Trials

Rationale:

Although there have been significant advances in the treatment of rectal cancer in the last decade, further improvements are necessary. Offering patients the option of participating in clinical trials should be a priority, and there should be a continued effort to design and accrue to trials that assess important patient-related outcomes such as quality of life and symptom control in addition to progression-free and overall survival (CCAC (mets)).

Clinical trials are an essential component to finding better treatments for rectal cancer.

Doctors should encourage patients with rectal cancer to consider participating in appropriate clinical trials for which they are eligible (NHMRC).

See Appendix 1 for additional sources of evidence.

Standards:

7.1 All rectal cancer patients (including patients with recurrent or metastatic disease) should be offered the option of participating in clinical trials for which they are eligible.

A searchable repository of all current open cancer clinical trials in Canada is available at: www.canadiancancertrials.ca.

8.0 Malignant Rectal Polyps

Definition:

An adenoma/adenomatous polyp containing a focus of malignancy.

Rationale:

To provide guidance on the appropriate management of malignant rectal polyps.

Standards:

8.1 All patients with malignant rectal polyps should be referred to a rectal cancer surgeon.

8.2 Management of malignant polyps by endoscopic polypectomy alone is appropriate in some cases. Factors used to make treatment decisions include:

- margin status
- tumour differentiation
- lymphatic and venous invasion
- polyp morphology
- individual patient factors or preferences

Malignant polyps with unfavourable features may require further treatment, but this decision should take into consideration the age, health and wishes of the patient. Treatment decisions will also be influenced by site, particularly in the case of low rectal lesions for which radical surgery would involve abdominoperineal resection and colostomy (NHMRC).

8.3 Appropriate histopathologic assessment of the polyp is essential to making treatment decisions and should include all of the features listed above.

(NCCN, NHMRC)

9.0 Neo-Adjuvant (Pre-operative) Therapy

Rationale:

Over the last two decades, evidence has been accumulating indicating that neo-adjuvant (pre-operative) radiation therapy with or without chemotherapy improves local control in patients with Stage II or III rectal cancer, although it does not improve overall survival when compared to post-operative treatment. This approach does cause increased toxicities compared with surgery alone.

Neo-adjuvant therapy for Stage II and III rectal cancer patients is an area where the evidence is rapidly evolving. Evidence is emerging that low risk Stage II and III patients may not require pre-operative radiation therapy. This reinforces the need for treatment plans for all patients to be reviewed in advance by the Rectal Cancer Treatment Assessment Committee. There is ongoing research to determine the optimal neo-adjuvant treatment of Stage II and III rectal cancer including comparing short-course (5 days) radiation therapy with long-course (5 weeks) and various systemic therapy regimens. Further research is required to determine the optimal timing of surgery following neo-adjuvant therapy.

The gains in local control from pre-operative radiotherapy are well established but they need to be balanced against the significant late side-effects in terms of sexual, urinary and bowel dysfunction and the potential risk of second malignancies (NICE).

See Appendix 1 for additional sources of evidence.

Standard:

These standards are updated recommendations from the Cancer Care Ontario (CCO) Program in Evidence-Based Care (PEBC) *Preoperative or postoperative therapy for stage II or III rectal cancer* (2008) and informed by an updated systematic review conducted in 2012 specifically for this Nova Scotia standard.

These recommendations are predicated on the assumption that adequate pre-operative staging investigations are conducted (see Pre-treatment Investigations for Clinical Staging recommendations) and that the neo-adjuvant therapy is followed by Total Mesorectal Excision (TME). The quality of surgery greatly influences the potential benefits of pre-operative treatments (CCO) (see Surgery recommendations).

9.1 Neo-adjuvant therapy should begin within six (6) weeks of biopsy date.

9.2 Pre-operative chemoradiotherapy is preferred to pre-operative radiotherapy alone (standard fractionation: longer course 45–50.4 Gy in 25–28 fractions) to decrease local recurrence. There is no difference in overall survival (OS) or disease-free survival (DFS). (CCO modified)

3. Pre-operative chemoradiotherapy is preferred to post-operative chemoradiotherapy, with evidence for enhanced local control with no difference in overall survival (OS) or disease-free survival (DFS) (CCO modified).

Capecitabine is an acceptable alternative to infusional 5-fluorouracil (5FU) in combination with radiation in the management of rectal cancer patients (Hofheinz).

As an oral drug, Capecitabine is filled by prescription at retail pharmacies. In NS, the payment of prescription medications is considered the responsibility of the patient, but Capecitabine is covered by most insurance drug plans and by all NS Pharmacare plans. Some plans, including Pharmacare, require "Special Authorization" paperwork to first be completed and approved before coverage is granted. Once granted, there may be leftover costs to the patient (e.g. co-payments). Capecitabine is now available in generic form, and many plans, including Pharmacare, will require the patient to be dispensed the generic version of the drug. If the patient or oncologist prefers the brand version, the patient can be provided a "patient assistance" card to cover any difference in price. It is billed to the manufacturer. These cards are available from the oncologist, oncology clinic nurse, or Cancer Patient Navigator.

There is no role for oxaliplatin in concurrent chemo-radiation for rectal cancer (CCNS Working Group consensus). Four randomized trials have demonstrated greater toxicity and no local control or survival benefit from oxaliplatin-containing CRT neo-adjuvant protocols (Aschele, Gérard, Rödel, Roh).

9.4 For patients with relative contraindications to chemotherapy in the pre-operative period, acceptable alternatives are: pre-operative standard fractionation radiotherapy alone (longer course 45–50.4 Gy in 25–28 fractions) or hypofractionated radiotherapy alone (short course 25 Gy in five fractions) followed by surgery. (CCO modified)

9.5 Pre-operative short course radiotherapy is an alternative to pre-operative chemo-radiation therapy for highly selected patients. All patients considered for this approach should be presented at Multidisciplinary Case Conference. (CCNS Working Group consensus)

9.6 Patients eligible for pre-operative radiotherapy, with or without chemotherapy, should also be considered for adjuvant (post-operative) chemotherapy, with the exception of those who have received short course radiation therapy and those with Stage I pathology. (CCO modified)

9.7 Advanced planning and good communication between the primary surgeon and the radiation and medical oncologists is required to coordinate scheduling. (CCNS Working Group consensus)

10.0 Surgery

Rationale:

Surgical treatment of rectal cancer is a special challenge that calls for the best possible clearance of the tumour in association with preservation of the anal sphincter mechanism and avoidance of injury to the pelvic autonomic nerves when possible. It requires the coordination of care of the surgeon, enterostomal therapy nurse, and medical and radiation oncologists.

The goal is to improve all aspects of the surgical management of patients with rectal cancer in order to improve overall and disease-free survival and improve health-related quality of life (SIGN).

Standards:

10.1 Where is Rectal Cancer Surgery Performed?

Rectal cancer surgery should be performed in institutions (usually tertiary and secondary hospitals) that provide appropriate facilities including:

- Surgeon trained in TME, enterostomal therapist, anaesthetic services, dietitian
- Intensive care and/or high dependency care unit
- 24 hour medical staff availability
- 24 hour operating room access
- On-site CT
- Access to MRI

10.2 Timelines

10.2.1 No Neo-Adjuvant Therapy

Surgery should be ideally performed within six (6) weeks from the biopsy date confirming the diagnosis if no neo-adjuvant therapy is to be undertaken.

10.2.2 Neo-Adjuvant Therapy

Curative surgery may be performed six to ten (6-10) weeks following the completion of neo-adjuvant long course chemoradiotherapy.

The exception is the use of short-course radiotherapy where, in relatively healthy patients, surgery can occur immediately after radiotherapy, and ideally within ten (10) days of the initiation of radiotherapy (CCO).

The optimal timing of surgery following neo-adjuvant long course chemoradiotherapy is currently under debate. A delay of six to ten (6-10) weeks following completion of therapy is commonly practiced; however, there is emerging evidence that delaying surgery beyond eight weeks is associated with improved tumour down-staging. Prospective studies addressing this issue are currently lacking. Based on the available

literature, it is reasonable to consider longer intervals.

10.3 Peri-operative Stoma Education and Marking

Rectal cancer patients report that bowel-related concerns have a significant and enduring negative impact on their quality of life.

10.3.1 All **rectal cancer patients who will receive a planned stoma** and those who have a reasonable chance of receiving a stoma or patients who the surgeon feels would benefit **will be referred to a qualified Enterstomal Therapy Nurse (ETN) prior to surgery** for pre-op counseling, education regarding care and management of stomas, and marking**.** (Registered Nurses Association of Ontario ((RNAO))

Patients will be assessed for their ability to manage stoma self-care. Education will be tailored to the patient's individual needs and abilities.

10.3.2 All rectal cancer **patients who have a stoma will be provided with information** about the **peer and community-based supports** for ostomy patients (e.g. United Ostomy Association of Canada peer support program) before surgery or prior to discharge.

10.3.3 The surgeon's **ostomy plan** (e.g. loop ileostomy, colostomy) will be **documented** and **reviewed by the RCTAC**.

10.3.4 Stoma site marking will be performed on all patients undergoing ostomy surgery by an ETN or a health-care professional who has been trained in the principles of stoma site marking and is aware of the implications of ostomy care and poor stoma site marking (RNAO).

10.3.4 **Assessment and follow-up by a qualified ETN are recommended** for patients and their family **after ostomy surgery** to decrease psychological distress, promote optimal quality of life and prevent complications (RNAO).

<u>Additional Sources of Evidence:</u>

Treatment for colorectal cancer often causes a change in bowel function. This can be distressing for patients and have other adverse effects, including dietary restrictions and changes in body image and sexual function. Patients want to know what to expect after surgery, what is normal and when they should seek further medical advice (NICE).

Feedback received from Nova Scotia rectal cancer patients emphasized the psychosocial health impact of ostomies and the need for information about ostomy care, implications and support both initially and at time of reversal. Rectal cancer patients with a variety of (dis)abilities also indicated the need for tailored education to meet their unique needs.

Regarding the need for support and information at the time of stoma reversal, a literature review (Taylor & Morgan) was conducted in 2011 into quality of life outcomes following stoma reversal in rectal cancer patients. The author concluded that patients often

experience a more negative experience post-reversal than expected. The alteration of bowel symptoms, particularly frequency and urgency of defecation and fecal incontinence, following stoma reversal has the greatest impact.

Two recent articles (Taylor & Bradshaw, Danielsen) suggest that patients are unprepared for the bowel symptoms and recovery period following stoma reversal. Prior expectations appear to be a factor. Patients have "over-optimistic expectations of recovery following this surgery" (Taylor & Bradshaw). Danielsen et al. found that patients waiting for stoma reversal were not worried about commonly reported symptoms (e.g. diarrhea, frequency and incontinence) post-reversal. Danielsen et al. proposed the view that patients expected the closure of the stoma to improve quality of life. As such, the possibility existed that informants' high expectations for life after stoma closure may lead to frustrations if complications regarding bodily function persisted. Thus, complications regarding bodily function might be judged more severely after closure of the stoma, than after creation of the stoma.

Taylor recommended that rectal cancer patients should be made aware of the potential for altered bowel function post-stoma closure and encouraged to report bothersome bowel elimination symptoms. Treatment should promote a proactive strategy to reduce distress and the risk of symptom chronicity (Taylor & Bradshaw).

It is estimated that anywhere from 60-90% of rectal cancer patients who have sphincter preserving surgery will experience changes in bowel habits such as LARS. The likelihood of experiencing LARS has been shown to increase with the use of neo-adjuvant therapy. For more details, see Appendix 4.

10.4 Prophylactic Antibiotics

All patients undergoing surgery for rectal cancer should receive a single peri-operative dose of parenteral antibiotics (administered within 30 minutes before skin incision)
An intra-operative dose of antibiotics should be given for prolonged cases (i.e. >3 hours). (Capital Health)

10.5 Venous Thromboembolic Prophylaxis

It is an Accreditation Canada Required Organizational Practice that patients at risk of VTE are identified and provided with appropriate thromboprophylaxis. Accreditation Canada notes that The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines are a helpful resource for the prevention of VTE. (Accreditation Canada) This recommendation is based on the American College of Chest Physicians guideline.

All patients undergoing surgery for rectal cancer should receive pharmacologic peri-operative prophylaxis with either *subcutaneous low molecular weight heparin* (LMWH, Dalteparin) or low dose unfractionated heparin (LDUH, Heparin)

AND

Mechanical prophylaxis with either graduated compression stockings (GCS) or intermittent pneumatic compression (IPC).
*associated with a lower risk of developing heparin-induced thrombocytopenia compared to unfractionated heparin.

"In patients who are not otherwise at high risk for major bleeding complications, consideration should be given to extended-duration pharmacologic prophylaxis (4 weeks of LMWH) over limited duration prophylaxis." (Gould, Level 1B).

10.6 Bowel Preparation

There are insufficient data to support or refute the use of oral mechanical bowel preparation in the treatment of rectal cancer. The decision to give an oral mechanical bowel preparation and/or Fleet enema should be at the discretion of the operating surgeon.

10.7 Surgical Approach for Stage I Rectal Cancer

Patients with suspected Stage I rectal cancer will be informed of their surgical options (radical excision or transanal/ transanal endoscopic microsurgery (TEM) excision ± chemoradiation) and provided with all of the necessary information to make an informed decision. This includes the increased risk of recurrence and mortality with local excision techniques relative to radical excision. Patients will be provided with decision-making educational tools and materials to assist them in reaching their decision.

Radical excision is the gold standard treatment for Stage I rectal cancer. For patients with Stage I disease who undergo radical surgery, the approach is identical to that described below for patients with stage II/III disease. However, there is a potential role for local excision (transanal excision (TAE) or transanal endoscopic microsurgery (TEM) ± chemoradiation) in patients with suspected Stage I rectal cancer. Therefore local excision options must be discussed with these patients.

Local excision is appropriate for those patients with co-morbidities who would not tolerate radical surgery, and for those who accept an increased risk of tumour recurrence, and a risk of decreased success after salvage surgery (AHS early, Johnston).

Local excision must be accompanied by a prolonged period of intensive post-operative surveillance in patients who would be candidates for salvage surgery or metastectomy.

<u>Rationale:</u>

As Stage I patients may only be seen by the surgeon, the onus is on the surgeon to discuss the risks and benefits of local excision +/-chemotherapy.

10.8 Surgical Approach for Stage II/III Rectal Cancer

Radical excision is required for patients who have stage II/III rectal cancer based on pre-operative evaluation.

10.8.1 For mid- (5-10 cm from anal verge) and low (<5 cm from anal verge) rectal tumours, TME is recommended.

10.8.2 Upper rectal cancers (11-15 cm from anal verge) should have a tumour-specific mesorectal excision with at least a 5 cm fresh distal resection margin (Reynolds).

The pelvic autonomic nerves and left ureter should be identified and documented with care taken to preserve them wherever this is possible without compromising tumour clearance.

(Adopted from BCSON Provincial Guidelines For Rectal Cancer)

*No evidence to suggest that a high ligation of the IMA has an impact on oncologic outcomes.

Evidence (SIGN):

There is evidence from large cohort studies using historical controls that the use of Total Mesorectal Excision (TME) reduces the risk of local recurrence after rectal cancer surgery, and improves survival. It is unlikely that tumours of the upper rectum will benefit from total excision of the mesorectum, as long as the principles of careful dissection in the plane immediately outside the mesorectum are applied. The low anastomosis necessitated by TME results in poorer functional results than a higher anastomosis, and should be avoided unless doing so would compromise adequate mesorectal excision. It is also important to preserve the autonomic nerves in the pelvis to minimize bladder and sexual dysfunction (SIGN).

10.9 Adequate Distal Resection Margin for Low Rectal Tumors

A distal margin of ≥1 cm is ideal. However if clear margins can be achieved and sphincter preservation is possible, a shorter margin may be acceptable. Such decisions will be at the discretion of the operating surgeon.

Measurement must be in the fresh state (not formalin-fixed) due to shrinkage of the specimen.

Rationale:

In the setting of a TME, a 1-2 cm distal margin is preferred; however, in patients with neo-adjuvant therapy, a negative microscopic margin may be acceptable.
The length of the distal margin may vary depending on whether the specimen is measured fresh, fresh and pinned out, fixed in formalin, or fixed in formalin and pinned out. The effect of fixation is minimal if the specimen is pinned out first.

Evidence is emerging that in the setting of neo-adjuvant radiation, a negative microscopic margin, regardless of length, may be adequate.

10.10 Circumferential Margins

The goal is to have a negative circumferential radial margin (CRM). If it does not appear that a standard TME can achieve a clear radial margin based on the pre-operative imaging (MRI), an *en bloc* resection of adjacent organs may be required. This may

require referral to a surgical oncologist or other specialist surgeon.

Rationale:

A positive circumferential margin is an independent risk factor for the development of distant metastases and mortality and is a short-term outcome measure predictive of local recurrence, distant metastases and survival (SIGN, Swellengrebel, Burton).

10.11 Sphincter Preservation

Sphincter-preserving surgery should be considered in any patient where the tumour does not involve the sphincter complex and a clear distal margin can be obtained.

However, other factors that may influence this decision include pelvic anatomy, pre-existing incontinence

- body habitus, tumour size, co-morbid medical status, patient choice, and prior pelvic surgery.

(NCCN)

10.12 Colonic Reservoir

Where technically feasible, a colonic reservoir (J-pouch) should be considered for low pelvic anastomosis (NZ). Other options include a side-to-end anastomosis or a a straight end-to-end anastomosis. There is no role for a coloplasty.

10.13 Diverting Ileostomy

10.13.1Temporary diversion should be at the discretion of the operating surgeon but strongly considered in the setting of low anastomosis following neo-adjuvant chemo/radiation (SIGN).

10.13.2 All patients (regardless of whether they have received pelvic radiation) will have an assessment of the anastomosis by DRE and flexible/rigid sigmoidoscopy at the discretion of the surgeon before closing the ileostomy.

10.14 Proximal Vascular Ligation

Proximal vascular ligation at the origin of the superior rectal artery with resection of all associated lymphatic drainage is appropriate for most rectal cancer resections (Monson).

10.15 Oophorectomy

Oophorectomy is advised for grossly abnormal ovaries or contiguous extension of a rectal cancer, but routine prophylactic oophorectomy is not necessary (Monson).

10.16 Leak Tests

Anastomotic leak is an important and potentially serious complication of colorectal

cancer surgery, and measures to minimize it should be taken. A leak test should be performed for all pelvic anastomoses when a diverting ileostomy is not planned. (The benefit of a leak test in the setting of a low anastomosis and planned diverting ileostomy is unclear.)

10.17 Laparoscopic Assisted Rectal Surgery in Stage II/III Rectal Cancer Surgery

The safety of laparoscopic surgery in the management of rectal cancer is unclear. Laparoscopic surgery for rectal cancer should only be performed in highly selected patients by surgeons with special training and experience in laparoscopic rectal cancer surgery.

All of the principles of open surgery (described above) must be followed (Zerey).

Handling and preparation of specimen in the OR

10.18 Mandatory information on the rectal cancer surgical pathology requisition includes:

- Procedure (e.g. transanal excision, TME, APR etc.)
- Tumour location (upper/mid/lower; anterior/posterior/lateral)
- History of neo-adjuvant therapy
- Tattoo location.

10.19 Transanal Specimens

(Communicate with pathologist on best way to handle and process at each institution)

- Submit whole specimen
- Mark margin(s) with suture(s)
- Pin fresh specimen on cork board in operating room and send to Pathology

10.20 Preparation of Rectal Specimens in the OR

Follow College of American Pathologists/Canadian Association of Pathologists (CAP) protocol for submitting specimen to pathology laboratory.

- Specimens should ideally be received fresh in the laboratory.
- Unless pathologist/assistant able to examine immediately, place in formalin. At such times, specimens should be placed in adequate volume of formalin (10:1 ratio of formalin: specimen volume) and sent intact to pathology lab.

If the specimen is removed after hours or on weekends, at least the proximal margin(s) should be opened to allow fixative into the lumen of the bowel. Place the specimen in an adequate volume of formalin as above (cut longitudinally but no closer than 5 cm from tumour). **Do not cut the mesorectum.**

Submit proximal and distal anastomotic tissue rings to Pathology in separate containers of fixative.

10.21 Final Pathology Report

The final pathology report will be reviewed with the patient and family and they will be included in any treatment decisions required as a result.

10.22 Ileostomy Reversal

10.22.1 Timing of Reversal

10.22.1 a)The timing of ileotomy reversal among patients who do not receive neo-adjuvant therapy is at the discretion of the surgeon and the patient. Typically, a minimum three (3) month period after the initial surgery is required.

10.22.1 b) Ileostomy reversal among patients who receive adjuvant therapy should occur no earlier than four to eight (4-8) weeks after completion of adjuvant therapy. However, this is a minimum timeline and ostomy-reversal may occur later.

10.22.2 Patient information

10.22.2 a) Patients undergoing ostomy-reversal surgery will receive information and education about the potential for altered bowel function (e.g. diarrhea, frequency and incontinence) post-stoma closure and that it may take considerable time for full recovery.

10.22.2 b) Patients who have had an ostomy-reversal will receive consistent information on diet and be referred by their surgeon to a Registered Dietitian for assessment and ongoing management that continues as necessary into the outpatient setting.

10.22.2 c) Rectal cancer patients who have received **sphincter-preserving surgery** will receive information about Low Anterior Resection Syndrome LARS.

11.0 Pathological Parameters in Rectal Cancer

Rationale:

Resection specimens for rectal cancer need to be carefully prepared and dissected to obtain accurate assessment of the tumor characteristics which may be used guide adjuvant therapies and counsel patients regarding prognosis. Tumour stage is an important prognostic parameter. It is recognized that local recurrence of rectal cancer can be accurately predicted by pathological assessment of circumferential margin involvement in these tumours. Optimal management is predicated on productive, open communication between the surgeon and the pathologist so that quality assurance and appropriate mechanisms for evaluation and improvement can be achieved.

11.1 Qualifications for Specimen Assessment

Assessment of tissue specimens by appropriately trained and supervised pathology assistants is critical to the diagnostic process. Fine needle aspiration (FNA) specimens for cytology may be obtained from sites of potential metastasis and expert cytopathologists are required to assess this material (SIGN).

11.2 Specimen Handling in Pathology Laboratory:

11.2.1 Prior to complete fixation:

- The TME quality will be graded on the intact specimen prior to inking the mesorectal margin (see Table 1).
- The circumferential mesorectal margin will be marked with ink.
- The specimen will be opened longitudinally from both the proximal and distal margins toward the tumour, leaving the bowel intact around the region of the tumour. Tissue or gauze will be placed into the unopened bowel lumen.
- The specimen will be placed into an appropriate volume of fixative for at least 48 hours (in formalin for at least the first 24 hours).

11.2.2 Following complete fixation:

The specimen will be sliced in cross-section through the entire region of the tumour at 4-5 mm intervals and each cross-section will be examined to determine:

- Depth of tumour invasion
- Closest distance to inked mesorectal (radial) margin
- Lymph node harvest; note distance of any grossly involved lymph node(s) to the mesorectal (radial) margin

The region of the tumour will be examined by slicing in serial thin (5 mm) transverse sections to allow for optimum assessment of depth of invasion and margins. At least five (5) blocks of tumour will be sampled. The fat will be carefully dissected to retrieve all lymph nodes.

11.3. Staging System

All rectal cancers will be staged using TNM staging system.

11.4. Reporting

Pathology reporting of all rectal cancer specimens will be reported using the Nova Scotia Health Authority pathology template when implemented and available (expected 2016-17).

11.5. TME Grade (complete, nearly complete, incomplete) will be included in the Synoptic Report

Table 1- Grading of quality and completeness of the mesorectum in a total mesorectal excision specimen based on Quirke

	Mesorectum	**Defects**	**Coning**	**Radial Margin**
Complete	Intact and smooth	None or <5 mm	None	Smooth and regular
Nearly Complete	Moderate bulk Irregular	Present, >5 mm but muscularis propria (MP) not visible	Moderate	Irregular
Incomplete	Little bulk	Deep defects where MP is visible	Moderate or marked	Irregular

11.6. Microsatellite Instability (MSI) Testing for Stage II Rectal Cancer

MSI-high rectal cancer patients have a better prognosis and may not benefit from 5FU chemotherapy.

Physicians may request MSI testing for a rectal cancer patient who is negative for lymph node metastasis (i.e. stage II rectal cancer) but positive for high-risk pathological features such as perforation, obstruction, T4 tumour and tumours with lymphovascular invasion.

Patients who are MSI-high should be offered a referral to Maritime Medical Genetics for discussion about genetic testing for Lynch Syndrome. The Referral Form and Guidelines for Genetic Consultation are available on the IWK Health Centre website: http://www.iwk.nshealth.ca/childrens-health/services#/mmgs.

12.0 Adjuvant (Post-operative) Therapy

Rationale:

As this is an area that is rapidly evolving, CCNS contracted with the Capacity Enhancement Program (CEP) of the Canadian Partnership Against Cancer (CPAC) to update the systematic review conducted by Cancer Care Ontario's (CCO) Program in Evidence-Based Care (PEBC) on this topic.

These standards are updated recommendations from the CCO PEBC *Preoperative or postoperative therapy for stage II or III rectal cancer* (2008) (CCO 2-4) and informed by an updated systematic review conducted in 2012 specifically for this Nova Scotia standard.

12.1 Patients with resected stage II or III rectal cancer who have <u>not</u> received any pre-operative chemotherapy or radiotherapy.

12.1.1 Patients with resected stage II or III rectal cancer who have not received pre-operative radiation therapy (RT) should be offered post-operative therapy with an adjuvant treatment protocol including concurrent fluoropyrimidine-based chemotherapy and radiation therapy delivered together (CRT) and fluoropyrimidine-based chemotherapy (CT), which may include oxaliplatin during the non-radiation cycles. (CCO 2-4 recommendation modified for clarity).

The evidence reviewed demonstrates that adjuvant CRT and CT treatment improves survival and reduces local recurrence rates compared to observation alone or RT alone after surgery.

12.1.2 For patients receiving post-operative CRT, use of IV 5-fluorouracil (5FU) or Capecitabine are options. Patient preference and access to oral Capecitabine should be considered. The optimal way of administering IV 5-fluorouracil (5FU) during CRT—via continuous infusion or bolus 5FU—is not clear, since neither method is definitively superior in terms of efficacy or toxicity. Either method of administration can be considered appropriate, and treatments for individual patients should be based on an informed discussion of the potential risks and benefits of each mode of delivery. Capecitabine is also an acceptable option for the CT alone component of adjuvant therapy (CCO 2-4 recommendation modified based on new evidence regarding capecitabine).

It was concluded in a non-inferiority trial (Hofheinz) that Capecitabine could replace fluorouracil in adjuvant or neo-adjuvant regimens for patients with locally-advanced rectal cancer.

There is evidence that patients prefer oral Capecitabine to IV 5FU. As an oral drug, Capecitabine is filled by prescription at retail pharmacies. In NS, the payment of prescription medications is considered the responsibility of the patient, but Capecitabine is covered by most insurance drug plans and by all NS Pharmacare plans. Some plans, including Pharmacare, require "Special Authorization" paperwork to first be completed and approved before coverage is granted. Once granted, there may be leftover costs to

the patient (e.g. co-payments). Capecitabine is now available in generic form, and many plans, including Pharmacare, will require the patient to be dispensed the generic version of the drug. If the patient or oncologist prefers the brand version, the patient can be provided a "patient assistance" card to cover any difference in price. It is billed to the manufacturer. These cards are available from the oncologist, oncology clinic nurse, or Cancer Patient Navigator.

12.1.3 There is no role for oxaliplatin concurrent with adjuvant radiation for rectal cancer (CCNS Working Group consensus based on neo-adjuvant studies).

Four randomized trials have demonstrated greater toxicity and no local control or survival benefit from oxaliplatin-containing CRT neo-adjuvant protocols (Aschele, Gérard, Rödel, Roh).

12.2 Patients who have received pre-operative CRT or RT

12.2.1 In keeping with general practice in North America, it is the expert opinion of the Rectal Cancer Treatment Standards Working Group that all patients who have received pre-operative CRT or RT should be offered fluoropyrimidine-based (5FU) CT post-operatively (CCO 2-4 recommendation modified for clarity).

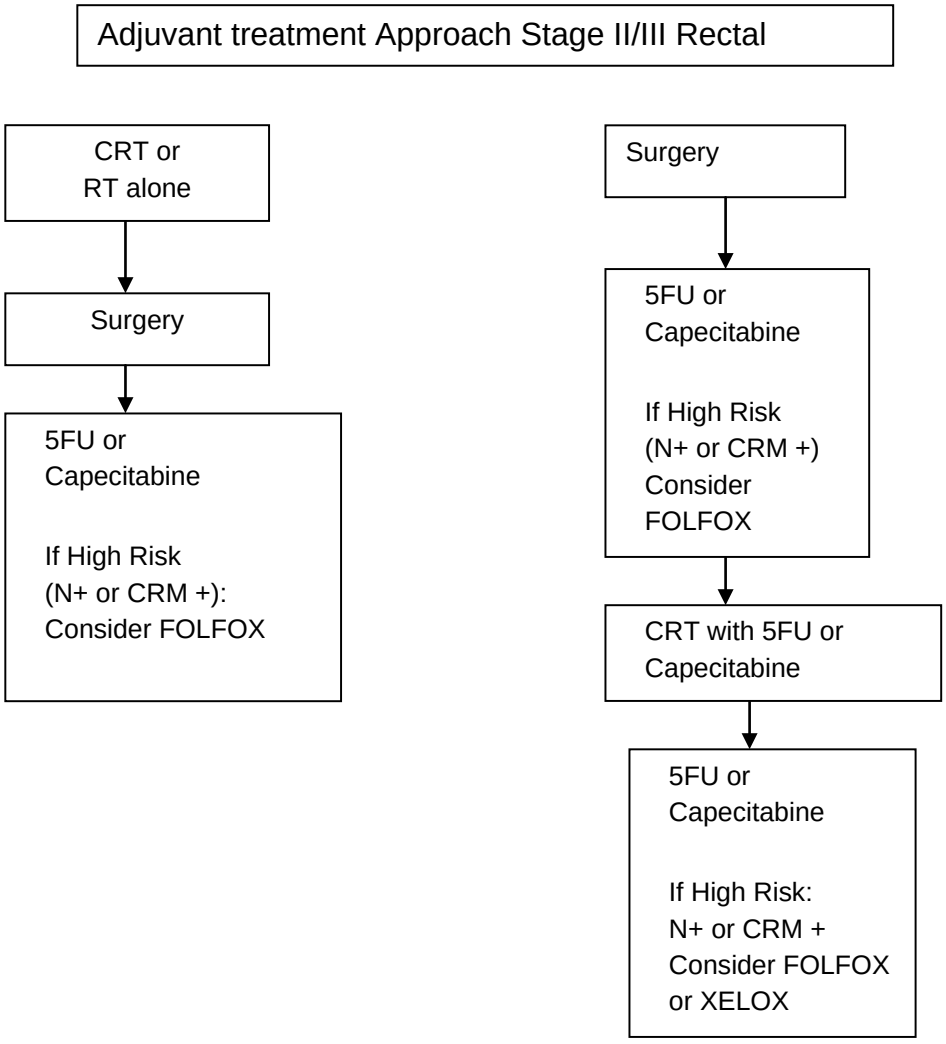
12.2.2 It is the expert opinion of the Rectal Cancer Treatment Standards Working Group that adjuvant oxaliplatin-fluoropyrimidine based CT (e.g. FOLFOX, CAPOX) should be considered for patients at high risk for systemic recurrence including, but not limited to, those who have:

- Clinical or pathologic stage III (node-positive) disease, including those who were node-positive before neo-adjuvant therapy whose pathologic specimens do not reveal any residual nodal disease.
- Circumferential resection margin (CRM) positive resections (CCAC (early))

There is no evidence for oxaliplatin to be given alone without fluoropyrimidine.

In North America, based on extrapolation from phase III trials of adjuvant treatment in colon cancer (MOSAIC trial) (Andre), oxaliplatin in combination with fluoropyrimidine has become accepted as the standard of care in the adjuvant treatment of high-risk rectal cancer. Rectal cancer trials that were underway at the time the MOSAIC trial was reported were closed prematurely. These trials did not meet their required sample sizes. There are no additional studies in the post-operative setting anticipated.

12.3**.** When making treatment decisions, patients should be informed of both the potential advantages of adjuvant therapy and the significant acute and long-term toxicity that can potentially occur with CRT and CT. Other factors to consider in decision-making include visit schedule and treatment location (CCO 2-4 recommendation modified).


Adjuvant treatment Approach Stage II/III Rectal
CRT or
RT alone
Surgery
5FU or
Capecitabine
If High Risk
(N+ or CRM +):
Consider FOLFOX
Surgery
5FU or
Capecitabine
If High Risk
(N+ or CRM +)
Consider
FOLFOX
CRT with 5FU or
Capecitabine
5FU or
Capecitabine
If High Risk:
N+ or CRM +
Consider FOLFOX
or XELOX

13.0 Survivorship and Post-treatment Surveillance

Rationale:

Cancer patients report challenges at the end of active treatment and in transition back to "normal". Survivors live with the fear of recurrence and many have physical and/or emotional treatment effects. Recent attention has been given to the need for support at the time of transition and into survivorship.

There is also emerging evidence that diet and lifestyle may have a role in secondary prevention of colorectal cancer

Between 60 to 80% of rectal cancer recurrences occur within 24 months following primary treatment, and 90% occur within four years. Improved clinical outcomes have been demonstrated when recurrent cancer is treated at an early stage. Therefore, most proposed surveillance protocols emphasize initial follow-up at shorter intervals (Hammond).

Post-treatment surveillance of patients with rectal cancer is performed to evaluate for possible therapeutic complications, discover a reoccurrence that is potentially resectable, and to identify metachronous neoplasms at a pre-invasive stage.

Survivorship Standards:

See Recommendation 9 "Survivorship Care Planning" in the Psychosocial Health Services and Supportive Care section.

Surveillance Standards:

13.1 Who Should Receive Surveillance?

13.1.1 All asymptomatic patients who have undergone potentially curative surgery and are fit for further intervention if disease is detected should be offered follow-up. Those who are unfit for further surgery or who have advanced disease require appropriate follow up directed at psychological support and symptom relief (Department of Health & Human Services, Melbourne).

Surveillance should be guided by presumed risk of recurrence and functional status of patient where early detection would lead to aggressive treatment including surgery. It is especially important in the first two to four (2-4) years, when the risk of recurrence is the greatest (Meyerhardt).

13.1.2 For patients without primary care providers, surveillance will be provided by the rectal cancer surgeon.

13.2 Coordination and Communication of Surveillance Plan

13.2.1 The follow-up plan should be individualized and agreed upon by the patient and the surgeon including who will coordinate surveillance. This will be clearly documented and available to the patient and the primary care physician, explicitly stating who is responsible for ordering the necessary tests.

At the end of adjuvant treatment, a standardized letter will be sent to the primary care provider by the treating oncologist including the recommended surveillance schedule to be followed, and indicating whether a referral to medical genetics should be discussed with the patient (see Appendix 6)

13.3. Investigation of Symptomatic Patients

Post-treatment patients who develop symptoms should have a complete clinical reassessment with appropriate investigations and follow-up regardless of the surveillance protocol.

Any new and persistent or worsening symptoms warrant the consideration of a recurrence, especially:

- abdominal pain, particularly in the right upper quadrant or flank (liver area)
- dry cough
- constitutional symptoms such as:
  - fatigue
  - nausea
- unexplained weight loss
- pelvic pain
- sciatica
- difficulty with urination or defecation (Earle)

The same urgency and time frame as for the symptomatic patient applies (see Guidelines for the Investigation of Patients with Symptoms Suggestive of Colorectal Cancer and the timelines in the Pre-treatment Investigations (not yet published bu submitted for approval)).

13.4 Surveillance Protocol

13.4.1 Stage I

Patients with stage I rectal cancer who have undergone radical surgery should have a colonoscopy twelve (12) months after surgery and then every three to five (3-5) years based on the clinician's judgment and the patient history. Additional surveillance is at the discretion of the surgeon, individualized to the patient and the disease characteristics. There is no evidence of improved survival with routine imaging or blood work (BCCA).

13.4.2 Stage II and III

Recommendations[5]	**Year 1 after surgery**	**Year 2 after surgery**	**Year 3 after surgery**	**Years 4 & 5 after surgery**
Clinic visit and physical exam[1]	Every 3 months	Every 3 months	Every 3 months	Every 6 months
CEA Test [2]	Every 3 months	Every 3 months	Every 3 months	Every 6 months
Assessment of the anastomosis[3]	6 months post-op DRE and flexible or rigid sigmoidoscopy if the anastomosis is not palpable	Assessment of the anastomosis repeated at 18, 24 and 36 months post-op.		
Colonoscopy (to be coordinated by the rectal cancer surgeon)	Yes			Colonoscopy thereafter as long as the patient remains in good health
CT Chest Abdomen and Pelvis[4]	Annually in patients considered fit for potential surgical resection of metastatic disease. Chest x-ray may be considered as an alternative to CT chest			Further routine imaging at physician discretion,particularly if clinical suspicions or elevated CEA.

[1]Clinical evaluation should attempt to highlight any new systemic symptoms, such as fatigue and shortness of breath, as well as more localized symptoms, such as pain, which might be suggestive of increased disease activity. History to elicit gastrointestinal and constitutional symptoms, including nutritional status. Physical examination with particular attention to the abdomen, liver and rectal evaluation (including DRE) (or perineal inspection and palpation in those patients who have had an abdominal perineal resection) (British Columbia Medical Association).

[2] The ASCO Panel asserted that CEA may be checked between the range of 3 to 6 months in the first 2 years, because 80%of recurrences occur in the first 2 to 2.5 years in patients with a high risk of recurrence (Meyerhardt).

[3]Assessment of the anastomosis for all patients (regardless of whether they have received pelvic radiation). The method of assessment (DRE, flexible or rigid sigmoidoscopy) is at the discretion of the surgeon. There is no data to support the use of rigid versus flexible sigmoidoscopy.

[4]Particularly worth noting here is the consensus among guideline developers for annual CT chest for rectal cancer patients for the first three years. There was significant discussion by the CCNS Rectal Cancer Treatment Standards Working Group of the relative harms and benefits of CT surveillance of the chest, particularly the additional exposure to radiation and the frequency of incidental findings, which can lead to further increased surveillance. The final decision was made to recommend CT chest to remain in line with other surveillance recommendations.

[4]These recommendations are based on the surveillance recommendations of the CCNS GI Cancer Site Team (GI CST). The GI CST recommendations themselves were based on the 2005 American Society of Clinical Oncology (ASCO) recommendations.

13.4.3 Stage IV

Although there is no randomized evidence, it is reasonable that all patients should have ongoing surveillance following potentially curative metastectomy consistent with the guidelines for follow-up for Stage II and III patients post-tumour resection.

Additional diagnostic imaging follow-up should be inclusive of the site of metastectomy.

PET/CT is appropriate follow up of elevated CEA with no evidence on CT (CCAC mets).

13.4.4 Special Circumstances

a) Patients who have undergone Transanal Excision

If the Transanal Excision (TAE) was done because of patient age or co-morbidities and inability to tolerate radical surgery then no surveillance is recommended.

Patients who would be candidates for resection of recurrent disease after TAE should undergo aggressive post-operative surveillance as per the surveillance recommended for patients who undergo radical resection of stage II/III disease (see above). However, given the risk of recurrent disease after TAE and the lack of evidence to guide surveillance in this patient population, more aggressive surveillance may be appropriate at the discretion of the surgeon in consultation with the patient.

b) A more frequent schedule may be recommended for patients known or suspected to have Lynch Syndrome (HNPCC) or other high-risk features.

13.5 Stopping Surveillance

Stop regular surveillance when the patient and healthcare professional have discussed and agreed that the likely benefits no longer outweigh the risks of further tests **or** when the patient cannot tolerate further treatments (NICE).

13.6 Follow-up of Positive Findings

13.6.1 Positive findings from surveillance testing should be followed up promptly. Patients with positive findings should be investigated for pelvic/anastomotic recurrence or metachronous metastases and treated appropriately (NCCN).

13.6.2 Primary care providers need to be informed who is providing follow-up for abnormal findings.

13.6.3 Patients with suspected recurrence will be referred back to the rectal cancer surgeon.

a) If CEA is mildly elevated from previously results, repeat test within 28 days (BCCA)
b) Management of patients with an elevated CEA level after resection should include colonoscopy; chest/abdominal/pelvic CT scans and consideration of a PET scan.
c) If imaging study results are normal in the face of a rising CEA, a PET scan should be performed with repeat CT scans recommended every three (3) months or until either disease is identified or CEA stabilizes or declines. There is no role for laproscopy if the imaging studies are normal (NCCN).
d) It may be appropriate to refer such patients to the Multidisciplinary Cancer Conference for discussion.

14.0 Lynch Syndrome Screening and Referral to Medical Genetics

Rationale:

Lynch Syndrome

Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer (HNPCC)) is the most common hereditary colorectal cancer (CRC) syndrome and it accounts for 3 to 5% of all CRC burden.

For more information, see Appendix 5.

Referral to Medical Genetics

Referral to Medical Genetics for patients who are suspected of having Lynch syndrome is important both for the patients themselves as well as for their family members. Family members of an individual with Lynch syndrome are at increased risk of Lynch syndrome themselves.

If the disease-causing mutation can be identified in an individual suspected to have Lynch syndrome, then predictive genetic testing can be offered to other at risk family members before they develop cancer. Early recognition of cancers associated with Lynch syndrome allows for timely intervention and improved final outcome; thus, surveillance of asymptomatic, at-risk relatives for early manifestations is appropriate.

The timing of the discussion about referral to Medical Genetics will be patient-dependent. There is some evidence (Tomiak) that some patients receiving active cancer treatment do not see genetics issues as a priority but may be more open during survivorship. Referrals could be made at any point along the continuum from diagnosis to survivorship based on patient readiness and circumstances such as the patient's health status. The discussion could be initiated by any physician involved with the care of the patient and the timing of the referral driven by patient preference.

Evidence also indicates a low awareness among health professionals about genetic testing for Lynch syndrome, and poor uptake by patients who are referred for genetic counseling. This suggests a need for better education and awareness for both health professionals and patients.

Standards:

14.1 Patients with rectal cancer who meet the following criteria should be offered MSI/IHC testing. This is currently initiated by referring patients to the Maritime Medical Genetics Service at the IWK Health Centre for discussion about possibility of testing:

- Anyone diagnosed before the age of 50
- Anyone with colonic polyps before age 40
- Any patient with a family history consistent with a clinical diagnosis of Lynch syndrome (Amsterdam criteria) (see Appendix 5)
- Any patient meeting the Bethesda criteria (see Appendix 5)
- Clinical pathology suggestive of Lynch syndrome (see Pathology section for specifics).

14.2 If not referred earlier, the discussion with the patient should occur during the first year post-treatment. If a physician has had the discussion with the patient, this should be communicated to the other members of the team.

The Referral Form and Guidelines for Genetic Consultation are available on the IWK Health Centre website: http://www.iwk.nshealth.ca/childrens-health/services#/mmgs

15.0 Locally Recurrent Rectal Cancer

Rationale:

Local recurrence is defined as an isolated pelvic/anastomotic recurrence arising from the original primary carcinoma.

About 50% of rectal cancer patients with local recurrence have disease confined to the pelvis. The vast majority of local recurrences are inoperable and incurable. There are no randomized, prospective trials to act as guides for the management of locally recurrent rectal cancer (Department of Health, Western Australia).

The risk of pelvic recurrence is higher in patients with rectal cancer compared to those with colon cancer, and locally recurrent rectal cancer has been associated with a poor prognosis (NCCN).

The management of locally recurrent rectal cancer is complex and will vary from patient to patient. Accordingly, standards relating to the specifics of treatment are beyond the scope of this document.

Standards:

15.1 Refer suspected local recurrence back to the rectal cancer operating surgeon.

15.2 For recurrence based on endoscopic findings, appropriate investigations will be done as soon as possible to rule out distant metastatic disease including:

- CT Chest, Abdomen, Pelvis
- CEA

15.3 All Rectal cancer patients with local recurrence will be referred to a tertiary cancer centre for an assessment by the MCC and discussion with the Rectal Cancer Treatment Assessment Committee in conjunction with the primary surgeon.

All patients with isolated locally recurrent rectal cancer will be offered assessment by surgical oncologist/ colorectal surgeon with expertise is recurrent rectal cancer and pelvic exenteration.

15.4 All patients with locally recurrent rectal cancer will be promptly:

- referred (or re-referred) to the Cancer Patient Navigator (or a designated health professional who can provide navigation function),
- screened for distress with appropriate management

The physician/surgeon who identifies the recurrence will ensure that the patient is referred to the navigator in a timely fashion.

15.5 Document a recurrence in the chart for monitoring purposes.

Note: a recurrence diagnosed by a physician may not be reported as such in the Nova Scotia Cancer Registry:

Under the rules of the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) Program, if there are rectal tumours diagnosed more than one year apart, even if the second is referred to as a recurrence by the physician, they would be recorded as two primaries in the cancer registry UNLESS a pathologist compares the two and states that one is a recurrence of the other. If the second one is referred to as a metastasis, it would be recorded as such. If an invasive rectal tumour follows an in situ rectal tumour more than 60 days from diagnosis, it would be recorded as a new primary in order that the invasive tumour be included in the dataset.

16.0 Management of Metastatic Rectal Cancer

Rationale:

Metastatic rectal cancer may be present at the time of initial diagnosis or may develop after initial treatment. There is the potential for long-term remission or cure of metastatic rectal cancer through the appropriate use of surgery and systemic therapies. This requires the involvement of the full Interprofessional Care Team, including sub-specialists as necessary (e.g. hepatobiliary surgeons for liver metastases and thoracic surgeons for lung metastases).

The first question in managing this group of patients is whether the primary tumour needs immediate treatment because of established or impending obstructive symptoms or hemorrhage, even in the presence of unresectable metastatic disease (NICE).

The second question is whether or not both the primary tumour and the metastases are surgically resectable with curative intent. If the disease sites are considered resectable then the next questions are whether there should be pre-operative or post-operative adjuvant treatments (or a combination of both) and whether the surgery should be a staged or combined procedure (NICE).

Where metastases are unresectable, currently patients fall into two groups:

- the extent of metastatic disease is such that although inoperable at presentation, patients might become resectable with curative intent if they have a good response to chemotherapy
- the extent of metastatic disease is such that patients are highly unlikely to be suitable for potentially curative surgery, even with a good response to chemotherapy (NICE)

Advances in systemic therapy over the last ten years have increased the potential for long-term survival and possible cure. However there remains uncertainty as to the best sequence of treatments to achieve optimal outcome (NICE).

Patients with metastatic rectal cancer should be thoroughly assessed and have a plan of care based on whether the patient is potentially curable and the patient's preferences.

Patients with metastatic rectal cancer should have their pain and symptoms managed.

The patient's general medical and psychosocial condition, goals and expectations will always be assessed and considered in determining the optimal treatment approaches.

Standards:

16.1 Referral

16.1.1 a) Metastatic rectal cancer patients with any potential for a curative intent approach (i.e. oligometastatic disease burden) should be referred to the tertiary cancer centre for evaluation by a full inter-professional team in a coordinated approach (see Interprofessional Care Team recommendations). Those for whom an ideal management

plan is not clear should be considered for referral to the MCC for recommendations regarding for treatment options.

b) The team's recommendation will be provided in writing to the referring physician/ surgeon and the primary care provider, and will be clearly documented in the medical record. It is the responsibility of the referring physician/surgeon to inform the patient of the team's recommendations.

16.1.2 Patients with metastatic rectal cancer who are not candidates for curative intent treatment their local palliative care team or psychosocial health professional as needed, as soon as possible. Patients who are not candidates for curative intent treatment may also be referred to the tertiary centre for consideration of palliative chemotherapy or radiation therapy.

16.2. All patients with metastatic rectal cancer will be promptly:

a) referred (or re-referred) to the Cancer Patient Navigator (or a designated health professional who can provide navigation function)
b) screened for distress with appropriate management
c) The physician/surgeon who identifies the metastatic disease will ensure that the patient is referred to the navigator in a timely fashion.

The CCNS Working Group has accepted the following recommendations from the Colorectal Cancer Association of Canada Management of Metastatic Colorectal Cancer and adapted them to fit the Nova Scotian context.

16.3 Diagnostic Imaging

- CT Chest/Abdomen/Pelvis
- Supplemental radiographic tests (PET, MRI, US) as needed

The purpose of imaging in the metastatic rectal cancer patient is to rule out distant, unresectable disease.

The use of multiple, correlative imaging modalities is recommended to ensure that all metastatic disease has been adequately delineated to inform therapeutic decision-making.

Diagnostic studies for a metastatic rectal cancer (mRC) patient should be interpreted by a radiologist experienced in oncology, within the setting of a multidisciplinary clinical interaction or meeting.

Evaluation of metastatic disease should include assessment of technical factors of resectability, including:

- number and location of metastases,
- proximity to vital structures, and
- adequacy of residual liver/lung function post-resection.

16.4 Patients being considered for metastectomy should have a colonoscopy within a

year of the onset of metastatic disease to evaluate recurrent, synchronous or metachronous disease in the colon.

16.5 All mRC patients will be assessed for candidacy for resection based on the results of the diagnostic imaging (see Table 2 for criteria to assess resectability).

Treatment Planning

16.6 For those patients who are potentially curable, the initial assessment should address whether it is more appropriate to proceed directly to surgery, or whether the initial use of systemic therapies will ultimately provide the best opportunity to subsequently resect all metastases.

16.7 Coordination of peri-operative systemic therapy and surgery requires close collaboration between medical and surgical oncologists to ensure surgery and systemic therapy occur in a coordinated and timely fashion in relation to each other.

16.8.1 The timing of primary resection in the face of synchronous mRC is critical and should be part of the Interprofessional Care Team/Multidisciplinary Case Conference discussion.

- An asymptomatic primary should be considered for resection in relation to the resectability of the synchronous metastatic disease.
- For patients with a symptomatic primary that is not amenable to treatment with systemic or radiation therapy, surgical resection of that primary, which may result in optimal palliation, should be considered.

16.8.2 For patients whose metastases become resectable, the timing of resection of the primary for those with synchronous metastases should be part of the Interprofessional Care Team/Multidisciplinary Case Conference discussion.

16.9 The goal of metastectomy is to have an R0 resection of all metastatic disease (the primary tumour must have been completely resected or have plans for primary tumour resection).

Management of Patients with Initially Resectable Disease
(see Table 3 for Criteria for Timing of Metastectomy)

16.10 For patients proceeding directly to surgical resection of metastases, it is recommended that surgery take place as soon as possible.

16.11. Patients with resectable liver metastases:

- should receive systemic therapy either peri- or post-operatively.
- The pre-operative period of treatment should not exceed 12-18 weeks of systemic therapy.
- Repeat imaging after 12 weeks - consider PET/CT.

Management of Patients with Potentially Resectable Disease

(See Table 3 for Criteria for Timing of Metastectomy)

16.12. The objective of therapy for this group of patients is to render the metastases resectable.

16.12.1

a) Select the systemic therapy that will maximize potential to become resectable.
b) Repeat imaging after 12 weeks.
c) Given the risk of liver toxicity from cumulative systemic therapy, patients should be assessed at 8−12-week intervals after the start of systemic therapy, to assess resectability on a regular basis.

16.12. 2 Non-surgical ablative therapies (radiofrequency ablation [RFA], microwave etc.) and interventional radiology strategies (e.g. portal vein embolization [PVE]) should be considered, where appropriate, to achieve potential resectability.

16.12.3 a) For patients whose metastases become resectable, the timing of resection of the primary for those with synchronous metastases should be part of the Interprofessionial Care Team/ Multidisciplinary Case Conference discussion.

b) Metastectomy should take place within 4−8 weeks following systemic therapy.

16.12.4 For patients whose metastases are rendered resectable with systemic therapy, it would be reasonable to consider post-operative systemic therapy.

Post Metastectomy Resection Surveillance

16.13.1 All patients should have ongoing surveillance following metastectomy consistent with the guidelines for follow-up for Stage II and III patients post-tumour resection (see Surveillance recommendations).

16.13.2. Additional diagnostic imaging follow-up should be inclusive of the site of metastectomy.

16.13.3. PET/CT is appropriate follow up of elevated CEA with no evidence of disease on CT. (CCNS Working Group consensus).

Management of the Non-surgical Patient

16.14 The recommendations in this section apply to patients with mRC who, after a rigorous assessment, are not considered candidates for potentially curative surgery. This assessment will be made in situations where the patient will not be able to tolerate surgery or, because of the extent of metastatic disease, would not be able to undergo complete surgical resection even with optimal response to systemic therapy.

16.14.1Notwithstanding the initial assessment, re-evaluation of any patient's resectability should they have an excellent response to systemic therapy is appropriate, giving due consideration to potential hepatotoxicity from the systemic therapy they have received.

16.14.2 Systemic Therapy

- First line: Doublet chemotherapy +/- Bevacizumab*
- Second line: Alternate Doublet chemotherapy +/- Bevacizumab*
- (patient should be tested for KRAS at this point)
- Third line: Cetuximab as single agent or in combination with irinotican for KRAS Wild Type patients.
- Consider sequential monotherapy strategy (e.g. capecitabine monotherapy).
- *Bevacizumab can only be used in one line.

16.14.3 Other therapeutic approaches

The use of non-surgical ablative (e.g. stereotactic body radiation therapy [SBRT] or RFA) techniques should be considered as part of the multidisciplinary discussion regarding the care of these patients.

Table 2 Criteria to Assess Resectability

Categorize patients based on the results of the diagnostic imaging		
Initially Resectable	**Potentially Resectable**	**Unresectable**
• Limited solid metastases (liver or lung) • No vital structures impeding resection • Sufficient hepatic reserve following planned resection • Limited comorbid disease • Pre-operative systemic therapy may be considered even if initially resectable	Not deemed initially resectable, but may become surgical candidates with response to localized and/or systemic intervention	Unresectable, widespread disease that will remain unresectable even with good response to systemic therapy

Table 3: **Criteria for Timing of Metastectomy**

Ideal candidate for immediate metastectomy	**Candidate for pre-operative systemic therapy and then metastectomy**
• Low number of metastases (e.g. single vs. multiple) • Low volume/size of metastases (e.g. <5cm) • 2 or more contiguous segments of adequate hepatic function without metastatic involvement • No involvement in the biliary hilum • No involvement of 1 portal vein and 1 ipsilateral hepatic vein • Metachronous disease • Otherwise favourable prognosis with low risk of further systemic recurrence • Health history indicates concern for potentially augmented hepatotoxicity from pre-operative systemic therapy (i.e. pre-existing steatosis)	• Liver function within normal limits • Less favourable prognosis for further local or systemic recurrence (i.e. N2 primary disease or close margin primary resection) • Concern for inability to perform R0 metastectomy due to the number, size or location of metastases.

17.0 Palliative Care

Rationale:

Patients with advanced cancer suffer from a variety of symptoms and disturbances that are common to all cancers, and not specific to rectal cancer. The management of these symptoms requires therapeutic measures that are part of the general care of patients with advanced cancer (NHMRC). There are many reports suggesting unmet needs, both physical and emotional, in patients with advanced rectal cancer leading to the view that patients may benefit from access to palliative care services before the 'terminal' phase (SIGN).

The management of these symptoms is beyond the scope of this document. This in no way underestimates the crucial significance of good pain and symptom management and palliative care for these patients. Management of these matters is the first priority of any clinician caring for a patient with advanced rectal cancer (NHMRC).

Palliative Care teams are available throughout the Nova Scotia Health Authority.

Standards:

1. Rectal cancer patients:
   - with advanced or life-limited disease
   - with significant co-morbidities which are life-limited or interfere with quality of life
   - whose physical or emotional symptoms are difficult to control
   - for whom no further active treatment is available

   will be referred to their local palliative care team, and the Cancer Patient Navigator, if not already referred, without delay.

2. Appropriate referrals to psychosocial supports for the patient and/or his/her family will be made in a timely fashion.

3. As in any advanced cancer it is important to help patients to understand where they are in their illness with regard to stage of advancement and what may or may not be realistically achieved (SIGN).

Appendix 1: Sources

This standards document was developed by the Cancer Care Nova Scotia Rectal Cancer Standards Working Group using informal consensus decision-making.

A number of existing guidelines were used as source material.

The source guidelines were identified in 2011 with the following approach:

- All Canadian Cancer Agencies websites
- Major international guideline developers websites
- Search of the SAGE guideline database of English-language cancer guidelines maintained by the Canadian Partnership Against Cancer (CPAC) for guidelines with “rectal” in title
- Search of the National Guideline Clearing House (database of English language guidelines maintained by the US Department of Health and Human Resources) using Keyword “rectal” and clinical specialty “oncology” publication years 2007-2011

43 guidelines were identified. A decision was made to restrict to Canadian and major international developers. Some of the guidelines were updated in 2012 and the revised guidelines were used.

Guidelines that used systematic reviews and meta-analysis to make their recommendations are identified in the table below with *. The remaining guidelines were consensus-based.

The source for each standard statement is identified in the statement.

- If a standard statement is based on a recommendation from a single source guideline, that guideline will be noted in parentheses. If that guideline rated the level of evidence, we have noted that as well.

- For some standard statements, the recommendation was supported by more than one source guideline, in which case all will be listed.

- Finally, some recommendations were developed by the Working Group itself to address either a specific Nova Scotia situation or where there was no guidance from the source documents.

For specific sections or recommendations, additional guidelines and primary literature may have informed the decision and these documents are listed in those sections.

The source guidelines and the abbreviations for them used in this document are:

Abbreviation	Developer	Title	Year of Publication
AHS (early)	Alberta Health Services	Early Stage Rectal	2011
AHS (mets)	Alberta Health Services	Metastatic Colorectal Cancer	2011
BCSON	British Columbia Surgical Oncology Network	Provincial Guidelines For Rectal Cancer	2006
BCCA	British Columbia Cancer Agency	Cancer Management Guidelines - Rectal Cancer	2012
CCAC (early)	Colorectal Cancer Association of Canada	Colorectal Cancer Association of Canada consensus meeting: raising the standards of care for early-stage rectal cancer	2009
CCAC (mets)	Colorectal Cancer Association of Canada	Standards of care for curative surgery and management of metastatic colorectal cancer	2010
CCO	Cancer Care Ontario*	Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer: Guideline Recommendations (NB this guideline has been identified by Cancer Care Ontario as being out of date. An updated systematic review was conducted in 2012)	2008
NHMRC	National Health and Medical Research Council (Australia)*	Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer	2005
NCCN	National Comprehensive Cancer Network (US)*	Rectal Cancer	2012
NICE	National Institute of Clinical Evidence*	Colorectal cancer: the diagnosis and management of colorectal cancer (England and Wales)	2011
NZ	New Zealand Guidelines Group*	Management of Early Colorectal Cancer	2011
SCA	Saskatchewan Cancer Agency	Provincial Colorectal Cancer Treatment Guidelines	2011
SIGN	Scottish Inter-collegiate Guideline Network*	Diagnosis and management of colorectal cancer	2011

Additional Sources of Evidence

In addition to the primary sources listed above, additional sources of evidence informed specific sections or recommendations. These additional sources of evidence are listed below by section and recommendation, where appropriate.

Diagnosis

Pretreatment staging: Diagnostic Imaging

Dewhurst C, Rosen MP, Blake MA, Baker ME, Cash BD, Fidler JL, Greene FL, Hindman NM, Jones B, Katz DS, Lalani T. ACR Appropriateness Criteria® Pretreatment Staging of Colorectal Cancer. Journal of the American College of Radiology. 2012 Nov 30; 9(11):775-81.

Kirke R, Rajesh A, Verma R, Bankart MJ. Rectal cancer: incidence of pulmonary metastases on thoracic CT and correlation with T staging. J Comput Assist Tomogr. 2007; 31(4):569-571.

Kronawitter U, Kemeny NE, Heelan R, Fata F, Fong Y. Evaluation of chest computed tomography in the staging of patients with potentially resectable liver metastases from colorectal carcinoma. Cancer. 1999; 86(2):229-235.

Parnaby CN, Bailey W, Balasingam A, Beckert L, Eglinton T, Fife J, Frizelle FA, Jeffery M, Watson AJ. Pulmonary staging in colorectal cancer: a review. Colorectal Disease. 2012 Jun 1; 14(6):660-70.

RadiologyInfo.org-For Patients [Internet]. Oak Brook (IL): Radiological Society of North America; 2016. Available from: www.radiologyinfo.org/

The Rectal Cancer Surgeon

The recommendations in this section were based on the clinical expertise of the Working Group members.

Rectal Cancer Treatment Assessment Committee

Augestad KM, Lindsetmo RO, Stulberg J, Reynolds H, Senagore A, Champagne B, et al. International Rectal Cancer Study Group. International preoperative rectal cancer management: staging, neoadjuvant treatment, and impact of multidisciplinary teams. World Journal of Surgery. 2010 Nov 1; 34(11):2689-700.

Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? Br J of Cancer 2006 Feb 13; 94(3):351-357.

Department of Health & Human Services. Patient management framework: Colorectal tumour stream: colon and rectal cancer [Internet]. Melbourne (AUS): Metropolitan Health and Aged Care Services Division; 2006. Available from: https://www2.health.vic.gov.au/Api/downloadmedia/%7B6F4EE729-393E-4A1C-96AB-20E027D4F96A%7D

Palmer G, Martling A, Cedermark B, Holm T. Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer. Colorectal Disease. 2011 Dec 1; 13(12):1361-9.

Simunovic M. Evaluating radial margins [Video]. Oncology Education; 2013 [cited 2014 July 9]. Available from: http://www.oncologyeducation.com/information/gi-updates/gi-cancer-videos/ec52013/ec52013simunovic/

Subendran J, Huang H, O'Connor B, Thipphovang S, Cummings B, Brierley J, Jhaveri K, Kirsch R, McLeod RS, Kennedy ED. Feasibility of using MRI based outcomes for quality indicators (QI) for rectal cancer multidisciplinary cancer conference (MCC). Can J Surg. 2013 Aug; 56(4 Suppl 3):S135-136.

Swellengrebel HA, Peters EG, Cats A, Visser O, Blaauwgeers HG, Verwaal VJ, et al. Multidisciplinary discussion and management of rectal cancer: a population-based study. World J Surg. 2011 Sep 1; 35(9):2125-33.

Wille-Jørgensen P, Sparre P, Glenthøj A, Holck S, Nørgaard Petersen L, Harling H, et al. Result of the implementation of multidisciplinary teams in rectal cancer. Colorectal Disease. 2013 Apr 1; 15(4):410-3.

Multidisciplinary Case Conference

American College of Surgeons Commission on Cancer. Cancer program standards 2012: Ensuring patient-centered care. V1.2.1. 2012. Available from: https://www.facs.org/quality%20programs/cancer/coc/standards

Wright F, De Vito C, Langer B, Hunter A. Multidisciplinary cancer conferences: A systematic review and development of practice standards. European Journal of Cancer. 2007 Apr 1; 43(6):1002-1010

Interprofessional Care Team

Feedback received from rectal cancer survivors and family members highlighted the need for communication between members of the Interprofessional Care Team.

Psychosocial Health Services and Supportive Care

In addition to the disease-specific guidelines, additional standards and guidelines related to supportive care for cancer patients generally and rectal cancer patients specifically were reviewed including those specific for Enterostomal Therapy Nurses, dietitians and Cancer Patient Navigators.

Accreditation Canada Qmentum [Internet]. Ottawa (ON); Accreditation Canada. Standards Cancer Care for surveys starting after January 01, 2017; 2016 Jan 12; Ver.1. Available from: https://accreditation.ca/cancer-care-and-oncology-services

Canadian Association of Psychosocial Oncology [Internet]. Standards of Psychosocial Health Services for Persons with Cancer and their Families; 2010 May 28. Available from: http://www.capo.ca/pdf/CAPOstandards.pdf

Howes J, Simpson J, McLeod D, Digout C, Spencer J, Maginley D, Broadfield L, Cleary J. Best practice guideline for the management of cancer-related distress in adults [Internet]. Halifax (NS): Supportive Care Cancer Site Team: Cancer Care Nova Scotia; 2014. Available from: http://www.cancercare.ns.ca/site-cc/media/cancercare/Distress%20Screening%20Guide%20QRVfinal.pdf

International Clinical Guidelines Group [Internet]. Guidelines on vaginal dilation after pelvic radiotherapy. Brook Hill (OX): Owen Mumford; 2012. Available from: http://www.ncsi.org.uk/wp-content/uploads/Inter-Best-Practice-Guide-Vaginal-Dilators-July-2012.pdf

Johnson H, Petrella J, McGee R, Bonang L, Butt R, Dunn M, Fraser H, Johnson P, Langley S, MacEachern A, MacIntosh D, Miller L, Mitchell A, and the Cancer Care Nova Scotia Diagnosis and Referral of Patients Clinically Suspicious For Colorectal Cancer Sub-committee. Guidelines for the investigation of patients with symptoms suggestive of colorectal cancer. Halifax, (NS): Cancer Care Nova Scotia; 2016 (not yet approved).

Murray A, Hutt D, Luther-Hiltz E, Smith D, Cleary J. Education standards for adults affected by cancer [Internet]. Halifax (NS): Crown Copyright: Province of Nova Scotia; 2011. Available from: http://www.cancercare.ns.ca/site-cc/media/cancercare/CCNS%20Pt%20Edn%20Standards%20Full%20Version.pdf

National Working Group Dietitians of Canada Oncology Network. Canadian Oncology Nutrition Standards of Practice [Internet]. Toronto (ON): Dietitians of Canada; 2004.

Registered Nurses Association of Ontario [Internet]. Ostomy care and management. Toronto (ON): Registered Nurses Association of Ontario; 2009. Available from: http://rnao.ca/sites/rnao-ca/files/Ostomy_Care__Management.pdf

Articles:

Cook S, Fillion L, Fitch MI, Veillette AM, Matheson T, Aubin M, et al. Core areas of practice and associated competencies for nurses working as professional cancer navigators. Canadian Oncology Nursing Journal. 2013; 23(1):44-52.

Fillion L, Cook S, Veillette AM, Aubin M, De Serres M, Rainville F, et al. Professional navigation framework: elaboration and validation in a Canadian context. Oncology Nursing Forum 2012 Jan 1; 39(1);E58-E69.

Scheer AS, O'Connor AM, Chan BP, Moloo H, Poulin EC, Mamazza J, et al. The myth of informed consent in rectal cancer surgery: what do patients retain? Diseases of the Colon & Rectum. 2012 Sep 1; 55(9):970-5.

Urquhart R, Folkes A, Babineau J, Grunfeld E. Views of breast and colorectal cancer survivors on their routine follow-up care. Curr Onc. 2012; 19(6):294-301.

Nova Scotia Rectal Cancer Patient Input:

The Cancer Outcomes Research (COR) Unit of CCNS conducted focus groups in 2010 with colorectal cancer survivors as part of an initiative on follow-up care (Urquhart). They found high levels of need related to ostomy support in this population including informational, body image, nutritional and financial needs.

A survey of rectal cancer survivors/family members conducted by CCNS through the Cancer Patient Family Network in summer 2011 in preparation for this standard development work and the rectal cancer patient members of the Working Group reinforced the ostomy support issues identified by the COR and also clearly indicated the need for emotional support, sexual health and information generally through the cancer journey.

Rectal cancer survivors and family members were also invited to provide feedback on the draft Rectal Cancer Treatment standards in June 2013. Parts of this section were revised based on their feedback, particularly the stoma therapy section.

Additional sources of evidence for specific recommendations

1.0 Access to Psychosocial Health Services

Cancer Care standard 17.13 states “Clients and families have access to psychosocial and/or supportive care services, as required.” Accreditation Canada Qmentum [Internet]. Ottawa (ON); Accreditation Canada. Standards Cancer Care for surveys starting after January 01, 2017; 2016 Jan 12; Ver.1. Available from: https://accreditation.ca/cancer-care-and-oncology-services

7.2 Ostomy Reversals

Danielsen AK, Soerensen EE, Burcharth K, Rosenberg J. Impact of a temporary stoma on patients' everyday lives: feelings of uncertainty while waiting for closure of the stoma. Journal of Clinical Nursing. 2013 May 1; 22(9-10):1343-52.

Taylor C, Morgan L. Quality of life following reversal of temporary stoma after rectal cancer treatment. European Journal of Oncology Nursing. 2011 Feb 28;15(1):59-66.

Taylor C, Bradshaw E. Tied to the toilet: lived experiences of altered bowel function (anterior resection syndrome) after temporary stoma reversal. Journal of Wound Ostomy & Continence Nursing. 2013 Jul 1; 40(4):415-21.

7.3 Low Anterior Resection Syndrome

Bryant CL, Lunniss PJ, Knowles CH, Thaha MA, Chan CL. Anterior resection syndrome. The Lancet Oncology. 2012 Sep 30;13(9):e403-8.

Chen TY, Emmertsen KJ, Laurberg S. Bowel dysfunction after rectal cancer treatment: a study comparing the specialist's versus patient's perspective. BMJ Open. 2014 Jan 1; 4(1):e003374.

Desnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. European Journal of Cancer Care. 2006 Jul 1;15(3):244-51.

Emmertsen KJ, Laurberg S. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. British Journal of Surgery. 2013 Sep 1; 100(10):1377-87.

Juul T, Ahlberg M, Biondo S, Emmertsen KJ, Espin E, Jimenez LM, Matzel KE, Palmer G, Sauermann A, Trenti L, Zhang W. International validation of the low anterior resection syndrome score. Annals of Surgery. 2014 Apr 1; 259(4):728-34.

Pucciani F. A review on functional results of sphincter-saving surgery for rectal cancer: the anterior resection syndrome. Updates in Surgery. 2013 Dec 1; 65(4):257-63.

Ziv Y, Zbar A, Bar-Shavit Y, Igov I. Low anterior resection syndrome (LARS): cause and effect and reconstructive considerations. Techniques in Coloproctology. 2013 Apr 1;17(2):151-62.

Clinical Trials

Department of Health & Human Services. Patient management framework: Colorectal tumour stream: colon and rectal cancer [Internet]. Melbourne (AUS): Metropolitan Health and Aged Care Services Division; 2006. Available from: https://www2.health.vic.gov.au/Api/downloadmedia/%7B6F4EE729-393E-4A1C-96AB-20E027D4F96A%7D

Malignant Rectal Polyps

No additional sources of evidence were used.

Neo-Adjuvant (Pre-operative) Therapy and Adjuvant (Post-operative) Therapy

Wong RK, Berry S, Spithoff K, Simunovic M, Chan K, Agboola O, Dingle B. Preoperative or postoperative therapy for stage II or III rectal cancer: an updated practice guideline. Clinical Oncology. 2010 May 31; 22(4):265-71.

The systematic review underpinning this guideline was more than three years old. With the permission of the PEBC, CCNS contracted with the Capacity Enhancement Program (CEP) of the Canadian Partnership Against Cancer (CPAC) to update it. Clinical expertise was provided by Dr. Stephanie Snow (Medical Oncologist) and Dr. Maureen Nolan (Radiation Oncologist), and members of the CCNS Rectal Cancer Standards Working Group. The summary of the evidence and the draft recommendations were reviewed with the Gastro-intestinal (GI) Cancer Site Team, which provides CCNS with expertise related to GI cancers, prior to discussion with the Rectal Cancer Treatment Standards Working Group.

See Appendix 8 for details of the systematic review.

Additionally, two systematic reviews (De Caluwé and Rahbari) were published in 2013 that addressed this topic. Both reached the same conclusions that there was no significant difference in overall survival or disease-free survival between neo-adjuvant chemoradiotherapy and radiotherapy but neo-adjuvant chemoradiotherapy improves local recurrence-free survival.

Source of the evidence related to neo-adjuvant chemoradiotherapy:

Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, Artale S, Tagliagambe A, Ambrosini G, Rosetti P, Bonetti A. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. Journal of Clinical Oncology. 2011 Jul 10; 29(20):2773-80.

De Caluwé L, Van Nieuwenhove Y, Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev. 2013 Feb; 2(2).

Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, Vendrely V, François E, de La Roche G, Bouché O, Mirabel X. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. Journal of Clinical Oncology. 2010 Apr 1; 28(10):1638-44.

Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, Müller L, Link H, Moehler M, Kettner E, Fritz E. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. The Lancet Oncology. 2012 Jun 30;13(6):579-88.

Rahbari NN, Elbers H, Askoxylakis V, Motschall E, Bork U, Büchler MW, Weitz J, Koch M. Neoadjuvant radiotherapy for rectal cancer: meta-analysis of randomized controlled trials. Annals of Surgical Oncology. 2013 Dec 1; 20(13):4169-82.

Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, Graeven U, Arnold D, Lang-Welzenbach M, Raab HR, Sülberg H. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. The Lancet Oncology. 2012 Jul 31;13(7):679-87.

Roh MS, Yothers GA, O'Connell MJ, Beart RW, Pitot HC, Shields AF, Parda DS, Sharif S, Allegra CJ, Petrelli NJ, Landry JC. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. In ASCO Annual Meeting Proceedings 2011 May 20; 29(15):3503.

Source of the evidence related to adjuvant chemoradiotherapy

André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. Journal of Clinical Oncology. 2009 Jul 1; 27(19):3109-16.

Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, Artale S, Tagliagambe A, Ambrosini G, Rosetti P, Bonetti A. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. Journal of Clinical Oncology. 2011 Jul 10; 29(20):2773-80.

Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, Vendrely V, François E, de La Roche G, Bouché O, Mirabel X. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. Journal of Clinical Oncology. 2010 Apr 1; 28(10):1638-44.

Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, Müller L, Link H, Moehler M, Kettner E, Fritz E. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. The Lancet Oncology. 2012 Jun 30;13(6):579-88.

Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, Graeven U, Arnold D, Lang-Welzenbach M, Raab HR, Sülberg H. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. The Lancet Oncology. 2012 Jul 31;13(7):679-87.

Roh MS, Yothers GA, O'Connell MJ, Beart RW, Pitot HC, Shields AF, Parda DS, Sharif S, Allegra CJ, Petrelli NJ, Landry JC. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. In ASCO Annual Meeting Proceedings 2011 May 20; 29(15):3503.

Surgery

Accreditation Canada Qmentum [Internet]. Ottawa (ON); Accreditation Canada. Standards Cancer Care for surveys starting after January 01, 2017; 2016 Jan 12; Ver.1. Available from: https://accreditation.ca/cancer-care-and-oncology-services

Archampong D, Borowski D, Wille-Jorgensen P, Iversen LH. Workload and surgeon's specialty for outcome after colorectal cancer surgery. Cochrane Database Syst Rev. 2012 Mar 14; 3.

Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins?. British Journal of Cancer. 2006 Feb 13; 94(3):351-7.

Capital Health. Antimicrobial handbook. Halifax: Antimicrobial Agents Subcommittee, District Drugs and Therapeutics Committee; 2012. Available from: http://cdhaintra.cdha.nshealth.ca/departmentservices/pharmacy/rxpublications.cfm

Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, Samama CM. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. CHEST Journal. 2012 Feb 1; 141(2_suppl):e227S-77S.

Johnston CF, Tomlinson G, Temple LK, Baxter NN. The management of patients with T1 adenocarcinoma of the low rectum: a decision analysis. Diseases of the Colon & Rectum. 2013 Apr 1; 56(4):400-7.

Monson JR, Weiser MR, Buie WD, Chang GJ, Rafferty JF, Buie WD, Rafferty J, Guillem J, Boushey R, Chang G, Feingold D. Practice parameters for the management of rectal cancer (revised). Diseases of the Colon & Rectum. 2013 May 1; 56(5):535-50.

Registered Nurses Association of Ontario [Internet]. Ostomy care and management. Toronto (ON): Registered Nurses Association of Ontario; 2009. Available from: http://rnao.ca/sites/rnao-ca/files/Ostomy_Care__Management.pdf

Reynolds JV, Joyce WP, Dolan J, Sheahan K, Hyland JM. Pathological evidence in support of total mesorectal excision in the management of rectal cancer. British Journal of Surgery. 1996 Aug 1; 83(8):1112-5.

Swellengrebel HA, Peters EG, Cats A, Visser O, Blaauwgeers HG, Verwaal VJ, et al. Multidisciplinary discussion and management of rectal cancer: a population-based study. World J Surg. 2011 Sep 1; 35(9):2125-33.

Zerey M, Hawver LM, Awad Z, Stefanidis D, Richardson W, Fanelli RD, SAGES Guidelines Committee. SAGES evidence-based guidelines for the laparoscopic resection of curable colon and rectal cancer. Surgical Endoscopy. 2013 Jan 1; 27(1):1-0.

Additional sources of evidence for specific recommendations

2.0 Timelines

Calvo FA, Morillo V, Santos M, Serrano J, Gomez-Espí M, Rodriguez M, del Vale E, Gracia-Sabrido JL, Ferrer C, Sole C. Interval between neoadjuvant treatment and definitive surgery in locally advanced rectal cancer: impact on response and oncologic outcomes. Journal of Cancer Research and Clinical Oncology. 2014 Oct 1;140(10):1651-60.

Foster JD, Jones EL, Falk S, Cooper EJ, Francis NK. Timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature. Diseases of the Colon & Rectum. 2013 Jul 1; 56(7):921-30.

Probst CP, Becerra AZ, Aquina CT, Tejani MA, Wexner SD, Garcia-Aguilar J, Remzi FH, Dietz DW, Monson JR, Fleming FJ. Extended intervals after neoadjuvant therapy in

locally advanced rectal cancer: the key to improved tumor response and potential organ preservation. Journal of the American College of Surgeons. 2015 Aug 31; 221(2):430-40.

Sloothaak DA, Geijsen DE, Van Leersum NJ, Punt CJ, Buskens CJ, Bemelman WA, Tanis PJ. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. British Journal of Surgery. 2013 Jun 1;100(7):933-9.

Wasserberg N. Interval to surgery after neoadjuvant treatment for colorectal cancer. World Journal of Gastroenterology. 14 Apr; 20(15):4256-62.

Wolthuis AM, Penninckx F, Haustermans K, De Hertogh G, Fieuws S, Van Cutsem E, D'Hoore A. Impact of interval between neoadjuvant chemoradiotherapy and TME for locally advanced rectal cancer on pathologic response and oncologic outcome. Annals of Surgical Oncology. 2012 Sep 1;19(9):2833-41.

Pathology

College of American Pathologists. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. Version 3.4.0.0 Jan 2016. Available from: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/cp-colon-16protocol-3400.pdf

Quirke P, Dixon MF. The prediction of local recurrence in rectal adenocarcinoma by histopathological examination. International Journal of Colorectal Disease. 1988 Jun 1; 3(2):127-31.

Quirke P, Morris E. Reporting colorectal cancer. Histopathology. 2007 Jan 1; 50(1):103-12.

Smith AJ, Driman DK, Spithoff K, Hunter A, McLeod RS, Simunovic M, Langer B. Guideline for optimization of colorectal cancer surgery and pathology. Journal of Surgical Oncology. 2010 Jan 1; 101(1):5-12.

Treanor D, Quirke P. Pathology of colorectal cancer. Clinical Oncology. 2007 Dec 31;19(10):769-76.

Survivorship and Post-treatment Surveillance

Department of Health & Human Services. Patient management framework: Colorectal tumour stream: colon and rectal cancer [Internet]. Melbourne (AUS): Metropolitan Health and Aged Care Services Division; 2006. Available from: https://www2.health.vic.gov.au/Api/downloadmedia/%7B6F4EE729-393E-4A1C-96AB-20E027D4F96A%7D

Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, Petrelli NJ, Ryan K, Schrag DH, Wong SL, Benson AB. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of

Clinical Oncology clinical practice guideline endorsement. Journal of Clinical Oncology. 2013 Dec 10; 31(35):4465-70.

Earle C, Annis R, Sussman J, Haynes AE, Vafaei A. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: Guideline recommendations. 2012 Feb 3. Available from: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=124839

Guidelines and Protocols Advisory Committee. Follow-up of colorectal polyps or cancer. Victoria (BC): British Columbia Medical Association; 2013 Jan 16. Available from: http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/colorectal-cancer-follow-up

Hammond K, Margolin DA. The role of postoperative surveillance in colorectal cancer. Clin Colon Rectal Surg. 2007 Aug; 20:249-54.

Lin Koo S, Wen JH, Hillmer A, Cheah PY, Tan P, Tan IB. Current and emerging surveillance strategies to expand the window of opportunity for curative treatment after surgery in colorectal cancer. Expert Review of Anticancer Therapy. 2013 Apr 1; 13(4):439-50.

Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, Petrelli NJ, Ryan K, Schrag DH, Wong SL, Benson AB. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. Journal of Clinical Oncology. 2013 Dec 10; 31(35):4465-70.

Lynch Syndrome Screening and Referral to Medical Genetics

Balmana J, Castells A, Cervantes A, ESMO Guidelines Working Group. Familial colorectal cancer risk: ESMO clinical practice guidelines. Annals of Oncology. 2010 May 1; 21(suppl 5):v78-81.

Kohlmann W, Gruber SB. Lynch Syndrome. 2004 Feb 5 [Updated 2012 Sep 20]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2013. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1211/

Munoz JC, Lambiase LR. Hereditary colorectal cancer [Internet]. Medscape; 2015 Apr 7. Available from: http://emedicine.medscape.com/article/188613-overview

Tomiak E, Samson A, Spector N, Mackey M, Gilpin C, Smith E, Jonker D, Allanson J, Asmis T. Reflex testing for Lynch syndrome: If we build it, will they come? Lessons learned from the uptake of clinical genetics services by individuals with newly diagnosed colorectal cancer (CRC). Familial Cancer. 2014 Mar 1; 13(1):75-82.

Locally Recurrent Rectal Cancer

Department of Health, Western Australia. Colorectal model of care. Perth: WA Cancer & Palliative Care Network, Department of Health, Western Australia; 2008. Available from:

http://www.healthnetworks.health.wa.gov.au/modelsofcare/docs/Colorectal_Model_of_Care.pdf

Management of Metastatic Rectal Cancer

No additional sources of evidence were used.

Palliative Care

No additional sources of evidence were used.

Appendix 2: Diagnostic Imaging Standards for Rectal Cancer

I. Staging

A. Requisitions for MRI and CT

Requisitions for MRI and CT for rectal cancer investigations should include the following information:

- Diagnosis of rectal cancer
- Distance of the tumor from the anal verge on sigmoidoscopy/colonoscopy
- If tumor or malignant polyp has been removed before MRI/CT, give site of resection including distance from anal verge
- If there is a history of distant metastases

B. Imaging Protocol for Rectal Cancer

1. MRI Protocol for Rectal Cancer

- Phased array 12 channel coil
- Field strength of 1.5 T or more
- High resolution matrix T2 images
- Small field of view (<25 cm)
- Thin sections (3-4 mm)
- Axial, coronal, and sagittal T2 planes
- Oblique T2 and T1 fat sat planes which are axial/perpendicular to the plane of the tumor
- Gadolinium enhanced T1 fat sat oblique and sagittal planes
- Diffusion weighted images optional B values 0/100 and 0/1000

2. CT Abdomen And Pelvis Protocol

- IV and oral contrast preparation
- Axial images with coronal/sagittal reformats if possible

C. Rectal Cancer Reporting Expectations

1. MRI Reports

Rectal Cancer MRI reports will include the following information, ideally in a standardized format:

- Distance from anal verge
- Craniocaudal and circumferential extent
- T stage
- Distance of tumor to mesorectal fascia (circumferential resection margin)
- Involvement of levator ani, anal sphincter, pelvic viscera, bones
- Suspicious mesorectal and pelvic lymph nodes/nodules including size and distance from mesorectal fascia

2. CT Reporting For Rectal Cancer Staging

Reports for rectal cancer staging CTs will include the following:

- Extent of local disease if visible
- Distant solid organ metastases
- Possible lymph node metastatic spread
- Other bowel pathology
- Peritoneal metastases
- Lung metastases
- Bone metastases
- Any other clinically significant findings

There is a paucity of data assessing the optimal chest staging strategy for patients presenting with rectal cancer. The CCNS Working Group discussed in detail the benefits and harms, and a vote was taken on the final recommendation.

Source of the Evidence:

Imaging

Dewhurst C, Rosen MP, Blake MA, Baker ME, Cash BD, Fidler JL, Greene FL, Hindman NM, Jones B, Katz DS, Lalani T. ACR Appropriateness Criteria® Pretreatment Staging of Colorectal Cancer. Journal of the American College of Radiology. 2012 Nov 30; 9(11):775-81.

Kirke R, Rajesh A, Verma R, Bankart MJ. Rectal cancer: incidence of pulmonary metastases on thoracic CT and correlation with T staging. J Comput Assist Tomogr. 2007; 31(4):569-571.

Kronawitter U, Kemeny NE, Heelan R, Fata F, Fong Y. Evaluation of chest computed tomography in the staging of patients with potentially resectable liver metastases from colorectal carcinoma. Cancer. 1999; 86(2):229-235.

Parnaby CN, Bailey W, Balasingam A, Beckert L, Eglinton T, Fife J, Frizelle FA, Jeffery M, Watson AJ. Pulmonary staging in colorectal cancer: a review. Colorectal Disease. 2012 Jun 1; 14(6):660-70.

RadiologyInfo.org-For Patients [Internet]. Oak Brook (IL): Radiological Society of North America; 2016. Available from: www.radiologyinfo.org/

Appendix 3: Multidisciplinary Team Discussions in Rectal Cancer Treatment

Two studies, one in England (Burton) and one in the Netherlands (Swellengrebel) examined the impact of pre-treatment Multi-disciplinary team (MDT) discussions on rectal cancer outcomes, specifically positive circumferential margins (CRM).

Burton found a CRM positivity rate of 26% in cases not discussed at MDT compared to 1% in those who were discussed (with a combined average of 12.5%). A re-audit following implementation of mandatory MDT discussion reduced the CRM positivity rate to 7%. This improvement was attributed to MRI-based MDT discussions in implementing pre-operative treatment strategies. In the initial audit, 76% of cases were discussed by the MDT. At the re-audit, 96% of cases were discussed. Discussion and demonstration of the MRI findings in the presence of all the MDT members appears more useful than issuing a standard report.

While Dutch guidelines recommend MDT discussion of rectal cancer cases, the Dutch study (Swellengrebel) only found documented evidence that 55% of cases were discussed. Swellengrebel et al. found that there was no difference in positive CRM rates if a case was discussed at MDT prior to treatment. However, cases discussed at MDT were more likely to be advanced cancers (≥T3, and/or N+) ($p=0.001$), to have been staged with MRI ($p=0.001$) and to have been completely staged ($p<0.001$).

A third study (Palmer) retrospectively reviewed all locally advanced rectal cancer patients in the Stockholm region of Sweden from 1995-2004 and classified them as to whether they had had 1) appropriate pre-operative radiological staging and MDT discussion, 2) appropriate pre-operative radiologic staging but no MDT discussion and 3) no appropriate pre-operative radiologic staging. More patients with a T2 or T3 tumour were discussed at MDT compared to the other two groups. Patients discussed at MDT were more likely to receive neo-adjuvant therapy. While outcomes (R0 resection and local control) were better for patients who had received pre-operative staging, they were further enhanced for those whose cases were discussed by the MDT. Multi-variate analysis failed to prove a significant impact of MDT assessment on survival.

A survey (Augestad) of 123 international colorectal centres indicated that regular multidisciplinary team meetings influence decisions about neo-adjuvant therapy and staging methods.

Wille-Jørgensen reported on a retrospective cohort study comparing the outcome of patients with primary rectal cancer before and after the establishment of colorectal multidisciplinary teams at two hospitals in Denmark. Aside from an improvement in post-operative mortality, there was no other difference between the two cohorts.

There have been two experiments with rectal cancer case conferencing in Ontario. LHIN-4 (Hamilton area) (Simunovic) has established CRC Collaborative Cancer Conferences of consecutive case presentation for group/individual learning using internet-based secure conferencing. The conference consists of at least two surgeons

who perform rectal surgery and a radiologist who provides dedicated assessment of cross-sectional imaging.

The treating surgeon indicates treatment plan in advance. Their experience is that 70% had a change in treatment plan. A pilot project among the specialist surgeons at the cancer centre still had 37% change in treatment plan and there was no “learning curve” – roughly the same number of cases had changes at the end of the study period as at the beginning.

Mount Sinai Hospital (Subendran) established weekly rounds for primary rectal cancer which is attended by surgeons, radiation oncologists, pathologists and radiologists. This has led to a change in management in 21% of presented cases.

Difference between Rectal Cancer Treatment Assessment Committee, Multidisciplinary Case Conference and Interprofessional Care Team

	Rectal Cancer Treatment Assessment Committee	**Multidisciplinary Cancer Conference (MCC) (GI Cancer Site Team)**	**Interprofessional Care Team**
Definition	A provincial treatment planning forum in which a team of surgeons reviews and discusses the medical condition and the **proposed treatment plan for all newly diagnosed and recurrent rectal cancer** patients eligible for curative treatment. The treating physician is responsible for making the ultimate treatment recommendation. The treatment decision is made by patient in consultation with treating physicians.	The multidisciplinary cancer conference (MCC) is a regularly scheduled multidisciplinary forum where **complex and/or metastatic GI cancer cases are discussed prospectively and recommendations** made for best management. The treating physicians are responsible for making the ultimate treatment recommendation. The treatment decision is made by patient in consultation with treating physicians.	The Interprofessional Care Team is a group of professionals from diverse disciplines who provide comprehensive assessment and consultation (i.e. a wider scope of participation and goals than those of the MCC) and may include nursing staff, palliative care staff, general practitioners, research staff, occupational therapists, ETN, pharmacists and psychologists with the aim of using their skills and knowledge to conduct a comprehensive

	Rectal Cancer Treatment Assessment Committee	**Multidisciplinary Cancer Conference (MCC) (GI Cancer Site Team)**	**Interprofessional Care Team**
			multidimensional screening, assessment and plan to maintain the best physical, mental, emotional, functional, sexual and social status of the patient. (NZ modified)
		The GI Cancer Site Team (MCC) is not the same as and should not be confused with the Rectal Cancer Treatment Assessment Committee or the Interprofessional Care Team. **There is a wider scope of participation and goals than in the Rectal Cancer Treatment Assessment Committee.**	
Membership	A pre-determined membership that will rotate on a scheduled basis. • 2 Colorectal surgeons or surgical oncologists • 1 Community general surgeon With ready access to a radiologist and a radiation oncologist. Radiation Oncologists	The GI Cancer Site Team (MCC) is based at the QEII and consists of health professionals with expertise/interest in GI cancers including but not limited to: • Surgical oncologists • General surgeons • Medical oncologists • Radiation oncologists • Pathologists • Radiologists • Pharmacists	The Interprofessional Care Team consists of all the health professionals involved in the patient's care and may cross DHA boundaries.

	Rectal Cancer Treatment Assessment Committee	**Multidisciplinary Cancer Conference (MCC) (GI Cancer Site Team)**	**Interprofessional Care Team**
	and radiologists may also be members of the RCTAC. Any surgeon with the appropriate experience in Nova Scotia can be a member of the RCTAC.	• Clinical Nurse Specialists • Nurse Practitioners • Nurses Non-QEII physicians and other health professionals who are interested may participate through distance technology.	

Appendix 4: Low Anterior Resection Syndrome (LARS)

Low anterior resection syndrome (LARS, also known as anterior resection syndrome (ARS)) is a disorder that commonly occurs after rectal cancer surgery and includes a wide range of symptoms with a significant negative impact on quality of life.[1,2,4] The use of the colon to create an anastomosis avoids the need for permanent colostomy, but lacks the storage capacity of the of the original rectal tissue.[10]

A review of the literature revealed that there is no consistent definition, clear etiology, measurement tool or standard treatment for LARS.[1] It is estimated that 60-90% of patients who undergo sphincter-preserving surgery will experience symptoms of LARS.[1,2,3,6,7,9]

The likelihood of experiencing LARS has been shown to be increased with the use of neo-adjuvant therapy[2,4], ultralow anastomosis and straight colorectal or coloanal anastomosis.

Some factors have been identified as predictive of LARS, but the cause is seen as multifactoral. Potential causes could be: mechanical or neurological sphincter injury, alterations in anorectal physiology, neorectal reservoir dysfunction, disappearance of rectoanal inhibitory reflex, altered colonic motility, and scarring after surgery.[7,8,9]

Symptoms of LARS typically consist of increased stool frequency, fecal urgency, fecal clustering, and incontinence to flatus and liquid stools.[2, 4, 6, 7, 8] Other symptoms may include fragmented bowel movements, constipation, incomplete evacuation, and excessive straining.[1, 2, 8, 9]

Symptoms may arise immediately after surgery and decrease after a few months, reaching a plateau within two years post surgery, although long term studies have reported symptoms up to 15 years after resection.[1, 4] Some patients recover almost normal bowel function but others will experience these lifelong symptoms with a significant impact on quality of life.[4]

There is no reported gold standard for treatment of LARS.[1, 7] Management of symptoms is based on existing therapies for the related symptoms.[1] Conservative therapy should be initiated and surgery is rarely required for the most severe cases.[7] Conservative therapies such as diet manipulation[3,10], anti-diarrhea medications[7, 8], pelvic floor rehabilitative treatment[7], rectal irrigation[1], biofeedback therapy[1,7], and sacral neuromodulation[1,7,8] have been shown to improve symptoms and quality of life

LARS has been shown to have a substantial negative impact on the quality of life, comparable to that of other chronic diseases.[1,3,9] A qualitative study reported that participants experienced fear, embarrassment and stigma around their LARS symptoms, affecting their confidence and social functioning, especially during the first year after stoma reversal.[3] The participants stated that their perception prior to stoma reversal was seen as the end of their cancer treatment and their lives would go back to normal again.[3] The same participants also confirmed that once they felt more confident, they increased their social activities and did prefer their current bowel patterns over an ileostomy.[3]

The literature describes potential preventative measures to be considered for LARS including nerve sparing surgery, use of colonic J pouch, and patient education about LARS prior to surgery and/or neo-adjuvant therapy.[1,2,3,4,7] Several articles identified the need for further health care provider education on LARS, one of which studied the perceptions of the impact of various LARS symptoms between physicians and patients and showed that the two did not align.[2]

Although there is no uniformly accepted scoring system for LARS, several are reported in the literature. [1,6]

1. Bryant CL, Lunniss PJ, Knowles CH, Thaha MA, Chan CL (2012). Anterior resection syndrome. *Lancet Oncol*, 13(9), 403-8. doi: 10.1016/S1470-2045(12)70236-X. PMID:22935240
2. Chen TY, Emmertsen KJ, Laurberg S (2014). Bowel dysfunction after rectal cancer treatment: A study comparing the specialist's versus patient's perspective. *BMJ Open*, 4(1) doi: 10.1136/bmjopen-2013-003374. PMID: 24448844
3. Desnoo L, Faithfull S (2006). A qualitative study of anterior resection syndrome: The experiences of cancer survivors who have undergone resection surgery. *Eur J Cancer Care,* 15(3), 244-51. PMID:16882120
4. Emmertsen KJ, Laurberg S (2013). Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. Rectal Cancer Function Study Group. *Br J Surg*, 100(10), 1377-87. doi: 10.1002/bjs.9223. PMID:23939851
5. Emmertsen KJ, Laurberg S (2012). Low anterior resection syndrome score: Development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg*, 255(5), 922-8. doi: 10.1097/SLA.0b013e31824f1c21. PMID:22504191
6. Juul T, Ahlberg M, Biondo S, Emmertsen KJ, Espin E, Jimenez LM, Matzel KE, Palmer G, Sauermann A, Trenti L, Zhang W, Laurberg S, Christensen P (2014). International validation of the low anterior resection syndrome score. *Ann Surg*, 259(4),728-34. doi: 10.1097/SLA.0b013e31828fac0b. PMID:23598379
7. Pucciani F (2013). A review on functional results of sphincter-saving surgery for rectal cancer: The anterior resection syndrome. *Updates Surg*, 65(4),257-63. doi: 10.1007/s13304-013-0220-5. PMID:23754496
8. Schwandner O (2013). Sacral neuromodulation for fecal incontinence and "low anterior resection syndrome" following neoadjuvant therapy for rectal cancer. *Int J Colorectal Dis*, 28(5), 665-9. doi: 10.1007/s00384-013-1687-8. PMID:23559414
9. Ziv Y, Zbar A, Bar-Shavit Y, Igov I (2013). Low anterior resection syndrome (LARS): cause and effect and reconstructive considerations. *Tech Coloproctol*, 17(2),151-62. doi: 10.1007/s10151-012-0909-3.PMID:23076289
10. Saint Vincent Health System. (2014). Low anterior resection syndrome. Patient Education. http://www.saintvincenthealth.com/Services/Colon-and-Rectal-Surgery/Patient-Education/Low-Anterior-Resection-Syndrome/Default.aspx

Appendix 5: Lynch Syndrome

Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer (HNPCC)) is the most common hereditary colorectal cancer (CRC) syndrome and it accounts for 3 to 5% of all CRC burden. Lynch syndrome is caused by a mutation in one of the mismatch repair genes and is associated with tumours exhibiting microsatellite instability (MSI) and/or abnormal immunohistochemistry (IHC). Colorectal cancer in persons with Lynch syndrome occurs at an earlier age than in the general population. Individuals with Lynch syndrome are also at risk of developing endometrial, ovarian, urothelial, upper GI and other cancers.

When matched stage for stage, colorectal cancers in individuals with Lynch syndrome are associated with a better prognosis than sporadic colon cancers, an unexpected finding because the poorly differentiated histology of Lynch syndrome-related colon cancers is typically associated with a poor prognosis.

Referral to Medical Genetics

Referral to Medical Genetics for patients who are suspected of having Lynch syndrome is important both for the patients themselves as well as for their family members. For the individual with possible Lynch syndrome, a genetics assessment to determine this likelihood is appropriate as approximately 45% of affected individuals develop multiple synchronous and metachronous colorectal cancers within ten years of resection and those individuals are also at risk of the other Lynch syndrome associated cancers. Family members of an individual with Lynch syndrome are at increased risk of Lynch syndrome themselves. Siblings and children of a person with Lynch syndrome have a 50% chance of also having Lynch syndrome (see below for the familial criteria for Lynch syndrome).

If the disease-causing mutation can be identified in an individual suspected to have Lynch syndrome, then predictive genetic testing can be offered to other at risk family members before they develop cancer. Early recognition of cancers associated with Lynch syndrome allows for timely intervention and improved final outcome; thus, surveillance of asymptomatic, at-risk relatives for early manifestations is appropriate. For some of the cancers associated with Lynch syndrome, prophylactic surgical options are available to reduce the likelihood of cancer developing. In individuals with Lynch syndrome the following life time risks for cancer are seen: 52 to 82% for colorectal cancer (mean age at diagnosis 44-61 years); 25 to 60% for endometrial cancer in women (mean age at diagnosis 48-62 years); 6 to 13% for gastric cancer (mean age at diagnosis 56 years); and 4 to 12% for ovarian cancer (mean age at diagnosis 42.5 years; approximately 30% are diagnosed before age 40 years).

The timing of the discussion about referral to Medical Genetics will be patient-dependent. There is some evidence (Tomiak) that some patients receiving active cancer treatment do not see genetics issues as a priority but may be more open during survivorship. Referrals could be made at any point along the continuum from diagnosis to survivorship based on patient readiness and circumstances such as patient's health status. The discussion could be initiated by any physician involved with the care of the patient and the timing of the referral driven by patient preference.

Evidence also indicates a low awareness among health professionals about genetic testing for Lynch syndrome, and poor uptake by patients who are referred for genetic counseling. This suggests a need for better education and awareness for both health professionals and patients.

Amsterdam and Amsterdam II Criteria for the Clinical Diagnosis of HNPCC

Lynch syndrome can be diagnosed based on family history criteria contained in the Amsterdam criteria, or in families that have evidence of defective mismatch repair based on tumour microsatellite instability (MSI) or abnormal immunohistochemistry (IHC) or on the basis of molecular genetic testing identifying a mutation in one of four mismatch repair (MMR) genes *(MLH1, MSH2, MSH6,* and *PMS2)* or in *EPCAM*.

The Amsterdam Criteria was first established to define Lynch syndrome for the purposes of enrolling families into research studies. It has also been used to make a clinical diagnosis of Lynch syndromes in families and continues to be a useful tool for that purpose. These criteria were later modified (Amsterdam II Criteria) to include the other hereditary nonpolyposis colon cancer (HNPCC) related cancers.

Amsterdam and Amsterdam II Criteria for the Clinical Diagnosis of HNPCC

The Amsterdam Criteria was first established to define Lynch syndrome for the purposes of enrolling families into research studies. It has also been used to make a clinical diagnosis of Lynch syndromes in families and continues to be a useful tool for that purpose. These criteria were later modified (Amsterdam II Criteria) to include the other hereditary nonpolyposis colon cancer (HNPCC) related cancers.

Amsterdam Criteria	**Amsterdam II Criteria**
Three or more family members, one of whom is a first-degree relative of the other two, with a confirmed diagnosis of colorectal cancer.	**Three** or more family members, one of whom is a first-degree relative of the other two, with HNPCC-related cancers.
Two successive affected generations	**Two** successive affected generations
One or more colon cancers diagnosed before age 50 years Exclusion of familial adenomatous polyposis (FAP)	**One** or more of the HNPCC-related cancers diagnosed before age 50 years Exclusion of familial adenomatous polyposis (FAP)

Although it has been demonstrated to be a useful tool to identify families with Lynch syndrome, not all families with a germline mutation in one of the Lynch syndrome associated genes will fulfill the Amsterdam criteria. As such, a third set of clinical criteria, the revised Bethesda Guidelines[3] for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability, was established to help improve on the

[3] Umar A, Boland CR, Terdiman JP, et al.: Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 96 (4): 261-8, 2004

identification of families whose colorectal tumours should be tested further with MSI (also applies to IHC).

The revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability (MSI)

Tumors from individuals should be tested for MSI in the following situations:

- Colorectal cancer diagnosed in a patient who is less than 50 years of age.

- Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours, regardless of age. ((HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel).

- Colorectal cancer with the MSI-High histology diagnosed in a patient who is less than 60 years of age. [*Note: Presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.]*

- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.

- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

Umar A, Boland CR, Terdiman JP, et al.: Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 96 (4): 261-8, 2004

Appendix 6: Template Transition of Care Letter to Primary Care Provider

Dear Doctor,

Re: Transition of [**John Smith**, ,]

Diagnosis: {}

Your patient has now completed adjuvant therapy for stage 2 or 3 colorectal cancer, and is ready for transfer to you for follow-up outside of the Cancer Centre. The patient's primary surgeon may continue to follow the patient as well. Generally, the first follow up colonoscopy is booked by the surgeon. If you have concerns that this has not been scheduled, please re-refer your patient to the original surgeon.

Recommended Follow Up

Attached please find a follow-up guideline with references. The guideline outlines the tests required for follow-up surveillance. This schedule has been developed using the best available evidence. This plan is found in the *Cancer Care Nova Scotia (CCNS)* Rectal Cancer Treatment Standards and represents a consensus opinion of the CCNS Gastrointestinal (GI) Cancer Site Team in 2011, and should not be interpreted as strict rules for practice. The guidelines will be revised if the evidence changes.

The purpose of follow-up is twofold: to detect new primary colorectal cancers and to detect loco-regional and metastatic recurrence. Early detection of either a new or recurrent colorectal cancer is important, as surgery is more likely to be curative at an earlier stage. The risk of a second cancer is estimated to be 3 to 5% in the 5 years following treatment. The risk of a metastatic recurrence of the previous cancer varies with stage, the adjuvant therapy received, and the time lapsed since surgery:

It is estimated that follow-up results in a 5% improvement in survival. However, this survival benefit is based on subsequent treatment such as resection of localized metastases. If a patient would not be a candidate for surgery (e.g. poor general health), then this surveillance would not be recommended.

Reasons for Re-Referral

- suspected recurrence of disease (local, regional or distant).
- suspected significant treatment-related side effects.

We remain interested to hear about this patient's course and would be pleased to review at any time, if felt to be indicated by the patient or supervising physician.

Sincerely,

/Encl.

Recommendations	Year 1 from date of definitive surgery	Year 2 from date of definitive surgery	Year 3 from date of definitive surgery	Year 4 & 5 from date of definitive surgery
Doctor's visit by the patient's preferred physician including a physical exam[1]	Every 3 months	Every 3 months	Every 3 months	Every 6 months
CEA Test [2]	Every 3 months	Every 3 months	Every 3 months	Every 6 months
Assessment of the anastomosis[3]	6 months post-op DRE and flexible or rigid sigmoidoscopy if the anastomosis is not palpable	Assessment of the anastomosis repeated at 18, 24 and 36 months post-op.		
Colonoscopy (to be coordinated by the rectal cancer surgeon)	Yes			Yes and then every 3-5 years thereafter as long as the patient remains in good health
CT Chest Abdomen and Pelvis	Annually in patients considered fit for potential surgical resection of metastatic lesions. Chest x-ray may be considered			Further imaging at physician discretion, particularly if clinical suspicions or elevated CEA.

Modified CCNS GI Cancer Site Team recommendations

[1]Clinical evaluation should attempt to highlight any new systemic symptoms, such as fatigue and shortness of breath, as well as more localized symptoms, such as pain, which might be suggestive of increased disease activity. History to elicit gastrointestinal and constitutional symptoms, including nutritional status. Physical examination with particular attention to the abdomen, liver and rectal evaluation (including DRE) (or perineal inspection and palpation in those patients who have had an abdominal perineal resection). (British Columbia Medical Association)

[2] The ASCO Panel asserted that CEA may be checked between the range of 3 to 6 months in the first 2 years, because 80%of recurrences occur in the first 2 to 2.5 years in patients with a high risk of recurrence.

[3]Assessment of the anastomosis for all patients (regardless of whether they have received pelvic radiation). The method of assessment (DRE, flexible or rigid sigmoidoscopy) is at the discretion of the surgeon. There is no data to support the use of rigid versus flexible sigmoidoscopy.

Appendix 7: Summary of Development Process

In 2011, Cancer Care Nova Scotia (CCNS) made the development of clinical standards an organizational priority. In making this decision, it was agreed that the approach would have to be sustainable using existing resources both for the development process itself as well as for the implementation of the standards, patient-centred and incorporate the broader patient experience of care and not just the "technical" aspects of treatment recommendations.

In order to work within existing resources, a guideline adaptation approach was chosen rather than starting "de novo" with primary literature using the CAN-ADAPTE (CAN-IMPLEMENT) approach). Guideline adaptation is a validated approach used to adapt existing guidelines to a new jurisdiction.

In 2011, an environmental scan of recent English-language guidelines for rectal cancer was conducted. Thirty-seven guidelines were identified. These were further limited to all Canadian cancer agencies with published rectal (or colorectal) cancer guidelines on their website (9 guidelines identified), major international guideline developers with recent (most were dated 2011) rectal/colorectal guidelines (5 guidelines identified). Recommendations from these guidelines were extracted into a spreadsheet so that they could easily be compared. This spreadsheet was used in the formulation of the recommendations (see Search Strategy).

Recruitment for the Working Group was conducted in fall 2011. A Working Group was established with members from across the province representing the key disciplines involved in rectal cancer treatment and a patient. All Working Group members were asked to complete Conflict of Interest forms. The Working Group began meeting in January 2012.

In addition to the regular Working Group members, representatives of the allied health professionals involved in rectal cancer care were invited to the meetings where the Supportive Care/Psychosocial Oncology recommendations were discussed. These included Cancer Patient Navigators, dietitians, social workers and Enterstomal Therapy Nurses.

One guideline identified in the search for source guidelines was *Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer: Guideline Recommendations* from Cancer Care Ontario (CCO) Program in Evidence-based Care (PEBC).[4] However, this guideline was flagged by the PEBC in fall 2011 as being more than three years old and under review for currency and relevance.

With the permission of the PEBC, CCNS contracted in February 2012 with the Capacity Enhancement Program (CEP) of the Canadian Partnership Against Cancer (CPAC) to update the systematic review underpinning the CCO guideline. The summary of the evidence and the draft recommendations were reviewed with the Gastro-intestinal (GI) Cancer Site Team, which provides CCNS with expertise related to GI Cancers, prior to

[4] Wong, R.; Berry, S.; Spithoff, K.; Simunovic, M.; Chan, K. et al Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer: Guideline Recommendations. Evidence-Based Series #2-4. Cancer Care Ontario

discussion with the Rectal Cancer Treatment Standards Working group. See Appendix 8 for details of the updated systematic review.

After the Working Group had completed a final draft, the full document was sent for validation by health professional and rectal cancer patient stakeholders across Nova Scotia.

The health professional review was conducted in February/March 2013. There were 42 responses: 7 group and 35 individual. Four respondents did not complete the survey but sent comments (two completed the survey and sent comments as well). Three did not complete the survey but sent messages that they had no concerns with the recommendations. There were responses from all disciplines and all health authorities.

The majority of respondents supported the proposed recommendations. The section with the least amount of support was the Rectal Cancer Tumour Board.

The patient review of the draft Rectal Cancer Treatment Standards occurred in June 2013. Rectal cancer survivors and family members were invited through a press release and CCNS social media to complete an online survey or participate in a focus group or both.

Three sections of the standard were chosen as most relevant for survivor/family member feedback: the timeline, surveillance and supportive care. Both the survey and the focus groups were focused on these three areas, however survey respondents were able to comment on any section of the standards. The draft standards and supporting background materials as well as the link to the survey were posted on the CCNS website.

There were 10 participants in 2 focus groups and 18 surveys were completed (representing 19 people, as one survey was completed by a couple). Some participants participated in both the focus groups and the survey so the results do not represent 29 separate individuals.

The feedback from the patient review was primarily positive and the majority supported the proposed standards in the timeline, surveillance and supportive care sections. Patients appreciated the opportunity to comment. Patient reviewers did suggest some modifications and identified topics missing from the standards.

The document was revised based on feedback from the health professional and patient review. Significant changes:

- Added a Timelines section which consolidated the timelines statements in one location.
- Added a statement that patients will be informed of the stage of their cancer.
- The Rectal Cancer Tumour Board section was rewritten and renamed the “Rectal Cancer Treatment Assessment Committee”.
- The Supportive Care section was re-titled ‘Psychosocial Health Services and Supportive Care” and sub-sections were rewritten, particularly the section on ostomy care which was broadened to “bowel-related concerns” with emphasis increased on the need for psychosocial support at time of

ostomy and ostomy reversal, and information added about Low Anterior Resection Syndrome (LARS).
- The Malignant Rectal Polyps section was rewritten.
- There were substantial edits to the Neo-Adjuvant Therapy section.
- Criteria for MSI testing were added to the Pathology section.
- A new section was added “Referral to Medical Genetics”.
- The Surveillance section was re-titled “Survivorship and Post-Treatment Surveillance”. Survivorship standards were added; the timeline for the start of surveillance was clarified and the role of the primary care provider vs. the surgeon in surveillance was clarified.

As part of the Department of Health and Wellness standard approval process requires an Impact Assessment to determine the resource implications of meeting the new expectations. The Impact Assessment was conducted in February-March 2015 and consisted of two components: a self-assessment by then-District Health Authorities and an electronic survey sent to general surgeons.

The results of the Impact Assessment indicated a minimal need for additional resources to meet the Rectal Cancer Standards. With some exceptions, the services are available and in place for rectal cancer patients, but there is variation in whether the patients access these services. With just under 300 new cases of rectal cancer diagnosed across the province each year, the impact on any one area is relatively small, and incremental impacts are difficult to cost.

Because most of the resources are already in place, implementation will be less about acquiring new resources and more about putting processes in place such as checklists and standing orders. The Nova Scotia Health Authority (NSHA) is responsible for ensuring these standards are achieved and maintained.

Cancer Care Nova Scotia Involvement

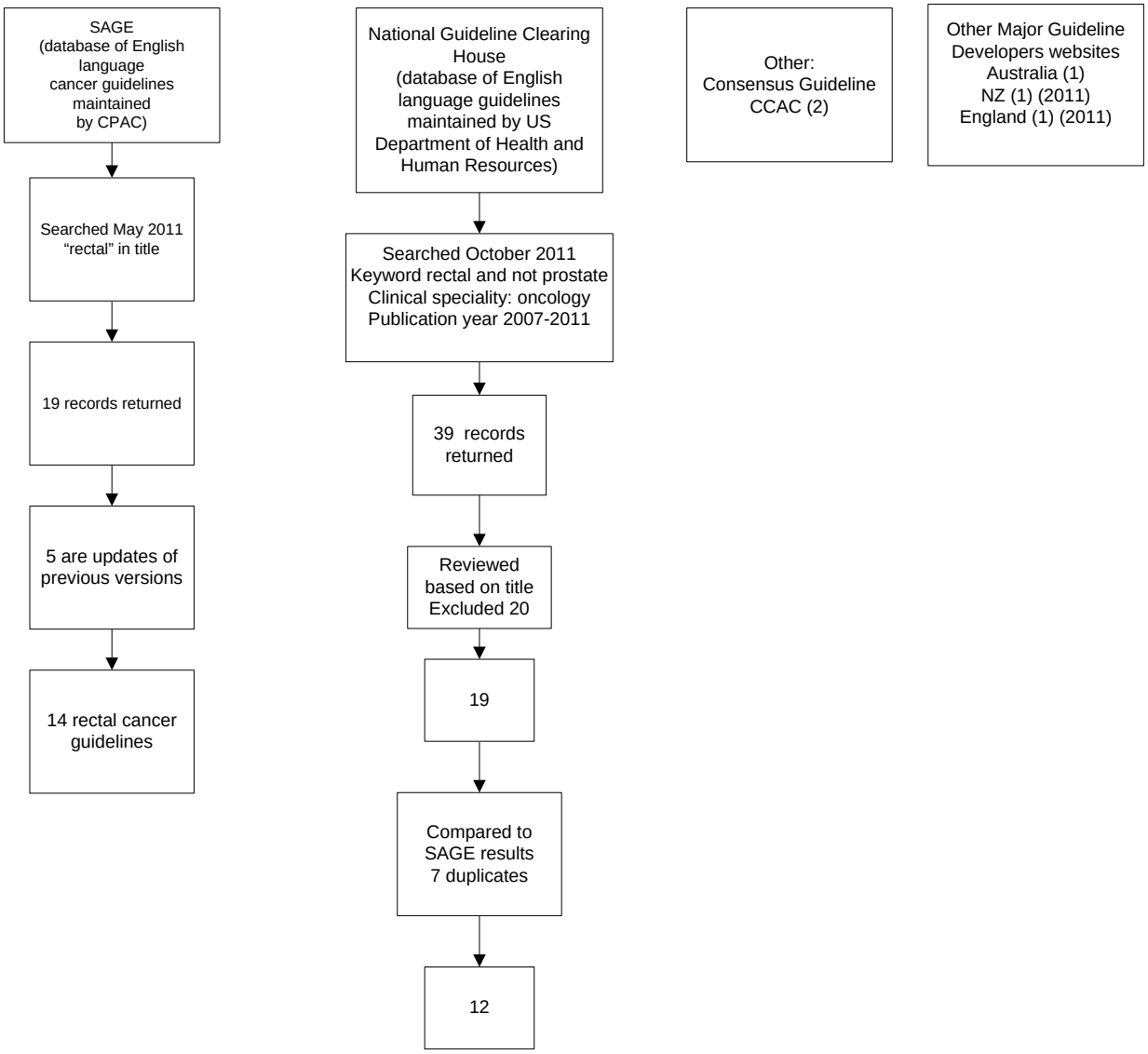
As the provincial cancer agency for Nova Scotia, the mandate for CCNS includes the development of provincial standards and guidelines related to cancer care and treatment. CCNS staff supported the Working Group in the development of the recommendations by providing meeting facilitation support and organization including all communication with members and logistical arrangements. CCNS staff also coordinated the writing and editing of the various drafts. The views and interests of CCNS did not influence the decision-making.

To facilitate the involvement of members, CCNS removed financial barriers by providing travel or distance technology for those participating from outside Halifax, and reimbursing fee for service physicians for their time during meetings (at the approved Department of Health and Wellness rate for administrative work).

The development process was supervised by the CCNS Clinical Standards Oversight Committee, which has representatives of the Nova Scotia Department of Health and Wellness, senior leaders of the District Health Authorities (until April 1, 2015)/Nova Scotia Health Authority (after April 1, 2015), Doctors Nova Scotia and Public Advisors.

As of April 1, 2016 CCNS will become part of the Nova Scotia Health Authority (NSHA). At this time, the Department of Health and Wellness will transfer responsibility for the setting of clinical standards for cancer to the NSHA. Decisions about the future processes of approval, dissemination/implementation and regular reviewing and updating of guidelines will be determined through discussions with the Department of Health and Wellness and the NSHA.

Search Strategy and Results



Appendix 8: Systematic Review Update for Neo-Adjuvant and Adjuvant Therapy

Background on Development of this Systematic Review:

One guideline identified in the search for source guidelines was *Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer: Guideline Recommendations* from Cancer Care Ontario (CCO) Program in Evidence-based Care (PEBC).[5] However, this guideline was flagged by the PEBC in fall 2011 as being more than 3 years old and under review for currency and relevance. Follow up with the PEBC indicated that they would not have an updated guideline to meet our timelines.

With the permission of the PEBC, CCNS contracted in February 2012 with the Capacity Enhancement Program (CEP) of the Canadian Partnership Against Cancer (CPAC) to update the systematic review underpinning the CCO guideline. Clinical expertise was provided by Dr. Stephanie Snow (Medical Oncologist), Dr. Maureen Nolan and Dr. Slawa Cwajna (Radiation Oncologists) who are members of the CCNS Rectal Cancer Treatment Standards Working Group.

The systematic review in the CCO guideline was performed in 2007 and reported on July 15, 2008 with an updated search completed in 2009. The objectives of the current project were to summarize the updated evidence from the 2007 guideline to mid-2012. The primary research question: What is the role of pre-operative (neo-adjuvant) and post-operative (adjuvant) interventions in adults with stage II/III resectable or resected rectal cancer?

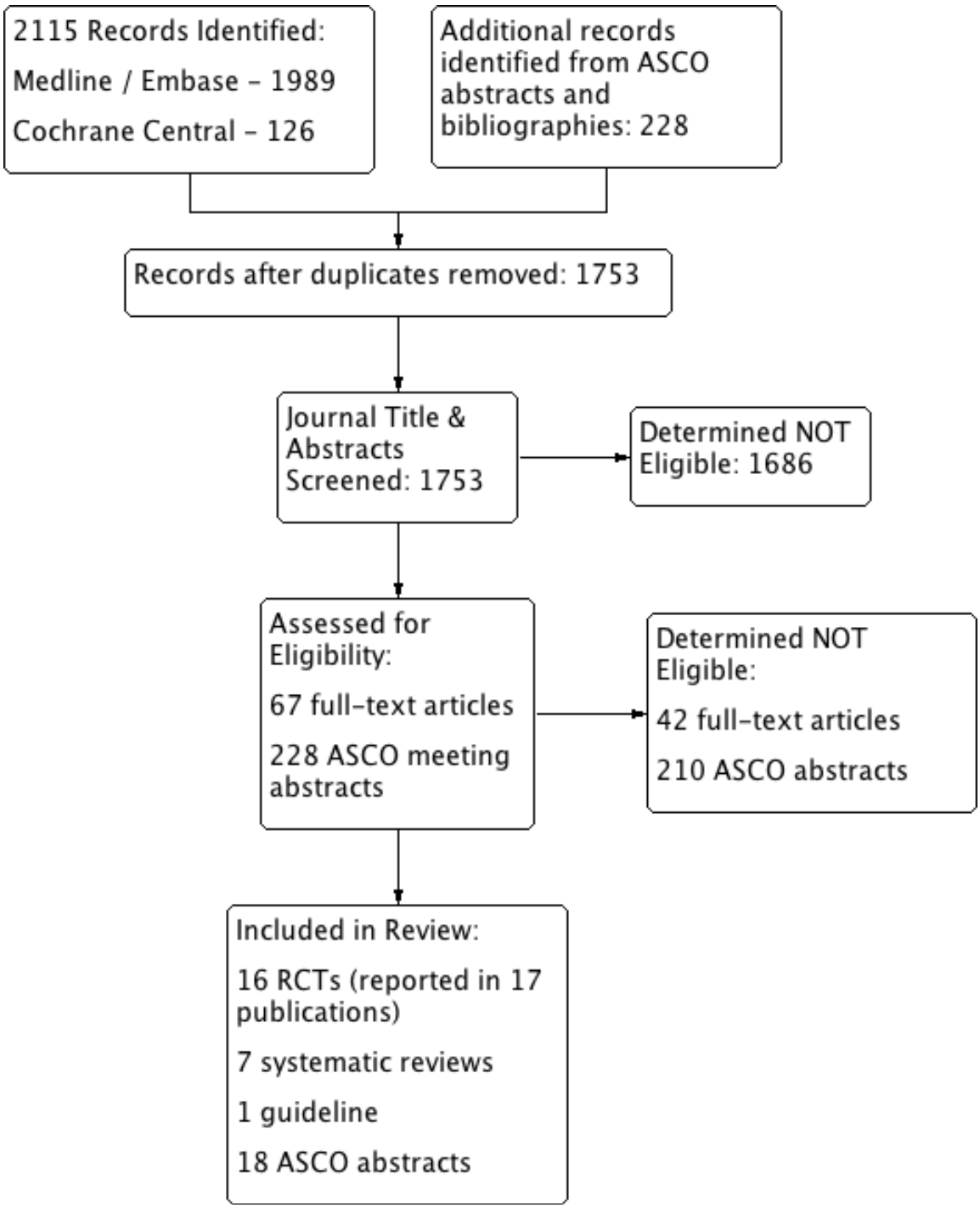
The summary of the evidence and the draft recommendations were reviewed with the Gastro-intestinal (GI) Cancer Site Team, which provides CCNS with expertise related to GI Cancers, prior to discussion with the Rectal Cancer Treatment Standards Working Group.

The systematic review has two parts: neo-adjuvant therapy and adjuvant therapy.

[5] Wong, R.; Berry, S.; Spithoff, K.; Simunovic, M.; Chan, K. et al Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer: Guideline Recommendations. Evidence-Based Series #2-4. Cancer Care Ontario

Part 1: Pre-operative (Neo-adjuvant) therapy for Stage II/III Rectal CA

Neo-adjuvant therapy Search Summary:



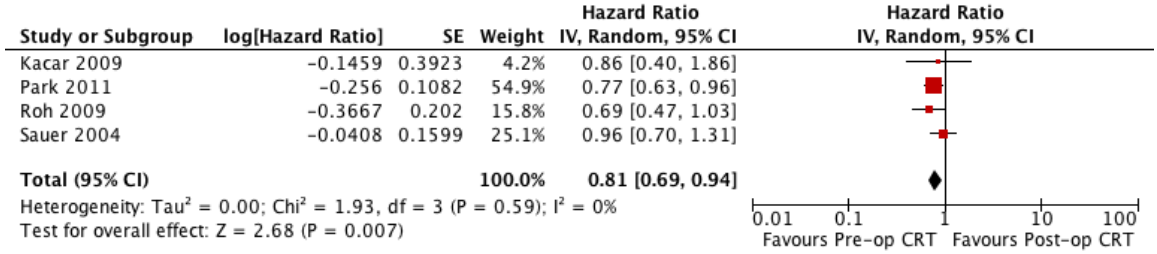
Based on this search of guidelines, systematic reviews and randomized controlled trials, there were a number of subject areas in which new comparisons were identified as potentially adding useful data to inform current recommendations.

What follows is a list of these subject areas reviewed, and a description of the newly identified data that applies to each:

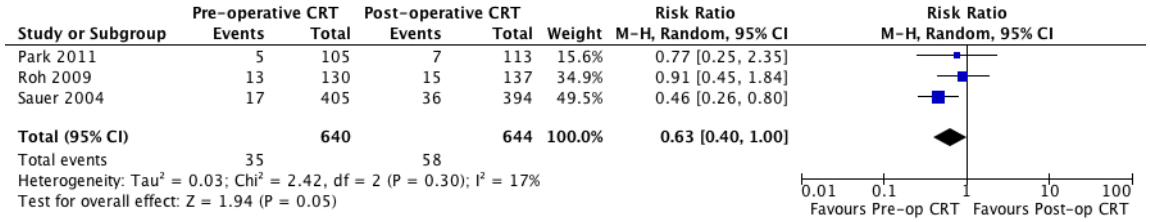
Comparisons from Trial / Abstracts / Systematic Reviews / Guidelines:

1. Pre-op versus Post-Op CRT Trial 1, Trial 3, Trial 14, Trial 16

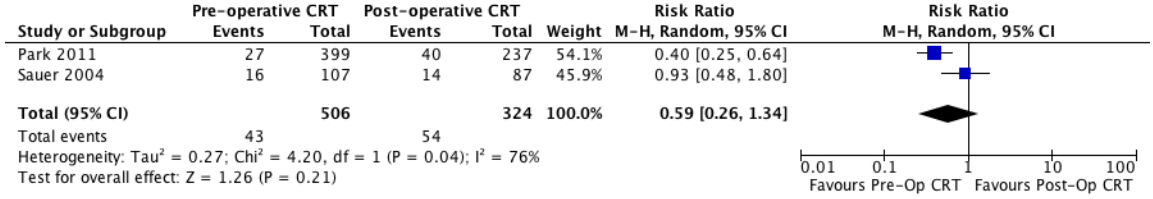
Disease-Free Survival:



Local Recurrence – 5 yrs

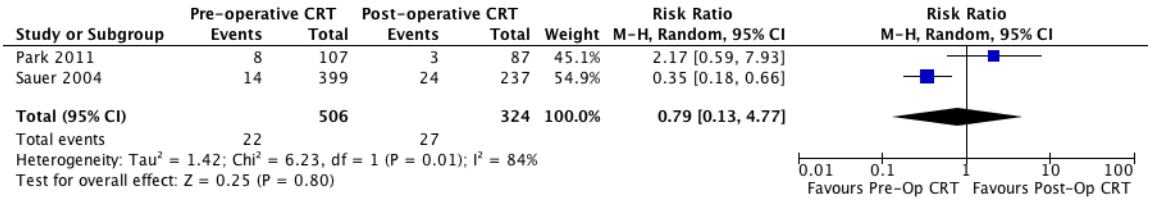


Acute Toxicity (Grade 3 or higher):



I-square of 75% indicates significant heterogeneity and will need to be explained by study methodology or intervention differences between trials.

Late Toxicity (Grade 3 or higher):



I-square of 84% indicates significant heterogeneity and will need to be explained by study methodology or intervention differences between trials.

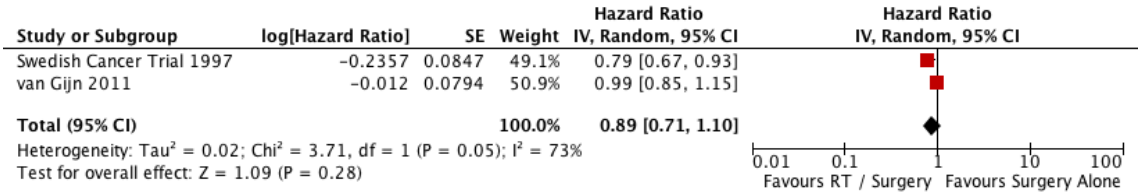
Sauer et al. 2012,[Trial 15] reported on long-term follow-up of outcomes from their 2004 study.[Trial 14] According to their intention-to-treat analysis, overall survival at 10 years was 59.6% in the pre-operative arm and 59.9% in the post-operative arm (p = 0.85). Also, no significant differences were noted in cumulative incidences of distant metastasis and disease-free survival. The 10-year local recurrence was 7.1% and 10.1% for these groups (p = 0.048). **They concluded a persisting significant improvement with pre-operative versus post-operative CRT on local recurrence; but no effect on overall survival.**

2. Short-course RT and Surgery versus Surgery Alone in Trials after 1990

Kapiteijn et al. 2001,[Trial 9] enrolled 1861 patients that assigned patients to arm 1: 5 x 5 GY with surgery versus arm 2: surgery alone. They reported on 2-year outcomes of overall survival (arm 1: 82% versus arm 2: 81.8%; p=0.84) and local recurrence (arm 1: 2.4% versus arm2: 8.2%; p<0.001).

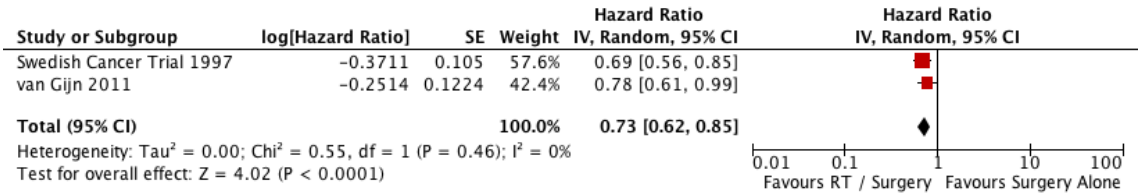
In 1997, The Swedish Rectal Cancer[Trial 10] enrolled 1168 patients and assigned them to 25 Gy delivered in five fractions in one week followed by surgery versus surgery alone. Van Gijn et al. 2011,[Trial 07] reported 12-year follow-up outcomes from the 1861 patients from the Kapitenijn et al. 2001 trial.[Trial 9] These two trials reported outcomes of at least five years duration with pooled estimates:

Overall Survival > 5 years:

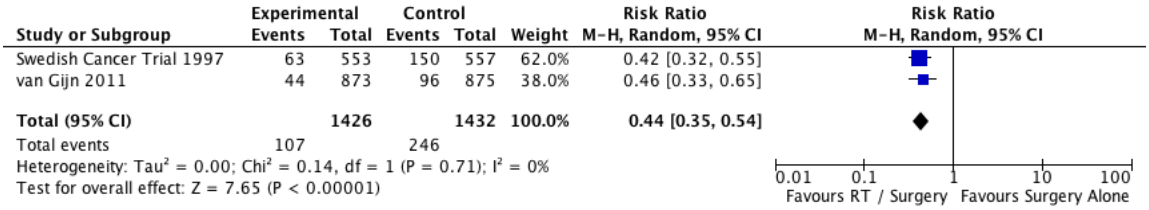


I-square of 73% indicates significant heterogeneity and will need to be explained by study methodology or intervention differences between trials.

Cancer-specific Survival > 5 years:



Local Recurrence:



Wong et al. 2007,[Systematic review 7] reviewed the literature from 1966 to December 2006 for RCTs that compared RT and Surgery with Surgery Alone. They indentified 19 trials that compared RT and surgery versus surgery alone. Overall survival was marginally improved (HR= 0.93 [95% CI -0.87-1](absolute difference is 2% if the expected survival rate is 60%)). Local recurrence (LR) was improved but the magnitude of benefit was heterogeneous across trials. Sensitivity analyses suggested greater benefits in patients treated with BED > 30Gy10 and multiple field RT techniques. There was significantly more pelvic or perineal wound infection, late rectal and sexual dysfunction. Nine trials compared RT versus other neoadjuvant / adjuvant treatment modalities. They concluded that evidence did not support an overall survival or sphincter preserving benefit with the use of combined chemoradiotherapy (CRT) or selective postoperative RT. CRT provides incremental benefit for local control compared with RT, which was independent of the timing of the CT. There was no significant difference in outcome for different intervals between RT and surgery (2 versus 8 wk). Dose escalation with endocavitary boost showed significant effect on sphincter preservation. **Their systematic review concluded that optimal RT improves LR, and overall survival compared to surgery alone, but offers no significant increase in sphincter sparing procedures. CRT further increases local control. They reported that if the goal is to increase the incidence of sphincter sparing surgery, endocavitary boost was described as showing the most promise.**

Viani et al. 2011,[Systematic review 4] reviewed literature from an unspecified date period for RCTs comparing pre-operative RT versus surgery alone. They identified 21 RCTs dating back to 1972 and included any stage of rectal cancer. Most of these trials have been excluded from more recent reviews likely due to differing surgical procedures that accompanied treatment at that timeframe. They concluded that a higher (> 30 Gy10) biologic effective dose was more efficient in reducing local recurrence and mortality rates than lower independent schedule of fractionation.

3. Pre-op CRT with versus without oxaliplatin

Aschele et al. 2009,[ASCO CRA4008] enrolled 747 patients and reported toxicity and on protocol-planned analysis of local tumor response to preoperative treatment related to arm A: infused FU (225 mg/msq/day) concomitant to external-beam pelvic radiation (50.4 Gy in 28 daily fractions) versus arm B: same regimen + weekly oxaliplatin (60 mg/msq x 6). Overall grade 3-4 toxicity rates on treated pts (mainly diarrhea) were 8% and 24% (arm A/B, p<0.001). 96/90% of pts (arm A/B) received > 90% of the planned RT. 82% of Arm B pts had > 5 oxaliplatin courses. 358/342 pts (arm A/B) had surgery at a median of 52/53 days from the end of CRT, 14 pts in each arm were not operated (progression 8, death 5, other/unknown 15) and surgery data are not yet available for 19 pts. Pathologic stage response for T0N0 were 16% and 15% (arm A/B, p = 0.982), for T1-2N0 were 27% and 28%, for N1-2 were 24% and 26% (arm A/B; p = 0.568) and for M1 were 3% and 0.5% (arm A/B, p = 0.014). **They concluded that oxaliplatin significantly increased toxicity without affecting pathologic tumor response.**

A second report by Aschele et al. 2009[ASCO GI - LBA290], from the same trial, reported 752 patients and reported on toxicity and all-cause mortality prior to surgery. The rate of grade 3-4 toxicity was 8% (arm A) versus 23% (arm B) with reporting of nausea, diarrhea, dermatitis and asthenia have p < 0.05. All-cause mortality before surgery was 0.3% in arm A and 1.0% in arm B.

Aschele et al. 2011,[Trial 4] further reported on the original cohort of 747 patients on a protocol-planned dissemination on the outcome for response to treatment. They noted Grade 3 or higher toxicities with oxaliplatin (24% versus 8%; p < 0.001), with no change in the rate of pathologic complete response (OR=0.98; 95%CI 0.66-1.44). **They concluded that adding oxaliplatin increases toxicity without affecting tumour response.**

Gerard et al. 2010,[Trial 2] reported on 598 patients treated with 5 weeks of treatment with radiotherapy 45 Gy/25 fractions with concurrent capecitabine 800 mg/m2 twice daily 5 days per week or radiotherapy 50 Gy/25 fractions with capecitabine 800 mg/m2 twice daily 5 days per week and oxaliplatin 50 mg/m2 once weekly using an endpoint of complete sterilization of operative specimen (ypCR) as the endpoint. Grade 3 or higher toxicity was reported with oxaliplatin (25.4% versus 10.9%; p < 0.001) with increases attributed to primarily diarrhea. There were no significant differences reported in permanent stomas (24.6% versus 25.4%) or overall rates of surgical / medical complications between groups. The rate of positive circumferential rectal margins (between 0-2 mm) was 9.9% versus 19.3%; p = 0.02. **They concluded that benefit of oxaliplatin was not demonstrated and suggested not using it with concurrent radiation.**

Gerard et al. 2009,[ASCO LBA4007] enrolled 598 patients and the final results were published in the Gerard et al. 2010 RCT included in this review. Three-year results comparing concurrent RT 45Gy/25f/5 weeks + capecitabine (800mg/m²/bid) versus concurrent RT 50Gy/25f/5 weeks + capecitabine (800mg/m²/bid/5/7days) + oxaliplatin 50mg/m²/week, with resection scheduled 6 weeks after the end of CT-RT, were reported in Gerard et al. 2012[ASCO GI - 389] and presented a pathological response outcome. There was no significant difference in local control (5% versus 4%), survival (71% versus 73% DFS; 85% versus 88% OS), toxicity (2.7% versus 1.3% grade 3 or higher) and functional results. In an exploratory analysis, clinical complete response (24 patients) before

surgery and pathological complete response (92 patients) were associated with an excellent disease free survival at 3 years respectively 92% and 90%. **They concluded based on group of trials that:**

(1) oxaliplatin should not be included in the protocol (increased early toxicity and no effect on the pCR rate).
(2) capecitabine is as efficient as fluorouracil.
(3) RT dose escalation to 50 Gy is improving pCR without increasing toxicity. A "CAP 50" regimen appears as safe and efficient in this neoadjuvant situation.

From the same cohort, Francois et al. 2012,[ASCO GI - 550] analyzed the trial results with respect to age. In the 142 of 584 patients who were 70 or greater in age: pre-operative toxicity (Grade 3 or higher) was 25.6% versus 15.8%, p = 0.01; discontinuation of RT was 4.2% versus 1.4%, p = 0.03; permanent stoma was 33.3% versus 22.8%, p = 0.014; and inpatient stay days was 22 (SD=18.8) versus 17 (SD=10.8), p < 0.001. Rates of post-operative complications and second surgery for complications were similar. They concluded that as tolerance of elderly patients treated with preoperative RTCT is worse than in younger patients, an appropriate therapeutic schedule is warranted.

Roh et al. 2011,[ASCO 3503] reported on 1608 patients assigned to continuous IV infusion 5-FU (225mg/m2 5 days/week), with or without IV oxaliplatin (50mg/m2 /week x 5) versus oral capecitabine (825 mg/m2 bid 5 days/week), with or without oxaliplatin (50mg/m2/wk x 5) with outcomes of complete pathologic response (pCR), sphincter-saving surgery and surgical down staging. No significant changes were reported in outcomes. They reported that patients treated with oxaliplatin experience more grades 3/4 diarrhea. **They concluded that addition of oxaliplatin did not improve outcomes but did add significant toxicity.**

Roedel et al. 2011,[ASCO LBA3505] enrolled 637 patients assigned to receive preoperative CRT, surgery, and adjuvant chemotherapy with 5-FU according to CAO/ARO/AIO-94 (arm 1), or preoperative CRT (50.4 Gy in 28 fractions) with 5-FU (250 mg/m2/days 1-14 and 22-35) and oxaliplatin (50 mg/m2/days 1, 8, 22, 29), surgery, and 8 cycles of adjuvant chemotherapy according to modified FOLFOX6 regimen (arm 2) and reported on secondary outcomes of acute toxicity, treatment compliance, and pCR-rates. Grade 3/4 toxicity occurred in 21.6% in arm 1 and in 22.9% in arm 2. The R0-resection rate was 95.4% in both arms, and abdominoperineal resections were limited to 11.9% and 12.2% in arms 1 and 2, respectively. Overall postoperative complications were not significantly different between arms (21.0% and 21.9%). The pCR rate (ypT0N0) was 13.1% in arm 1 and 17.6% in arm 2 (p = 0.033). **They concluded that the addition of oxaliplatin to 5-FU based CRT was well tolerated and associated with increased pCR-rates compared with 5-FU-CRT alone.**

4. Pre-op CRT with Capecitabine versus with 5-FU

Hofheinz et al. 2011,[ASCO 3504] reported on 401 patients assigned to Arm A: CRT: 50.4 Gy + Capecitabine 1,650 mg/m2 days 1-38 plus five courses of Cape 2,500 mg/m2 d 1-14, rep. d 22 (S I: 2 x Capecitabine, CRT, 3 x Cape; S II: CRT, TME surgery, 5 x Capecitabine) versus Arm B: CRT: 50.4 Gy + 5-FU 225 mg/m2 c.i. daily [S I] or 5-FU 1,000 mg/m2 c.i. d 1-5 and 29-33 [S II] plus 4 cycles of bolus 5-FU 500mg/m2 d 1-5, rep. d 29 (S I: 2 x 5-FU, CRT, 2 x 5-FU; S II: CRT, TME surgery, 4 x 5-FU) on outcomes for OS, DFS and safety. They reported that local recurrence rate was equal (Capecitabine

6%, 5-FU 7%; p = 0.665). Capecitabine was reported as non-inferior to 5-FU at 5-years for overall survival. The year DFS was significantly better with Capecitabine (75.2% versus 66.6%; p = 0.034). In 2009, Hofheinz et al.[ASCO 4014] also reported on safety results. Regarding overall safety (NCI-CTC), patients receiving Capecitabine experienced significantly less leukopenia (25 versus 35%; p=0.04), but more hand-foot syndrome (31 versus 2%; p<0.001). Stomatitis / mucositis, diarrhea, nausea / vomiting, and radiodermatitis were not significantly different between both arms. In summary, both treatment regimens were well tolerated. Cape patients had more all grade HFS, proctitis, diarrhea and fatigue, while alopecia and leukopenia were more frequently observed with 5-FU. In the neo-adjuvant stratum evidence suggested better activity for capecitabine, based on trend to improved downstaging, numerical higher rate of pCR. In addition, they performed an exploratory test for superiority that trended toward significance for 3-year DFS and was significantly better with capecitabine.

Since beginning search for relevant citations for this updated guideline, Hofheinz et al. 2012,[Trial 17] was published and reported that 5-year overall survival in the capecitabine group was non-inferior to that in the fluorouracil group (76% [95% CI 67–82] versus 67% [58–74]; p=0·0004; post-hoc test for superiority p=0·05). 3-year disease-free survival was 75% (95% CI 68–81) in the capecitabine group and 67% (59–73) in the fluorouracil group (p=0·07). Similar numbers of patients had local recurrences in each group (12 [6%] in the capecitabine group versus 14 [7%] in the fluorouracil group, p=0·67), but fewer patients developed distant metastases in the capecitabine group (37 [19%] versus 54 [28%]; p=0·04). Diarrhea was the most common adverse event in both groups (any grade: 104 [53%] patients in the capecitabine group versus 85 [44%] in the fluorouracil group; grade 3–4: 17 [9%] versus four [2%]). Patients in the capecitabine group had more hand-foot skin reactions (62 [31%] any grade, four [2%] grade 3–4 versus three [2%] any grade, no grade 3–4), fatigue (55 [28%] any grade, no grade 3–4 versus 29 [15%], two [1%] grade 3–4), and proctitis (31 [16%] any grade, one [<1%] grade 3–4 versus ten [5%], one [<1%] grade 3–4) than did those in the fluorouracil group, whereas leucopenia was more frequent with fluorouracil than with capecitabine (68 [35%] any grade, 16 [8%] grade 3–4 versus 50 [25%] any grade, three [2%] grade 3–4). **They concluded that capecitabine could replace fluorouracil in adjuvant or neoadjuvant chemoradiotherapy regimens for patients with locally advanced rectal cancer.**

5. Pre-op RT versus Pre-op CRT

Gerard et al. 2006,[Trial 11] reported on 733 patients for the primary endpoint of OS at 5 years, local recurrence, toxicity and sphincter preservation. Grade 3 or 4 acute toxicity was more frequent with chemoradiotherapy (14.6% v 2.7%; P < .05). There was no difference in sphincter preservation. Complete sterilization of the operative specimen was more frequent with chemoradiotherapy (11.4% v 3.6%; P < .05). The 5-year incidence of local recurrence was lower with chemoradiotherapy (8.1% v 16.5%; P < .05). Overall 5-year survival in the two groups did not differ. **They concluded that pre-operative CRT had no impact on overall survival, increases acute toxicity moderately, but improves local control.**

Gamelin et al. 2009,[ASCO 4104] enrolled 177 patients and reported on the primary endpoint of pathological complete response rate (pCR) with secondary endpoints included down staging, quality of life, sphincter preservation, recurrence rates, disease-free and overall survival. Both RT and CRT were well tolerated. No neutropenia and only 1 grade IV diarrhea in the CRT arm were observed. Treatment related death occurred in 4 patients,

3 in the RT arm and 1 in the CRT arm respectively. With a median follow-up at 22.3 months, median OS is not yet reached. They concluded that neoadjuvant radiotherapy combined with tegafur-uracil increases significantly the pCR rate with an acceptable toxicity. However, tegafur-uracil is not available or in use in North America to inform on this guideline applicable to Nova Scotia.

Wong et al. 2009,[Guideline] reviewed the literature up to 2007 for studies using RCTs or systematic review methodologies that evaluated preoperative or postoperative radiotherapy (with or without chemotherapy) for stage II or III rectal cancer. Specific to pre-operative approaches, they identified 6 trials and one systematic review with recommendations as described at the beginning of this document.

Latkauskas et al. 2009,[Systematic review 2] reviewed literature from 1960 to 2007 for RCTs randomizing to pre-operative therapy (including RT) or CRT followed by surgery. They identified 5 trials with 4 being before 1990 making most of these surgical procedures outdated for the scope of this review. One new abstract identified not listed in previous reviews Rouanet et al. 2006,[ASCO 3527] enrolled 2007 patients and reported 83% (45 + 18 GY) rate versus 86% (45 Gy + 5-FU continous infusion) rate for sphincter conservative surgery due to down staging induced by preoperative treatment. No significant difference was seen between 45 + 18Gy and 45 Gy + 5-FU continuous infusion with a trend for more morbidity in 45 + 18Gy. **They concluded that the complete response rate was significantly better with pre-operative CRT versus RT alone; but that the rate of toxicity was higher.**

Ceelen et al. 2009,[Systematic review 3] reviewed literature from 1975 to June 2007 for RCTs comparing pre-operative RT with CRT with patients having resectable stage II and III rectal cancer. They identified 4 trials concluding that the addition of chemotherapy to preoperative RT significantly increased grade III and IV acute toxicity (OR 1.68-10, P = 0.002) while no differences were observed in postoperative morbidity or mortality. Compared to preoperative RT alone, preoperative CRT significantly increased the rate of complete pathological response (OR 2.52- 5.27, P < 0.001) although this did not translate into a higher sphincter preservation rate (OR 0.92-1.31, P = 0.29). **The incidence of local recurrence at 5 years was significantly lower in the CRT group compared to RT alone (OR 0.39-0.72, P < 0.001). No statistically significant differences were observed in DFS (OR 0.92-1.34, P = 0.27) or OS (OR 0.79-1.14, P = 0.58) at 5 years.**

6. Induction CAPOX + Pre-op CRT versus Pre-op CRT + Post-op CAPOX

Fernandez-Martos et al. 2010,[Trial 5] reported on 108 patients for pathologic complete response rate (pCR) as the primary endpoint. During CRT, grade 3 or higher toxicities were similar; but significantly higher during postoperative adjuvant CRT than with induction CT. For both study arms pCR was 13.5% (95%CI 5.6-25.8) and 14.3% (95%CI 6.4-26.2) respectively. There were no statistically significant changes in down staging, tumor regression or R0 resection. They concluded that induction CAPOX before CRT had similar rates compared to post-operative adjuvant CAPOX.

Fernandes-Martos et al 2011,[ASCO 3552] reported on the cumulative incidence of local-regional (LRF) and distance failure (DF), disease-free (DFS) and overall (OS) at 3 years in the same 108 patients. With a median follow-up time of 39.3 months (0.1-53), the 36 DFS rates were 68% (95% CI, 53% to 80%) for arm A and 70% (95% CI, 55% to 80%) in

arm B. (p=0.97). The 36-month overall survival rates were 90% (95% CI, 77% to 96%) and 81%(95% CI, 68%to 89%) for arms A and B, respectively (p= 0.18). 11 patients experienced relapse in arm A (1 local, 10 distant), and 12 experienced relapse in arm B (2 local, and 10 distant). p = 0.6036. They concluded that all outcomes were similar and identified a need for larger trials to address the question of induction chemotherapy as a potential strategy to reduce acute toxicity and improve compliance.

Safety results were reported in 2009,[ASCO 4103] noting that during treatment period 6 patients died A/B: 2 vascular, 1 suicide/ 3 post-op. Patients with any grade ¾ toxicity during CRT were arm A/B: 29% (14/49) and 23% (12/53). Any grade 3 or higher toxicity during adjuvant/induction CT were 51% (19/37) and 17% (9/54); $\chi 2$,p= 0.0004. On an intent-to-treat basis the pCR for Arm A/B was achieved in seven (13.5%; 95% CI, 5.6%-25.8%) and eight (14.3%; 95% CI, 6.4%-26.2%). R0 resections were achieved in 92% (45/49) and 88% (48/54). 51% (25/49) and 93% (50/54) received all four cycles of adjuvant/induction CT ($\chi 2$;p<0.0001). Relative Median Dose intensity of adjuvant /induction CT was 0.74/0.96 (Wilcoxon; p<0.0001) for Cap and 0.75/1.0 (Wilcoxon; p<0.0001) for Ox.

7. Short-course Pre-op RT versus Selective Post-op CRT (i.e. reserved for patients who had involvement of the circumferential resection margin)

Sebag-Montefiore et al. 2009,[Trial 6] reported on 1350 patients for local recurrence as the primary endpoint. At 3 years with short-course RT, there was reduction of local recurrence (HR=0.39; 95%CI 0.27-0.58) and an absolute difference of 6.2% (95%CI 5.3-7.1). As well, disease-free survival improved (HR=0.76; 95%CI 0.62-0.94) with an absolute difference of 6.0% (95%CI 5.3-6.8). Overall survival was not significantly different (HR=0.91; 95%CI 0.73-1.13). **They concluded that short-course pre-op RT was as effective as selective post-op CRT.**

8. Short-course Pre-op RT versus Pre-op CRT

Bujko et al. 2006,[Trial 13] reported on 312 patients for survival, local control and late toxicity for a median follow up of 4 years. Early toxicity was higher in the CRT group (18.2% versus 3.2%; P <0.001). OS at 4 years was 67.2% in the short-course RT group and 66.2% in the CRT group (P = 0.960). Disease-free survival was 58.4% versus 55.6% (p = 0.820). Local recurrence was 9.0% versus 14.2% (P = 0.170) and severe late toxicity was 10.1% versus 7.1% (P = 0.360). **They concluded that pre-operative short-course RT did not improve outcomes.**

9. Pre-op RT versus Pre-op RT + Post-op CRT

Bosset et al. 2006,[Trial 12] used a factorial methodology and reported on overall survival at 5 years, local recurrence at 5 years, late side-effects and treatment adherence rates. Of 1011 patients enrolled, there was no significant difference in overall survival across groups with pre-operative (p = 0.84) and post-operative (p = 0.12) CRT regimens. Local recurrence was significantly increased in the non-CRT group (17.1%, p = 0.002). The rate of adherence to CRT was 82.0% in the pre-operative group and 42.9% in the post-operative group. **They concluded that adding flouracil-based CRT has no significant impact on survival, although it did provide a significant reduction in local recurrence.**

10. Short-course Pre-op RT versus long-course Pre-op RT

Ngan et al 2010,[ASCO 3509] enrolled 326 patients and reported on local recurrence rates at 3 and 5 years, overall survival and late toxicity. The 3-year LR rates were 7.5% (SC) and 4.4% (LC); difference = 3.1%, 95% CI -2.0 to 8.3 (p = 0.24). There were no apparent differences in rates of distant recurrence (5-year distant recurrence-free rates were 72% SC, 69% LC; log rank p = 0.85; HR (SC:LC) = 0.96, 95% CI 0.64 to 1.45). The overall survival rates at 5 years were 74% SC and 70% LC (log rank p = 0.56; HR (SC:LC) = 0.89, 95% CI 0.60 to 1.32). Late treatment-related toxicity rates were not substantially different between arms (RTOG grade 3-4: SC 7.6%, LC 8.8%; p = 0.84). **They concluded that there was no clear evidence of difference between long (4-6 weeks) and short course (1 week) RT.**

11. Induction CT + Pre-op CRT versus Pre-op CRT

Maréchal et al. 2010,[ASCO 3637] enrolled 57 patients and reported on primary endpoint of ypT0-1 stage rate and secondary endpoints were tolerance, toxicity, sphincter preservation rate and tumor regression grade rate. Completion of full sequence was similar in both groups: 27/29 (96%, A) versus 25/28 (88%, B) patients (p = ns). About surgery, there was no significant difference in terms of type, R0 resection, number of lymph nodes resected or invaded, longitudinal and circumferential margin. ypT0-1 stage were reported in 10/29 (34%, A) versus 8/28 patients (29%, B) (p = ns). T and N down staging occurred in 14/29 (58%, A), 13/28 (65%, B) and 16/29 (55%, A), 12/28 (43%, B) patients, respectively (p = ns). pCR was observed in 8/29 (27%, A) versus 7/28 (25%, B) patients (p = ns) and the tumor regression grades (Dworak) distribution was similar. Sphincter preservation was obtained in 67% (A) versus 100% (B) (p = 0.058). Overall grade 3/4 toxicity was significantly higher in chemotherapy induction group: 8% (A) versus 35% (B) (p = 0.017). They concluded CT induction was feasible although did not have an improved local-regional impact over standard care.

12. Pre-op CRT (CapeOx) + cetuximab versus Pre-op CRT (CapeOx)

Dewdney et al. 2011,[ASCO GI - 360] enrolled 165 patients in a phase II randomized trial of neoadjuvant and adjuvant therapy in rectal cancer patients with or without cetuximab. All patients received neoadjuvant CAPOX (oxaliplatin 130 mg/m2 d1 and capecitabine 1700 mg/m2/d x 14d q21d) x 4 cycles, followed by CRT (50.4Gy/28 fractions with capecitabine 1650 mg/m2/d). All patients were treated with TME, and 4 further cycles of adjuvant CAPOX. This treatment was delivered either with our without concurrent cetuximab given at a loading dose of 400 mg/m2 and then continued weekly at a dose of 250 mg/m2 during the neoadjuvant and adjuvant portions of the treatment. When analysis was limited to those patients who were known to be kras and braf wild type (n=90), there was a significantly higher rate of radiographic response in those patients receiving cetuximab when they were assessed (1) after neoadjuvant chemotherapy (50% vs 70% p=0.038); and (2) after neoadjuvant chemo-radiotherapy (72% vs 89% p=0.028). There was no difference in rates of R0 resections, sphincter preserving surgeries or surgical complications between the two groups, however, and was there also no difference in rates of pCR (primary endpoint of the trial). There was no difference in progression free survival, however, three year overall survival rates favoured the cetuximab arm (81% vs 96%, p=0.035, HR 0.27). These benefits were lost when the analysis included all treated patients, regardless of kras/braf status. The addition of cetuximab was associated with increased skin rash, and increased diarrhea during the

CRT portion of therapy. The presenters concluded that the use of cetuximab in the neoadjuvant and adjuvant setting is associated with a higher rate of radiographic response and confers a survival advantage at 3 years.

13. Timing of Pre-op RT or CRT

Pach et al. 2011,[Trial 8] enrolled 154 patients and reported on type of subsequent surgery, recurrence, long-term survival and downstaging as a result of 2 different time points of RT (operated at 7-10 days or 4-5 weeks after the end of irradiation). The 5-year survival rate in patients operated on 7–10 days after irradiation was 63%, whereas in those operated on after 4–5 weeks, it was 73%—the difference was not statistically significant (log rank, p00.24). A statistically significant increase in 5-year survival rate was observed only in patients with downstaging after radiotherapy—90% in comparison with 60% in patients without response to neoadjuvant treatment (log rank, p=0.004). Recurrence was diagnosed in 13.2% of patients. A lower rate of systemic recurrence was observed in patients operated on 4–5 weeks after the end of irradiation (2.8% versus. 12.3% in the subgroup with a shorter interval, p=0.035). No differences in local recurrence rates were observed in both subgroups of irradiated patients (p=0.119). The longer time interval between radiotherapy and surgery resulted in higher downstaging rate (44.2% versus. 13% in patients with a shorter interval, p=0.0001) although it did not increase the rate of sphincter-saving procedures (p=0.627) and curative resections (p=0.132).
They concluded:

- **Improved 5-year survival rate is observed only in patients with downstaging after preoperative irradiation dose of 25 Gy.**
- **Longer time interval after preoperative radiotherapy 25 Gy does not improve the rate of sphincter-saving procedures and curative resections (R0) despite higher downstaging rate observed in this regimen.**

Garcia-Aguilar et al. 2010,[ASCO GI - 421] enrolled 125 patients and reported on tumor response and patient morbidity based on timing of CRT. Group 1 received CRT alone with surgery following 6 weeks later. A total of 7 (10%) patients from the group 2 using timing of RT with suspected clinical stable disease 4 weeks after CRT had immediate surgery without additional chemotherapy. Of these patients, six had a pathologic partial response (pPR), and one had a pathologic complete response (pCR). Of 60 patients who received modified FOLFOX-6 before surgery, 18 (30%) had a pCR and 3 (5%) developed grade III+ AE during that portion of treatment. **They concluded that adding chemotherapy after CRT and delaying surgery may increase the rate of pCR without additional complications.**

14. Pre-op CRT effectiveness on pCR

Beg et al. 2012,[ASCO GI - 597] performed a systematic review to quantify pCR and adverse event rates for bevacizumab (B) and cetuximab (C) CRT in trials between 2000 and 2011. <u>These agents are not currently available for use for these conditions in Nova Scotia.</u>

Out of 24 trials identified, 15 trials with a total of 457 (range 8-61) patients incorporated B-CRT. Five studies used 5-FU, ten used capecitabine. A third chemotherapeutic agent was also utilized in 7 trials of B-CRT. There were 9 trials incorporating C-CRT with a total of 332 (range 20-50) patients. Two studies used 5-FU, 7 used capecitabine, while

four studies also included a third therapeutic agent. The pooled pCR rate for B-CRT of 20.8% (95% CI 17.3-24.8), was significantly higher than the 9.6% (95%CI 6.92-13.2) pCR rate for C-CRT ($p < 0.001$). The rate of grade 3-4 adverse events was significantly lower for B-CRT at 0.38 per patient studied (95% CI 0.34-0.43) compared to C-CRT at 0.55 per patient (95%CI 0.49-0.60) ($p<0.001$). Surgery was performed in 92% of B-CRT and 94% of C-CRT patients.

They concluded:

- **Addition of either B or C to conventional neoadjuvant CRT does not yield higher pCR rates than those with conventional CRT alone.**
- **Insufficient evidence to support routine use of these novel agents in this treatment strategy for rectal cancer.**
- **Although surgical rates are high in both groups, C-CRT has significantly lower rates of pathologic complete response and significantly higher rates of toxicity than B-CRT.**

15. Short-course Pre-op CRT versus Long-course Pre-op CRT

Sajid et al. 2010,[Systematic Review 1] reviewed literature from 1980 to August 2008 for RCTs that compared the efficacy of short and long-course CRT for any stage of lower rectal cancer. They identified two trials (Klenova et al. 2007 and Bujko et al. 2004); however both these trials had mixed populations from T2-T4 cancer staging that would not meet inclusion criteria for the scope of this guideline.

16. Multiple-Comparisons:

<u>Pre-Op CRT versus RT alone (pre/post operative)</u>

Fiorica et al. 2010,[Systematic review 5] reviewed literature from 1970 to 2008 for RCTs comparing pre-operative or postoperative CRT to preoperative or postoperative RT alone. They identified 7 RCTs comparing pre-operative CRT versus RT and two pre-operative RT versus postoperative CRT. Preoperative CRT compared to preoperative RT alone significantly reduces the 5-year local recurrence rate (RR 1.05; 95%CI 1.01–1.10). No increase was observed in 5-year overall survival rate (RR 0.94; 95%CI 0.94–1.09), and in the occurrence of distant metastases (RR 0.97; 95%CI 0.93–1.02). Instead, postoperative CRT did not reduce local recurrence (RR 0.96; 95%CI 0.80–1.16), distant metastases (RR 1.11; 95%CI 0.94–1.31) and overall mortality (RR 1.09; 95%CI 0.83–1.41). By pooling data on postoperative CRT versus preoperative RT a significant reduction of local recurrence was found for the preoperative approach (RR 0.93; 95%CI 0.90–0.96), though no difference was found in distant metastases rates and overall survival. Finally, the risk of mortality related to toxic events was significantly higher when adding chemotherapy to radiotherapy (RR 2.86; 95%CI 0.99–8.26).

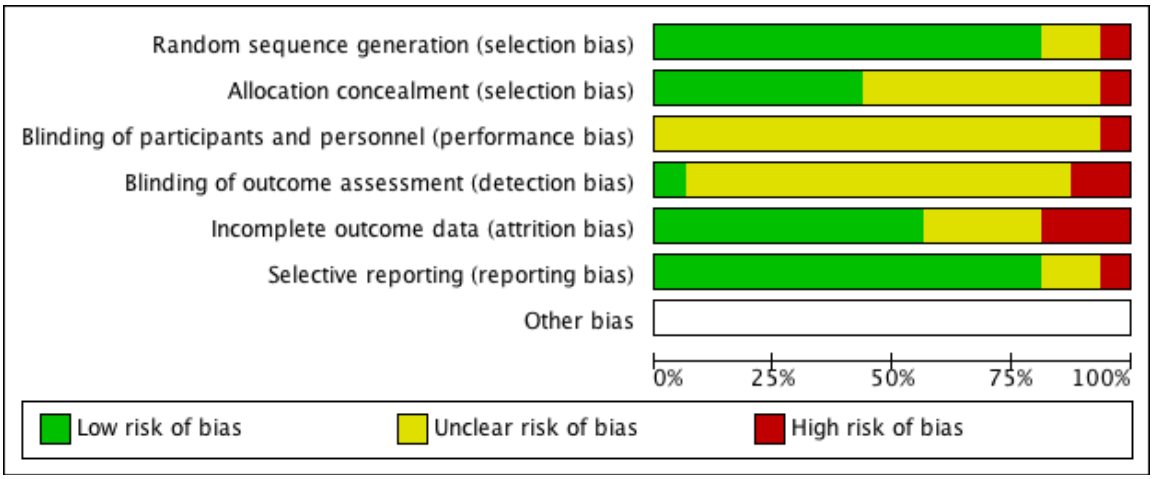
They concluded:

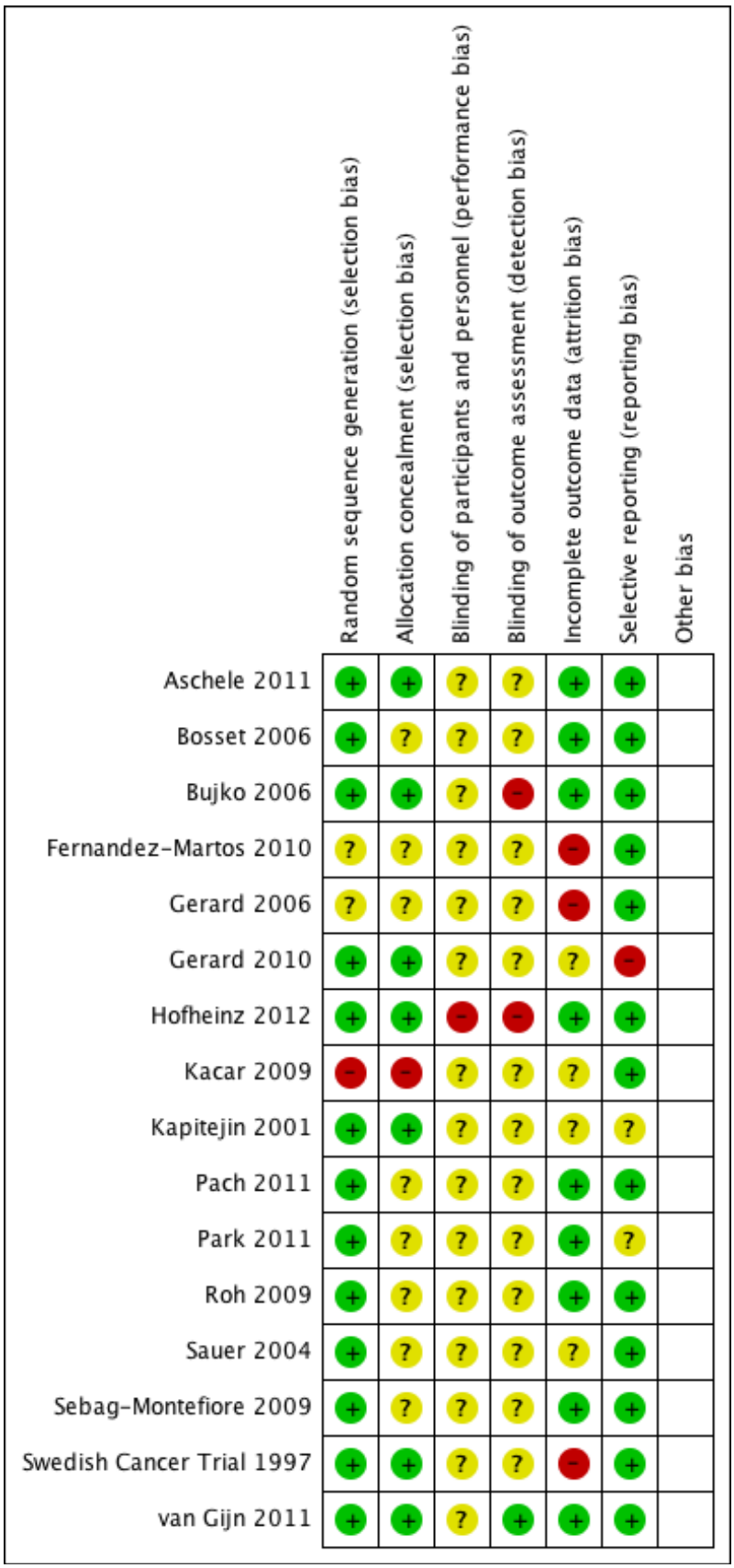
- **CRT does not increase overall survival, despite significantly reducing the risk of the local recurrence.**
- **No reduction in the distant metastases rate was found.**
- **Toxicity-related mortality is significantly increased by the concomitant approach, emphasizing a need for safer treatment combinations.**

Pre-op RT or Pre-op CRT for any comparisons

Fleming et al. 2011,[Systematic review 6] reviewed the literature from 1990 up to March 2010 using RT or CRT in a pre-surgical setting. They identified 12 RCTs and reported descriptively on summaries of these studies. **They concluded that both short-course RT and long-course CRT can offer a relative risk reduction of 50% in local recurrence in stage II/III rectal cancer. This benefit however, comes at the cost of a relative risk increase of 50% in both acute treatment-related toxicity and long-term anorectal dysfunction.**

Quality Summary of Included Trials:




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Aschele 2011
Bosset 2006
Bujko 2006
Fernandez-Martos 2010
Gerard 2006
Gerard 2010
Hofheinz 2012
Kacar 2009
Kapitejin 2001
Pach 2011
Park 2011
Roh 2009
Sauer 2004
Sebag-Montefiore 2009
Swedish Cancer Trial 1997
van Gijn 2011

References

Systematic Reviews and Guidelines:

(Guideline)
Wong RK, Berry S, Spithoff K, Simunovic M, Chan K, Agboola O, Dingle B; Gastrointestinal Cancer Disease Site Group. Preoperative or postoperative therapy for stage II or III rectal cancer: an updated practice guideline. Clin Oncol (R Coll Radiol). 2010 May;22(4):265-71.

(Systematic Review 1)
Sajid MS, Siddiqui MR, Kianifard B, Baig MK. Short-course versus long-course neoadjuvant radiotherapy for lower rectal cancer: a systematic review. Ir J Med Sci. 2010 Jun;179(2):165-71. Epub 2009 Jun 30.

(Systematic Review 2)
Latkauskas T, Paskauskas S, Dambrauskas Z, Gudaityte J, Saladzinskas S, Tamelis A, Pavalkis D. Preoperative chemoradiation vs radiation alone for stage II and III resectable rectal cancer: a meta-analysis. Colorectal Dis. 2010 Nov;12(11):1075-83.

(Systematic Review 3)
Ceelen WP, Van Nieuwenhove Y, Fierens K. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006041.

(Systematic Review 4)
Viani GA, Stefano EJ, Soares FV, Afonso SL. Evaluation of biologic effective dose and schedule of fractionation for preoperative radiotherapy for rectal cancer: meta-analyses and meta-regression. Int J Radiat Oncol Biol Phys. 2011 Jul 15;80(4):985-91.

(Systematic Review 5)
Fiorica F, Cartei F, Licata A, Enea M, Ursino S, Colosimo C, Cammà C. Can chemotherapy concomitantly delivered with radiotherapy improve survival of patients with resectable rectal cancer? A meta-analysis of literature data. Cancer Treat Rev. 2010 Nov;36(7):539-49.

(Systematic Review 6)
Fleming FJ, Påhlman L, Monson JR. Neoadjuvant therapy in rectal cancer. Dis Colon Rectum. 2011 Jul;54(7):901-12.

(Systematic Review 7)
Wong RK, Tandan V, De Silva S, Figueredo A. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD002102.

Randomized Controlled Trials:

(Trial 1)
Park JH, Yoon SM, Yu CS, Kim JH, Kim TW, Kim JC. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer. 2011 Aug 15;117(16):3703-12.

(Trial 2)
Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol. 2010 Apr 1;28(10):1638-44.

(Trial 3)
Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009 Nov 1;27(31):5124-30.

(Trial 4)
Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol. 2011 Jul 10;29(20):2773-80.

(Trial 5)
Fernández-Martos C, Pericay C, Aparicio J, Salud A, Safont M, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol. 2010 Feb 10;28(5):859-65.

(Trial 6)
Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve 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. 2009 Mar 7;373(9666):811-20.

(Trial 7)
van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011 Jun;12(6):575-82.

(Trial 8)
Pach R, Kulig J, Richter P, Gach T, Szura M, Kowalska T. Randomized clinical trial on preoperative radiotherapy 25 Gy in rectal cancer-treatment results at 5-year follow-up. Langenbecks Arch Surg. 2012 Jun;397(5):801-7.

(Trial 9)
Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001 Aug 30;345(9):638-46.

(Trial 10)
Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med. 1997 Apr 3;336(14):980-7.
(Trial 11)

Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol. 2006 Oct 1;24(28):4620-5.

(Trial 12)
Bosset JF, Collette L, Calais G, Mineur L, Maingon P., et al; EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006 Sep 14;355(11):1114-23.

(Trial 13)
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. 2006 Oct;93(10):1215-23.

(Trial 14)
Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004 Oct 21;351(17):1731-40.

(Trial 15)
Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, et al. Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years. J Clin Oncol. 2012 Apr 23. [Epub ahead of print]

(Trial 16)
Kaçar S, Varilsüha C, Gürkan A, Karaca C. Pre-operative radiochemotherapy for rectal cancer. A prospective randomized trial comparing pre-operative vs. postoperative radiochemotherapy in rectal cancer patients. Acta Chir Belg. 2009 Nov-Dec;109(6):701-7.

(Trial 17)
Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol. 2012 Apr 12. [Epub ahead of print]

<u>ASCO GI Symposium:</u>

(LBA290)
C. Aschele, C. Pinto, S. Cordio, G. Rosati, A. Tagliagambe, et al. on behalf of STAR Network Investigators. Final safety findings from a randomized phase III trial of preoperative FU-based chemoradiation +/- weekly oxaliplatin as neoadjuvant therapy for patients with locally advanced rectal cancer: The STAR (Studio Terapia Adiuvante Retto)-01 randomized trial. ASCO 2009 Gastrointestinal Cancers Symposium, abstract #LBA290.

(389)

J-P. Gérard, D. Azria, S. Gourgou-Bourgade, T. Conroy, L. Bedenne. Clinical results at 3 years of the ACCORD 12 randomized trial in rectal cancer. J Clin Oncol 30, 2012 (suppl 4; abstr 389).

(550)
E. Francois, D. Azria, S. Gourgou-Bourgade, I. Martel-Lafay, C. Hennequin, et al. Influence of age on chemoradiotherapy outcome in patients with rectal cancer: Exploratory analysis from the phase III study ACCORD 12/0405 PRODIGE 2. J Clin Oncol 30, 2012 (suppl 4; abstr 550).

(597)
M.S. Beg, J. Meyer, G.C. Balch, X-J. Xie, A.G. Singal. Pathologic complete response rates after neoadjuvant chemoradiation (CRT) for rectal cancer: Do novel agents have a role? J Clin Oncol 30, 2012 (suppl 4; abstr 597).

(360)
A. Dewdney, D. Cunningham, J. Tabernero, B. Glimelius, A. Cervantes, et al. EXPERT-C: A randomized phase II European multicenter trial of neoadjuvant chemotherapy (capecitabine/oxaliplatin) and chemoradiation (CRT) with or without cetuximab followed by total mesorectal excision (TME) in patients with MRI-defined high-risk rectal cancer. J Clin Oncol 29: 2011 (suppl 4; abstr 360).

(421)
J. Garcia-Aguilar, K. Avila, E. K. Bergsland, P. Chu, R. Krieg, D. D. Smith, Timing of Rectal Cancer Response to Chemoradiation Consortium; Optimal timing of surgery after chemoradiation for advanced rectal cancer. ASCO 2010 Gastrointestinal Cancers Symposium, abstract #421.

(3527)
P. Rouanet, M. Rivoire, B. Lelong, E. Rullier, F. Dravet, L. Mineur, L. Vanseymortier, M. Pocard, J. Faucheron, S. Gourgou, B. Saint Aubert. Sphincter preserving surgery after preoperative treatment for ultra-low rectal carcinoma. A French multicenter prospective trial: GRECCAR 1. Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement),
2006: 3527

ASCO General Meeting:

(3503)
M.S. Roh, G.A. Yothers, M.J. O'Connell, R.W. Beart, H.C. Pitot, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. J Clin Oncol 29: 2011 (suppl; abstr 3503).

(3504)
R. Hofheinz, F.K. Wenz, S. Post, A. Matzdorff, S. Laechelt, et al. Capecitabine (Cape) versus 5-fluorouracil (5-FU)–based (neo)adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC): Long-term results of a randomized, phase III trial. J Clin Oncol 29: 2011 (suppl; abstr 3504).

(3509)

S. Ngan, R. Fisher, D. Goldstein, M. Solomon, B. Burmeister, J. Mackay, TROG, AGITG, CSSANZ, RACS; A randomized trial comparing local recurrence (LR) rates between short-course (SC) and long-course (LC) preoperative radiotherapy (RT) for clinical T3 rectal cancer: An intergroup trial (TROG, AGITG, CSSANZ, RACS). J Clin Oncol 28:15s, 2010 (suppl; abstr 3509).

(3552)
C. Fernandez-Martos, C. Pericay, A. Salud, B. Massuti, V. Alonso, et al. Three-year outcomes of GCR-3: A phase II randomized trial comparing conventional preoperative chemoradiation (CRT) followed by surgery and postoperative adjuvant chemotherapy (CT) with induction CT followed by CRT and surgery in locally advanced rectal cancer. J Clin Oncol 29: 2011 (suppl; abstr 3552).

(3637)
R. Maréchal, B. Vos, M. Polus, T. Delaunoit, M. Peeters, et al. Chemotherapy induction followed by preoperative chemoradiation versus preoperative chemoradiation alone in locally advanced rectal cancer (LARC): A randomized controlled phase II study. J Clin Oncol 28:15s, 2010 (suppl; abstr 3637).

(4014)
R. Hofheinz, F. Wenz, S. Post, A. Matzdorff, S. Laechelt, et al. Capecitabine (Cape) versus 5-fluorouracil (5-FU)-based (neo-) adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC): Safety results of a randomized, phase III trial. J Clin Oncol 27:15s, 2009 (suppl; abstr 4014).

(4103)
C. Fernandez-Martos, J. Aparicio, A. Salud, V. Alonso, B. Massuti, et al. Multicenter randomized phase II study of chemoradiation (CRT) followed by surgery (S) and chemotherapy (CT) versus induction CT followed by CRT and S in high-risk rectal cancer: GCR-3 final efficacy and safety results. J Clin Oncol 27:15s, 2009 (suppl; abstr 4103).

(4104)
E. Gamelin, L. Mineur, C. Chevelle, P. Cailleux, L. Martin, et al. Neoadjuvant radiotherapy ± tegafur-uracil plus leucovorin in rectal adenocarcinoma: Final results of a French multicenter phase III study. J Clin Oncol 27:15s, 2009 (suppl; abstr 4104).

(CRA4008)
C. Aschele, C. Pinto, S. Cordio, G. Rosati, A. Tagliagambe, on behalf of STAR Network Investigators; Preoperative fluorouracil (FU)-based chemoradiation with and without weekly oxaliplatin in locally advanced rectal cancer: Pathologic response analysis of the Studio Terapia Adiuvante Retto (STAR)-01 randomized phase III trial. J Clin Oncol 27:18s, 2009 (suppl; abstr CRA4008).

(LBA3505)
C. Roedel, H. Becker, R. Fietkau, U. Graeven, W. Hohenberger, German Rectal Cancer Study Group; Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: First results of the German CAO/ARO/AIO-04 randomized phase III trial. J Clin Oncol 29: 2011 (suppl; abstr LBA3505).

(LBA4007)
J. Gerard, D. Azria, S. Gourgou-Bourgade, I. Martel-Laffay, C. Hennequin, et al. Randomized multicenter phase III trial comparing two neoadjuvant chemoradiotherapy (CT-RT) regimens (RT45-Cap versus RT50-Capox) in patients (pts) with locally advanced rectal cancer (LARC): Results of the ACCORD 12/0405 PRODIGE 2. J Clin Oncol 27:18s, 2009 (suppl; abstr LBA4007).

Search Strategy – EMBASE / Medline up to February 8, 2012

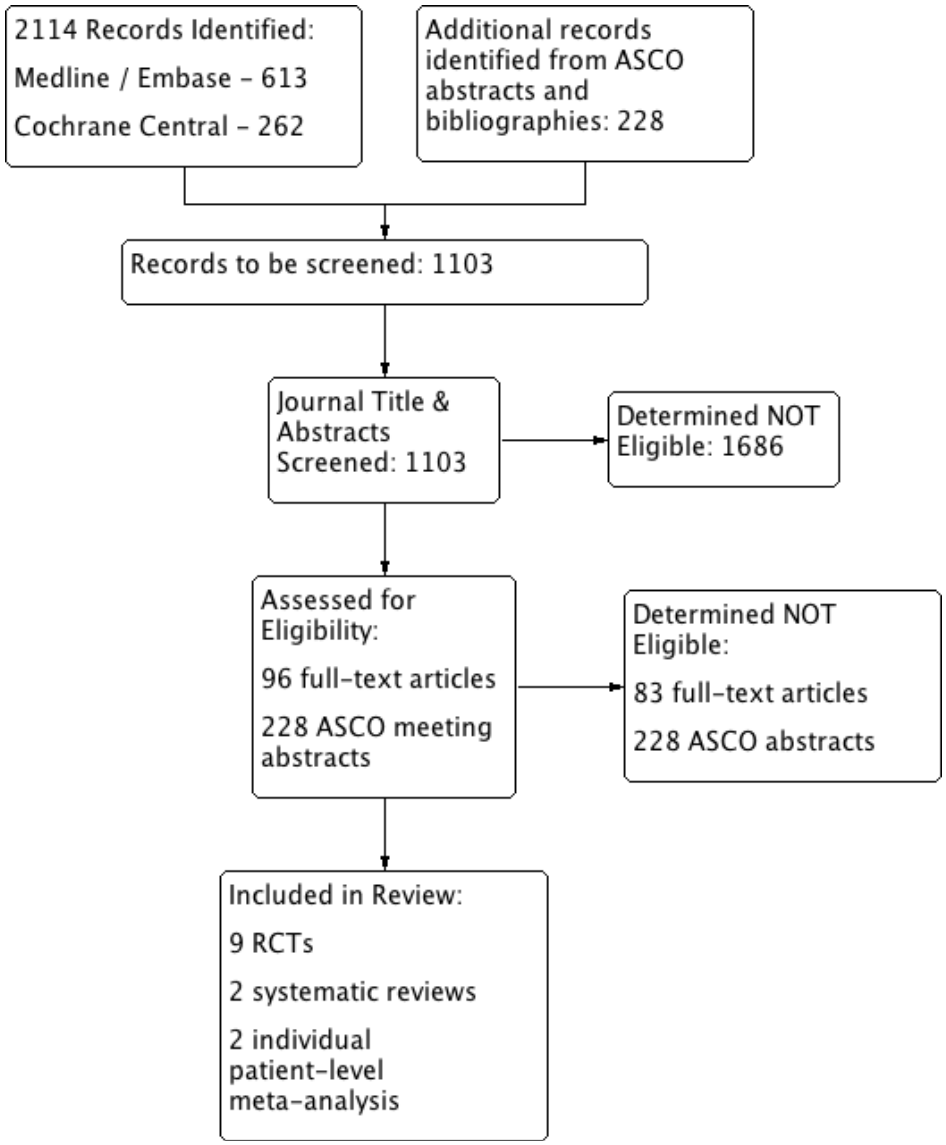
---

1 exp clinical trials/ (448963)
2 random allocation/ (53688)
3 double-blind method/ or double blind procedure/ (108508)
4 single blind method/ or single blind procedure/ (17250)
5 triple blind procedure/ (13)
6 (clin: adj1 trial:).tw. (186578)
7 ((singl: or doubl: or trebl: or tripl:) adj (blind: or mask:)).tw. (107127)
8 placebos/ (97257)
9 placebo:.tw. (139261)
10 random:.tw. (601207)
11 research design/ (93153)
12 comparative study/ (799265)
13 exp evaluation studies/ (169289)
14 follow-up studies/ (462281)
15 prospective studies/ (252615)
16 (control: or prospectiv: or volunteer:).tw. (2399419)
17 randomized controlled trial.pt. or randomized controlled trial/ (309710)
18 controlled clinical trial.pt. or controlled clinical trial/ (93327)
19 clinical trial.pt. or clinical trial/ (692730)
20 or/1-7 (698242)
21 or/8-13 (1608674)
22 or/14-19 (3167485)
23 or/20-22 (4080199)
24 limit 23 to humans (3005457)
25 combined modality therapy/ or multimodality cancer therapy/ (65695)
26 preoperative care/ (24795)
27 preop:.tw. (161740)
28 neoadjuv:.tw. (14481)
29 or/25-28 (244635)
30 rectal neoplasms/rt, su, th or exp rectum cancer/ (56189)
31 colorectal neoplasms/rt, su, th or colorectal cancer/ (59022)
32 30 or 31 (84376)
33 24 and 29 (115377)
34 32 and 33 (5090)
35 limit 34 to english language (4368)
36 remove duplicates from 35 (3220)
37 36 and (200705: or 200706: or 200707: or 200708: or 200709: or 20071: or 2008: or 2009:).ed. (284)
38 36 and (2007: or 2008: or 2009:).ew. (594)
39 37 or 38 (878)
40 from 39 keep 1-878 (878)

****

Part II Post-operative (Adjuvant) Therapy for Stage II/III Rectal CA

Adjuvant Therapy Search strategy:



New studies and comparisons:

1) Adjuvant CT versus Surgery Alone

Hamaguchi et al. 2011,[1] enrolled 276 Stage III rectal cancer patients randomly assigned them to either surgery alone or surgery followed by Uracil-Tegafur (UFT) 400mg/m2/day for five consecutive days/week for 1 year. They reported a relapse-free (RFS), overall survival (OS) and toxicity. The 5-year RFS was 68.9% (95% CI: 61.1-76.8) in the UFT group versus 56.3% (95% CI: 47.9-64.8) in the surgery alone group, which was statistically significant (p = 0.033) in favour of UFT. The 5-year OS was 85.3% (95% CI: 79.4-91.3) in the UFT group versus 72.1% (95% CI: 64.4-79.7), which was statistically significant (p = 0.034) in favour of UFT. There was one grade-4 toxicity (diarrhea) reported. They concluded that UFT improves RFS and OS; **however UFT is not available or in use in North America**.

The QUASAR Collaborative Group in 2007,[2] enrolled 948 patients with Stage II rectal cancer and assigned them, following surgery, to either flouracil with folinic acid (6 5-day courses every 4 weeks or as 30 once-weekly courses) or observation by considering chemotherapy on recurrence. The primary outcome was all-cause mortality. The risk of death was RR=0.77 (95% CI: 0.55-1.08) in the adjuvant group versus surgery and observation alone. **They concluded that the adjuvant treatment could improve survival.**

Sakamoto et al. 2007,[3] reviewed individual patient-level data via meta-analysis from 2091 patients enrolled across five randomized controlled trials that compared UFT versus surgery alone. Outcomes were OS, disease-free survival (DFS) and RFS. Their pooled analysis found that UFT was significantly better than surgery alone in OS (HR=0.82; 95% CI: 0.70-0.97; p = 0.02) and DFS (HR=0.73; 95% CI: 0.63-0.84); **however UFT is not available or in use in North America**.

Dahl et al. 2009,[4] 244 rectal cancer patients were randomized to either 5-FU with levamisole or surgery alone. Outcomes were OS, DFS and toxicity showing no statistical differences in groups at 5 years. The reported outcomes were on colorectal patients; but they concluded that rectal cancer does not benefit from this regimen implying a non-reported analysis that was not included in the manuscript. **Levamisole is not in use in North America.**

Adjuvant CT versus Surgery Alone: study characteristics

Trial	Inclusion criteria	N	Type of Surgery	Intervention	Median follow-up (mos)
Hamaguchi 2011	Stage III colon and rectal cancer	276 rectal cancer	NR	Surgery + UFT 400mg/m^2/d for 5 consecutive d/wk/1 yr Surgery alone	36
QUASAR Collaborative Group 2007	Stage II rectal cancer, node negative	948	NR	Surgery + 5-FU + L-folinic acid (either high dose 175mg IV or low dose 25mg IV) six 5d courses every 4 wk or 1x/wk for 30wk Surgery alone	66 (range 0-127)
Sakamoto 2007	RCTs on UFT for curatively resected rectal cancer without evidence of distant metastasis	2091 (5 trials)	NR	Surgery + UFT Surgery alone	
Dahl 2009*	Patients with a radical resection for colon or rectal adenocarcinoma with no evidence of distant metastases	244	Low anterior resection, abdominalperineal resection, TME	5-FU (450mg/m2) for 5 consecutive d + levamisole 50mg, 3x daily for d1-3; after, 5-FU weekly from d28: 450mg/m2 for 48 wk + levamisole 50mg, 3xdaily for 3 days every second wk Surgery alone	

Notes: 5-FU, 5-fluorouracil; IV, intravenous; NR, not reported; UFT, Uracil-Tegafur; * includes some colon cancer subjects

Adjuvant CT versus Surgery Alone: Outcomes

Trial	Treatment	N	Overall Survival			Disease-free Survival			Recurrence-free Survival		
			%	HR (95% CI)	p value	%	HR (95% CI)	P value	%	HR (95% CI)	p value
Hamaguchi 2011	Surgery + UFT Surgery	139 135	85.3 (79.4-91.3) 72.1 (64.4-79.7)	0.60 (0.38-0.97)	p=0.034	NR			68.9 (61.1-76.8) [a] 56.3 (47.9-64.8) [a]	0.66 (0.45-0.97)	p=0.033
QUASAR Collaborative Group 2007	Surgery + 5-FU Surgery	474 474	NR			NR				0.68 (0.52-0.88) [b]	p=0.004
Sakamoto 2007				0.82 (0.70-0.97)	p=0.02		0.73 (0.63-0.84)	P<0.0001		0.68 (0.53-0.87) [a]	p=0.0026
Dahl 2009	CT Surgery		71 (65-78) 66 (60-73)		p=0.40	73 (67-79) 67(61-74)		NR	NR		NR

Notes: 5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; N, number of patients evaluated; NR, not reported; RR, risk ratio; UFT, Uracil-Tegafur

[a] Relapse-free survival

[b] relative risk

During the course of the write-up of this review, Petersen et al. 2012,[5] published a systematic review that reported on 21 identified RCTs, between 1975 and March 2011, comparing any cancer stage of patients undergoing surgery for rectal cancer who received no adjuvant chemotherapy with those receiving any postoperative chemotherapy regimen. They reported, “The results of this meta-analysis **support the use of 5-FU based postoperative adjuvant chemotherapy for patients undergoing apparently radical surgery for non-metastatic rectal carcinoma**. Available data do not allow us to define whether the efficacy of this treatment is highest in one specific TNM stage.”

2) CT/CRT following Neo-adjuvant CT/CRT

Collette et al. 2007,[6] performed in individual patient-level data meta-analysis on 785 patients in a 2x2 factorial trial (who previously received pre-operative RT or CRT). The factorial design allowed for 2 comparisons on effectiveness of adjuvant CT (flouracil):

1) Pre-operative RT-CT versus postoperative RT-CT
2) Adjuvant CT versus surgery alone

Outcomes were DFS and OS and both were found not to be significant for all outcomes ($p > 0.5$).

Zhang et al. 2008,[7] randomized 260 patients in a three-arm trial comparing neo-adjuvant in conjunction versus post-operative CRT/surgery and further versus post-operative CRT and surgery-alone. They concluded surgery combined with preoperative and postoperative RT could improve overall survival and reduce local recurrence.

Bujko et al. 2010,[8] performed a systematic review to determine if post-operative fluoropyrimidine-based CT has benefit in patients who have already received neo-adjuvant RT or CT. Four RCTs were identified with no beneficial effects identified in outcomes of survival or progressive-free interval.

CT/CRT following Neo-adjuvant: study characteristics

Trial	Inclusion criteria	N	Type of Surgery	Intervention	Median follow-up (mos)
Collette 2007	Studies of potentially resectable cT3-4 M0 rectal cancer located within 15cm of the anal margin	785	TME; Anterior resection; abdomino-perineal resection	Pre-op: 45Gy in 25fr to the posterior pelvis, CT[a] in two 5d courses on wk 1 + 5; surgery; adjuvant CT[a] started 3-10wk after surgery	65
Zhang 2008	Aged 28-70 years; Karnofsky score ≥ 70; diagnosed by pathology; blood and urine testing were normal; no heart, liver or kidney disease; operation and RT can be tolerated, and had received no prior treatment	260	Radical operation	Pre-operative continuous hyper-fractionation accelerated radiation therapy by 6mV or 10mV	60
Bujko 2010	Studies with patients curatively resected of rectal adenocarcinoma				

Notes: TME, total mesorectal excision

[a] 5-fluorouracil (350mg/m^2/d) and leucovorin (20mg/m^2/d) administered as a short intravenous infusion

CT/CRT following Neo-adjuvant: Outcomes

Trial	Treatment	N	Overall Survival		
			%	HR (95% CI)	p value
Collette 2007*	RT	199	63.2		
	CRT	204			
	RT + adj CT	190	67.2	0.82 (0.68-1.04)	
	CRT + adj CT	192			
Zhang 2008	Pre-Op RT and Post-OP CRT	92	68.5		0.003
	Post-Op RT	98	54.1		
	Surgery alone	70	41.4		
Bujko 2010					

Notes: CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio; N, number of patients evaluated; NR, not reported; RR, risk ratio; RT, radiotherapy *meta-analysis

3) Timing of Adjuvant after surgery

Kim et al. 2011,[9] randomized 308 patients to either early (starting first chemotherapy cycle) or late (starting 3rd cycle) RT – flouracil 275 mg/m2/day and leucovorin 20 mg/m2/day at 4-week intervals and pelvic RT of 45 Gy in 25 fractions. Outcomes were OS and DFS at 10 years showing no statistical differences between groups aside from specifically patients who underwent abdominoperineal resection where DFS was statically greater in the early RT group (63% versus 40%; p = 0.043). **They concluded that consideration should be given for post-operative patients requiring abdominoperineal resection.**

Timing of Adjuvant after Surgery: study characteristics

Trial	Inclusion criteria	N	Type of Surgery	Intervention	Median follow-up (mos)
Kim 2011	Stage II or stage III adenocarcinoma of te rectym without evidence of distant metastasis	308	Anterior resection; abdomino-perineal resection	Early: 8 x (5-FU 375mg/m^2/day + LV 20mg/m^2/day at 4 wk intervals) + pelvic RT of 45 Gy in 25 fr, starting 1st cycle of CT Late: 8 x (5-FU 375mg/m^2/day + LV 20mg/m^2/day at 4 wk intervals) + pelvic RT of 45 Gy in 25 fr, starting 3rd cycle of CT	121

Notes: 5-FU, 5-fluorouracil; fr, fractions; Gy, Gray; LV, leucovorin

Timing of Adjuvant after Surgery: Outcomes

Trial	Treatment	N	Overall Survival			Disease-free Survival		
			%	HR (95% CI)	p value	%	HR (95% CI)	p value
Kim 2011	Early	155	66.4 [a]		p=0.652	71.2 [a]		p=0.162
	Late	153	64.0 [a]			62.7 [a]		

Notes: CI, confidence interval; HR, hazard ratio; N, number of patients evaluated; NR, not reported; RR, risk ratio
[a] 10 year survival

4) Modulation of Adjuvant CT after surgery

Kornmann et al. 2010,[10] randomized 796 patients to 3 CRT groups: 5-FU and folinic acid; 5-FU and interferon; or 5-FU alone. Outcomes were local recurrence (LR), OS, DFS and toxicity at 5 years. 5-FU and folinic acid in the stage II sub-group tended to reduce LR rate by 55% and increase OS and DFS by 13% and 12% respectively, relative to the group using 5-FU alone. Toxicities were reported in 58% in the interferon group versus 32% and 28% in the 5-FU and 5-FU plus folinic acid groups. **There concluded that interferon is not recommended and that addition of folinic acid to 5-FU may benefit specifically stage II patients.**

Modulation of Adjuvant CT after Surgery: study characteristics

Trial	Inclusion criteria	N	Type of Surgery	Intervention	Median follow-up (mos)
Kormann 2010	Stage II and III rectal adenocarcinoma with lower tumour edge within 12 cm from anal verge	796	Anterior resection; abdomino-perineal resection	CT: 14 days after surgery, levamisol (50mg) orally 3x/day for 3 consecutive d every 2 wks (d 1-3) + 5-FU (450mg/m^2) on d 1-5; after 28 d, 5-FU 1x weekly for 48wk + folinic acid (200mg/m^2) given before 5-FU Interferon-a: 6x 10^6 IU 3x weekly RT: 50.4Gy (45Gy with 5.4Gy boost) in 28 fr, 5x weekly starting 6-8wk after surgery	59

Notes: 5-FU, 5-fluorouracil

Modulation of Adjuvant CT after Surgery: Outcomes

Trial	Treatment	N	Overall Survival			Disease-free Survival			Local Recurrence		
			% (95% CI)	HR (95% CI)	p value	% (95% CI)	HR (95% CI)	p value	% (95% CI)	HR (95% CI)	p value
Korman 2010	5-FU	282	60.3 (54.3-65.8)			NR			16.7 (12.3-22.5		
	5-FU + FA	291	60.4 (54.4-65.8)						13.6 (9.6-19.0)		
	5-FU + IFN-a	223	59.9 (53.0-66.1)						17.1 (12.2-23.8)		

Notes: 5-FU, 5-fluorouracil; CI, confidence interval; FA, folinic acid; HR, hazard ratio; IFN-a, interferon alpha; N, number of patients evaluated; NR, not reported

5) Comparing CT/CRT adjuvant regimes

Hata et al. 2008,[11] randomized a mixed colon and rectal group (specifically 62 rectal cancer patients), with no previous CT/RT treatment, to receive either daily divided dose cisplatin daily for 21 days followed by oral 5-FU or oral 5-FU alone after surgery. Outcomes were OS, DFS and toxicities showing no statistical difference between groups at 5 years and only rare Grade III or IV toxicities in either group.

Kalofonos et al. 2008,[12] randomized 321 patients to either irinotecan and leucovorin with 5-FU or leucovorin with 5-FU alone after TME. Outcomes were 3-year OS, DFS, local relapse-free survival and toxicities showing no statistical differences between groups aside from higher Grade3/4 toxicities in the irinotecan group.

Koda et al. 2011,[13] randomized 100 stage III colorectal patients to either uracil-tegafur (UFT) or oral fluoropyrimidine (S-1). Outcomes were relapse-free survival, OS and safety. Relapse was significantly higher in the UFT group (11/25 versus 4/21; $p < 0.01$) while OS not significantly different in either group. They concluded that S-1 was no less effective that UFT as an adjuvant therapy for stage III patients. This was an abstract and it was unable to ascertain if the full study included a sub-group specific to rectal cancer. As well, **UFT and S-1 are not available for use in North America.**

Hofheinz et al. 2012,[14] randomized 401 stage II/III rectal cancer patients to either capecitabine or fluorouracil in a non-inferiority trial. Outcomes were 5-year OS, local recurrence and toxicities. **They concluded Capecitabine could replace fluorouracil in adjuvant or neoadjuvant CRT regimens for patients with locally advanced rectal cancer.**

Comparing CT/CRT adjuvant regimens: study characteristics

Trial	Inclusion criteria	N	Type of Surgery	Intervention	Median follow-up (mos)
Hata 2008	Stage II or III colorectal cancer patients	62 rectal cancer	NR	5-FU + CDDP: 5-FU 320mg/m2 + CDDP 3.5mg/m^2 daily for 21 + 5 FU (200mg/body daily for 2 yrs) 5-FU: Oral 5-FU exclusively (200mg/body daily for 2 yrs) starting 3wk after surgery	78.0 76.4
Kalofonos 2008	Patients underwent complete surgery for Rectal adenocarcinoma within 12cm of anal verge	321	TME	6 x (4 weekly administration of Irinotecan (80mg/m^2) + IV (200mg/m^2) + 5-FU (450mg/m^2)) 6 x(weekly administration of LV (200mg/m^2) + 5-FU (450mg/m^2))	52 (range: 0.1-90)
Koda 2011	Stage III colorectal cancer	100	NR	UFT: (400mg/m^2/day, 5d/wk for 1 year, starting 6wk after resection S-1: (80mg/m^2/day, 28d per 6wks) for 1 year, starting 6wk after resection	41
Hofheinz 2012	Stage II/III local advanced rectal cancer	401	TME or PME	2 cycles of capecitabine (2500 mg/m² days 1–14, repeated day 22), followed by CRT (50·4 Gy plus capecitabine 1650 mg/m² days 1–38),then three cycles of capecitabine 2 cycles of bolus fluorouracil (500 mg/m² days 1–5, repeated day 29), followed by CRT (50·4 Gy plus infusional fluorouracil 225 mg/m² daily), then two cycles of bolus fluorouracil.	52 (IQR 41–72)

Notes: 5-FU, 5-fluorouracil; S-1, oral fluoropyrimidine; CDDP, cisplatin daily divided dose; TME, total mesorectal excision; PME, partial mesorectal excision; UFT, uracil-tegafur; IQR, interquartile range; NR, not reported.

Comparing CT/CRT adjuvant regimens: Outcomes

Trial	Treatment	N	Overall Survival			Disease-free Survival			Local Relapse Free Rate		
			%	HR (95% CI)	p value	%	HR (95% CI)	p value	%	HR (95% CI)	p value
Hata 2008	5-FU + CDDP 5-FU	32 30	68.8 73.2		p=0.623		0.671 (0.296-1.524)		NR		NR
Kalofonos 2008	Irinotecan and LV with 5-FU LV + 5-FU	119 127	81 86	0.73 (0.46-1.15)	p=0.129	66 72	0.92 (0.63-1.34)		94% 94%		0.837
Koda 2011	UFT S-1	100	86.6 95.9		p=0.06	NR			NR		
Hofheinz 2012	Capecitibine 5-FU	197 195	67 76		P=0.0004	NR			NR		

Notes: 5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; LV, leucovorin; N, number of patients evaluated; NR, not reported; RR, risk ratio

6) Adverse Events

Birgisson et al. 2007,[15] performed a systematic review summarizing late adverse effects of RT. They identified 11 RCTs; but only studies between the years of 1976 and 2002.

References of Studies Included in Review

1. Hamaguchi T, Shirao K, Moriya Y, Yoshida S, Kodaira S, Ohashi Y; NSAS-CC Group. Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC). Cancer Chemother Pharmacol. 2011; 67:587-96.

2. Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet. 2007; 370: 2020-9.

3. Sakamoto J, Hamada C, Yoshida S, Kodaira S, Yasutomi M, et al. An individual patient data meta-analysis of adjuvant therapy with uracil-tegafur (UFT) in patients with curatively resected rectal cancer. Br J Cancer. 2007; 96: 1170-7.

4. Dahl O, Fluge Ø, Carlsen E, Wiig JN, Myrvold HE, et al; Norwegian Gastrointestinal Cancer Group. Final results of a randomised phase III study on adjuvant chemotherapy with 5 FU and levamisol in colon and rectum cancer stage II and III by the Norwegian Gastrointestinal Cancer Group. Acta Oncol. 2009; 48: 368-76.

5. Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev. 2012; 3: CD004078.

6. Collette L, Bosset JF, den Dulk M, Nguyen F, Mineur L, et al; European Organisation for Research and Treatment of Cancer Radiation Oncology Group. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. J Clin Oncol. 2007; 25: 4379-86.

7. Zhang X, Hongbing M, Dong Rob, Huaiek D, Fan S. Prospective randomized trial of surgery combined with pre-operative and post-operative radiotherapy for rectal carcinoma.

8. Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. Ann Oncol. 2010; 21: 1743-50.

9. Kim T-W, Lee J-H, Lee J-H, Ahn J-H, Kang Y-K, et al. Randomized trial of postoperative adjuvant therapy in stage II and III rectal cancer to defein the optimal sequence of chemotherapy and radiotherapy: 10-year follow-up. Int J Radiation Oncology Biol Phys. 2011; 81: 1025–31.

10. Kornmann M, Staib L, Wiegel T, Kreuser ED, Kron M, et al. Adjuvant chemoradiotherapy of advanced resectable rectal cancer: results of a randomised trial comparing modulation of 5-fluorouracil with folinic acid or with interferon-α. Br J Cancer. 2010; 103: 1163-72.

11. Hata F, Sasaki K, Hirata K, Yamamitsu S, Shirasaka T. Efficacy of a continuous venous infusion of fluorouracil and daily divided dose cisplatin as adjuvant therapy in

resectable colorectal cancer: a prospective randomized trial. Surg Today. 2008; 38: 623-32.

12. Kalofonos HP, Bamias A, Koutras A, Papakostas P, Basdanis G, et al; Hellenic Cooperative Oncology Group Study. A randomised phase III trial of adjuvant radio-chemotherapy comparing Irinotecan, 5FU and Leucovorin to 5FU and Leucovorin in patients with rectal cancer: a Hellenic Cooperative Oncology Group Study. Eur J Cancer. 2008; 44: 1693-700.

13. Koda K, Miyauchi H, Ochiai T, Yasuda H, Kaiho T, et al. Randomized, controlled trial comparing UFT with S-1 as adjuvant therapy for curatively resected stage III colorectal cancer. Journal of Clinical Oncology. Conference: 2011 Gastrointestinal Cancers Symposium San Francisco, CA, United States. 29 (4 SUPPL. 1), 2011.

14. Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol. 2012; 13: 579-88.

15. Birgisson H, Påhlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation therapy for rectal cancer - a systematic overview. Acta Oncol. 2007; 46: 504-16.

Search Strategy[*] – EMBASE / Medline

MEDLINE: 2007 to May week 3 2012 | EMBASE: 1996 to week 21 2012 | ASCO Meetings: 2010-2012, GI 2010-2012

1 exp clinical trials/
2 random allocation/
3 double-blind method/ or double blind procedure/
4 single blind method/ or single blind procedure/
5 triple blind procedure/
6 placebo:.tw.
7 random:.tw.
8 phase III.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dc, kw, nm, ps, rs, a, ui]
9 or/1-8
10 postop:.tw.
11 adjuv:.tw.
12 or/10-11
13 rectal neoplasms/rt, su, th or exp rectum cancer/
14 colorectal neoplasms/rt, su, th or colorectal cancer/
15 or/13-14
16 limit 9 to humans
17 16 and 12
18 15 and 17
19 remove duplicates from 18
20 limit 19 to english language
21 20 and (2007: or 2008: or 2009: or 2010: or 2010: or 2011: or 2012:).ew.
22 20 and (2007: or 2008: or 2009: or 2010: or 2010: or 2011: or 2012:).ed.
23 21 or 22

[*] Free-text combinations were used for Cochrane Central and ASCO abstracts: (Postoperative OR adjuv*) AND (rectal OR colorectal) AND cancer

Appendix 9: Rectal Cancer Treatment Standards Working Group Members

Individual	Title
Paul Johnson	Co-Chair, Colorectal Cancer Surgeon, Capital District Health Authority
Don Clark	Co-Chair, General Surgeon, Annapolis Valley District Health Authority
Larry Broadfield	Manager Systemic Therapy (Pharmacist), Cancer Care Nova Scotia
Robinette Butt	Radiologist, Capital District Health Authority
Sandra Cook	Manager Navigation and Surgical Oncology Network, Cancer Care Nova Scotia (to May 2013)
Slawa Cwajna	Radiation Oncologist, Capital District Health Authority (September 2012-present)
Donna Grant	Nurse Practitioner, Capital District Health Authority
Colin Harris	Radiologist, Annapolis Valley District Health Authority
Heather Johnson	Family Physician Representative, Bridgewater, NS
Robin McGee	Rectal Cancer Survivor
Chris Murphy	General Surgeon, Southwest District Health Authority
Maureen Nolan	Radiation Oncologist, Capital District Health Authority (January-September 2012)
Jill Petrella	Project Lead Manager, Quality and Cancer Site Teams, Cancer Care Nova Scotia
Heidi Sapp	Pathologist, Capital District Health Authority
Robert Sers	General Surgeon, GASHA
Phil Smith	General Surgeon, Cape Breton District Health Authority
Stephanie Snow	Medical Oncologist, Capital District Health Authority
Todd Stoddart	General Surgeon, South Shore District Health Authority
Cuneyt Tatlidil	Pathologist, Annapolis Valley District Health Authority Southwest District Health Authority
Lara Williams	Colorectal Cancer Surgeon, Capital District Health Authority (to July 2015)

Appendix 10: Clinical Standards Oversight Committee Members

Role	Name	District
Council of Vice Presidents Medicine	Jeremy Hillyard	GASHA
Council of Vice Presidents Patient Care	Mary Lou O'Neill Janet Simm (to February 2014)	CBDHA SSH
Council of CEOs	John Malcom (to May 2012)	CBDHA
. Quality, Safety and Wait Times Improvement	MJ MacDonald (to January 2014) Suzanne Rhodenizer-Rose (January 2014 to present)	Department of Health and Wellness (DHW)
CCNS Board member	Archie MacEachern (to Sept 2013)	CBDHA
	Mary Lou O'Neill	CBDHA
Clinical Head, Capital Health Cancer Care Program	Drew Bethune	CDHA
Clinical Head Cape Breton Cancer Centre	William Harless	CBDHA
Chief, Division of Medical Oncology, CDHA	Mark Dorreen	CDHA
Chief, Department of Radiation Oncology, CH	Tetteh Ago (to Feb 2013) Slawa Cwajna	CDHA

	(February 2013 to present)	
Nova Scotia Surgical Care Council	Anne Yuill (to February 2013)	DHW
Perioperative Advisory Committee	Nancy MacLeod (February 2013 to present)	Department of Health and Wellness
DHA Quality Manager	Margie Jenkins (to January 2014)	AVH
	Catherine Gaulton (March 2014 to present)	CDHA
Family Physicians (Doctors Nova Scotia)	Andrew Wawer (Sept 2011-Nov 2013)	CBDHA
	John Paleta (April 2014-Present)	CDHA
Representative of Survivor(s)/Lay people	Archie MacEachern (from September 2013)	CBDHA
	Robin McGee	AVH
	Kathleen Trott	CH
CCNS Chief Medical Director	Carman Giacomantonio (to June 2014)	CCNS
CCNS Chief Operating Officer	Theresa Marie Underhill (to Sept 2012) Chris Collier (Sept 2012 to March 2016)	CCNS