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PRACTICE GUIDELINE

Eastern Canadian Colorectal Cancer Consensus Conference: standards of care for the treatment of patients with rectal, pancreatic, and gastrointestinal stromal tumours and pancreatic neuroendocrine tumours

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ABSTRACT

The annual Eastern Canadian Colorectal Cancer Consensus Conference was held in Halifax, Nova Scotia, October 20–22, 2011. Health care professionals involved in the care of patients with colorectal cancer participated in presentation and discussion sessions for the purposes of developing the recommendations presented here. This consensus statement addresses current issues in the management of rectal cancer, including pathology reporting, neoadjuvant systemic and radiation therapy, surgical techniques, and palliative care of rectal cancer patients. Other topics discussed include multidisciplinary cancer conferences, treatment of gastrointestinal stromal tumours and pancreatic neuroendocrine tumours, the use of FOLFIRINOX in pancreatic cancer, and treatment of stage II colon cancer.

KEY WORDS

Consensus guideline, palliative care, rectal cancer, gastrointestinal stromal tumours, pancreatic neuroendocrine tumours, FOLFIRINOX, MCCS

1. INTRODUCTION

The Eastern Canadian Colorectal Cancer Consensus Conference was held in Halifax, Nova Scotia, October 20–22, 2011. The conference is held annually, and some of the terms of reference and opening statements are adapted from a previous publication[1].

As in previous years, the resulting report, presented here, is a consensus opinion produced by oncologists and allied health professionals invited from across Eastern Canada for the purpose of recommending management strategies for patients with colorectal cancer (CRC) and other selected gastrointestinal cancers.

1.1 Terms of Reference

The participants in the 2011 Eastern Canadian Colorectal Cancer Consensus Conference consisted of oncology professionals from across Ontario, Quebec, and the Atlantic provinces. Several invited participants from Western Canada also attended.

The target audience for this report is primarily health care professionals involved in the care of patients with CRC and other selected gastrointestinal cancers. The report provides information about standards of care to administrators responsible for program funding decisions and to key players in the implementation of best practices. While not specifically targeted to patients, the report also provides information that may be useful in guiding patients who must make decisions about their own care.

1.2 Basis of Recommendations

The recommendations provided here are based on presentation and discussion of the best available evidence. Where applicable, references are cited.

These levels of evidence were used in the conference presentations[2]:

- Level I: Evidence from randomized controlled trials
- Level II-1: Evidence from controlled trials without randomization

- Level II-2: Evidence from analytic cohort or case–control studies, preferably from more than one centre or research group
- Level II-3: Evidence from comparisons between times or places with and without the intervention (dramatic results in uncontrolled experiments could be included here)
- Level III-3: Opinions of respected authorities, based on clinical experience; descriptive

2. OPENING STATEMENTS

2.1 Application of Recommendations

The consensus statements apply to broad populations of patients and may therefore not apply to the unique circumstances of an individual patient. Individual decisions for care are always made within a doctor–patient relationship.

2.2 Clinical Trials

Where possible, patients should be encouraged to participate in clinical trials.

3. STANDARDS OF STAGING IN RECTAL CANCER

Question: What is the appropriate imaging modality for the staging of rectal cancer?

- The standard of care for the treatment of T3 or 4 or N1 rectal cancer includes neoadjuvant chemoradiation.
- Magnetic resonance imaging (MRI) is the preferred preoperative imaging test for the regional staging of T3 or 4 rectal cancer (level III)[3].
- Endoscopic rectal ultrasonography can complement MRI for the local staging of rectal cancer. It can potentially provide additional information in the case of T1 and 2 tumours[4,5].
- Computed tomography imaging should not routinely be used for the local staging of rectal cancer (level III). However, it is useful for the detection and staging of distant metastatic disease (level III)[3].

Question: What is required for MRI to be adequate for the staging of rectal cancer?

- If an MRI scanner is to be used for the staging of rectal cancer, it must meet certain minimal quality criteria (level III)[6]:
  - It must produce high-resolution phased-array T2 images.
  - It must operate at 1.5 T at a minimum.
  - It has to provide prognostic features of the tumour and assist in surgical and radiation treatment planning (level III).
- Imaging by MRI is more accurate in delineating tumour involvement of the mesorectal fascia (level I).
- Imaging by MRI and positron-emission tomography–computed tomography may be useful for evaluating local recurrence.

Question: What information should be included in the MRI report for a rectal cancer?

- The following information should be included in the MRI report after imaging of a rectal cancer[7]:
  - Location of tumour
  - Extramural spread
  - Extramural vascular invasion
  - Distance from mesorectal fascia
  - Lymph node status (including distance from mesorectal fascia, spiculation, indistinct margin)
  - Presence and location of metastases

4. STANDARDS IN SURGICAL CARE OF RECTAL CANCER

Question: What is the optimal surgery for rectal cancer?

- For mid- or distal rectal cancers, total mesorectal excision (TME) should be the standard of care because it has been shown to improve local recurrence rates (level I)[8–10].
  - Aim for a 2-cm resection margin in the setting of non-neoadjuvant chemoradiotherapy (CRT).
  - In the presence of long-course neoadjuvant treatment, the ideal margin is controversial and may require as little as less than 1 cm.
  - An adequate lymph node dissection is required. Although controversial, a 12-node benchmark has been widely adopted.

Question: What details should be documented in a TME surgical report?

- The following items should be documented in the surgical report[8]:
  - Documentation of the TME
  - Location of tumour
  - Extent of resection
  - Lymph node dissection
  - Resection margins
- The use of synoptic operative reports is endorsed.

Question: Is laparoscopic surgery equal to open surgery in rectal cancer?

- The role of laparoscopic resection in rectal cancer remains controversial. Evidence is evolving, and more data are needed before a firm recommendation can be made[11].

5. RECTAL CANCER PATHOLOGY

Question: What is the optimal method for reporting pathology in rectal cancer?

- Standardized reporting forms are recommended for use in reporting rectal cancer pathology (level III).
- The following items should be documented in the pathology report for rectal cancer (level III):
  - Procedure type
  - Completeness of TME specimen (Quirke grade 3, 2, or 1)
  - Histologic type and grade of tumour
  - Size of tumour
  - Extent of invasion (pT)
  - Tumour response grade after neoadjuvant treatment [tumour regression grading (TRG)]
  - Lymph nodes (pN)
  - Margins: proximal, distal, and circumferential (CRM)
  - Lymphatic, vascular, and perineural invasion
  - Polyps or other findings
- The use of synoptic reports is preferred.

Question: What is the standardized grading system for completeness of a TME?

- The recommended method to assess the TME specimen is the Quirke system (level I)[12]:
  - Quirke grade 3: Good plane of surgery achieved
  - Quirke grade 2: Moderate plane of surgery achieved
  - Quirke grade 1: Poor plane of surgery achieved
- This grading is independent of neoadjuvant treatment.

Question: What is considered a positive CRM in a TME?

- The status of the CRM is the most important factor in predicting local recurrence, especially after neoadjuvant treatment (level I)[13].
- There are various levels of CRM involvement (level I):
  - Direct tumour spread (<1–2 mm from CRM)
  - Discontinuous tumour spread (<1–2 mm from CRM)
  - Lymph node metastases (<1–2 mm from CRM)
  - Venous invasion
  - Lymphatic invasion
  - Perineural spread

Question: What should be included in the standard gross TME specimen?

- Mandatory sections should include
  - 3–5 sections of the tumour, including the CRM;
  - proximal and distal margins; and
  - all lymph nodes (minimum of 12 in neoadjuvant-naïve patients; fewer than 12 might be provided in the post-neoadjuvant setting).

Question: Which grading system should be used to assess response to neoadjuvant treatment?

- Tumour regression grading is a measurement of tumour response after neoadjuvant therapy in a rectal cancer patient[14].
- The TRG should be included in the standardized pathology report (level III):
  - TRG1: Pathologic complete response or almost complete response
  - TRG2: Moderate response
  - TRG3: Little or no response

6. STANDARDS OF RADIATION THERAPY IN RECTAL CANCER

Question: Who should be considered for external-beam radiation treatment (EBRT) for rectal cancer?

- In the treatment of rectal cancer, EBRT is the standard of care (level I)[15].
- In rectal cancer patients, EBRT should be considered for
  - stage I patients who are not candidates for surgery (level III),
  - stage II/III rectal cancer patients (level I), and
  - stage IV patients if palliation or local control is indicated (level II/III).

Question: What is the best way to administer EBRT in rectal cancer?

- The statements that follow assume that a complete TME is the surgical standard.
- Preoperative radiation treatment is considered a standard of care.
- Standards of care for radiation treatment of rectal cancer treatment include these approaches[15]:
  - Long-course preoperative EBRT (45–50.4 Gy or 25–28 Gy) given concurrently with fluoropyrimidine chemotherapy (level I).
  - Short-course preoperative EBRT (25 Gy in 5 fractions) (level I).
  - In patients who are receiving surgery up front and who have a stage II/III tumour, adjuvant treatment with EBRT and 5-flourouacil (5FU)–based chemotherapy should be considered.
  - There is a role for brachytherapy in the treatment of rectal cancer in select situations (level III).
  - When used for rectal cancer treatment, brachytherapy can be delivered interstitially or endoluminally.

7. OPTIMAL NEOADJUVANT THERAPY IN RECTAL CANCER

Question: What are the optimal treatment options for neoadjuvant therapy in rectal cancer?

- The recommendations that follow apply to the neoadjuvant treatment of rectal cancer and are not applicable to adjuvant treatment.
- Fluoropyrimidine (5FU)–based CRT before surgery is recognized as a standard of care for a T3/T4 rectal tumour.
- Advantages of neoadjuvant CRT include
  - downstaging of rectal tumours (level I),
  - reduction in the risk of local recurrence (level I), and
  - improvement in tolerance to systemic therapy (level I).

Question: Can capecitabine replace infusional 5FU in the neoadjuvant treatment of rectal cancer?

- We endorse the alternative use of capecitabine in neoadjuvant concurrent CRT for rectal cancer (level I).
- A large randomized controlled trial[16] showed that, compared with infusional 5FU, capecitabine (given either 5 or 7 days per week) was noninferior with respect to these outcomes:
  - Pathologic complete response
  - Sphincter sparing
  - Quality of life
  - Toxicity
- It should be noted that overall survival (OS) and progression-free survival (PFS) have not yet been reported.

Question: Should oxaliplatin be added to 5FU CRT in the neoadjuvant treatment of rectal cancer?

- Given the current level of evidence, we do not endorse the addition of oxaliplatin.
- Oxaliplatin added to 5FU in the neoadjuvant setting showed no improvement in pathologic complete response or downstaging of rectal cancer (level I).
- In a randomized controlled trial[17], toxicity was greater in the patients who received oxaliplatin in the neoadjuvant setting.
- Overall survival and recurrence rate outcomes have yet to be reported.

8. OPTIMAL PALLIATIVE CARE IN RECURRENT RECTAL CANCER

Question: What is the definition of palliative care?

- The World Health Organization offers the following definition for palliative care:

  > Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Question: What is the role of palliative care in advanced rectal cancer?

- There is a need to recognize that rectal cancer patients can require a long course of palliative care (level III).
- Some of the goals of palliative care in advanced rectal cancer include
  - helping to clarify the goals of care in complex cancer patients.
  - providing pain management, including visceral, neurologic, post-pubic-radiation, and surgical pain.
  - assisting with wound problems.
  - assisting with supportive care for psychosocial distress.
  - providing a liaison between medical oncology, radiation oncology, surgery, and other health professionals.

Question: What is the optimal timing for referral to palliative care?

- In a recent randomized controlled trial[18] that compared early palliative care intervention with best supportive care in metastatic lung cancer patients, OS and quality of life were observed to be improved (level I).
- Early palliative care referral should be considered for rectal cancer patients who have significant symptoms at any stage of their disease (level III).

Question: What should be the first-line treatment for rectal pain from rectal cancer or its complications?

- Expert consensus suggests that morphine should be used in the first-line setting for moderate-to-severe cancer pain (level IV); however, other opioids can be considered.
- In cases of neuropathic pain, a tricyclic antidepressant or an anticonvulsant can be considered. Those medications may have a faster onset, but data to support their use are lacking (level III).
- Methadone should be considered in cases of renal impairment, if the patient is experiencing refractory pain, or if there is an intolerance or allergy to other opioids.
- The following factors should be taken into account when using methadone[19]:

- Methadone must be used with caution because it can cause QT prolongation and interact with multiple drugs.
- Methadone use requires the involvement of health care providers trained in its use and of a multidisciplinary team to properly monitor the patient.
- There is no strong evidence to support the use of methadone over other opioids.

Question: What regional pain control techniques should be considered for complex rectal pain?

- The following pain control procedures should be considered if life expectancy exceeds a few weeks (level IV)[20]:
  - Superior hypogastric plexus block for rectal pain
  - Epidural
  - Spinal analgesia

Question: What is the optimal strategy for palliation of terminal bowel obstruction?

- The first step in managing patients with terminal bowel obstruction is proper imaging and a determination about whether a palliative surgical procedure is appropriate[21].
- A small 20-patient study showed that patients who underwent surgery experienced better overall survival (level III)[22].
- Medical management of malignant bowel obstruction is based on level III and IV evidence. The following strategies should be considered:
  - Initiation of intravenous fluids.
  - Evidence supporting total parenteral nutrition is lacking; we recommend against its standard use.
  - Data concerning the use of steroids is conflicting; however, these agents may help with symptom relief (level III).
  - If the obstruction remains unresolved after 3 days, the addition of octreotide can be considered.

Questions: Should stents be used use in the treatment of large bowel obstructions for nonsurgical patients?

- Studies assessing the topic of stents had small sample sizes (level III) and were limited by bias.
- Specialized technical expertise is needed to effectively and safely carry out this strategy[23].

9. MULTIDISCIPLINARY CANCER CONFERENCES IN CANCER CARE

Question: What is multidisciplinary cancer care?

- Cancer Care Ontario defines multidisciplinary cancer conferences (MCCS) as follows:

  > [A] regularly scheduled meeting where representatives from surgery, medical oncology, radiation oncology, nursing, pathology, and diagnostic imaging discuss all appropriate diagnostic tests and suitable treatment options for an individual cancer patient[24].

- Another way to deliver integrated cancer care is the multidisciplinary oncology clinic, where health professionals from various disciplines meet the patient and determine a care plan together.

Question: Are there advantages to MCCS?

- Although no randomized controlled studies into the benefits of MCCS have been conducted, potential advantages highlighted in the literature include these[25]:
  - They improve quality of care and cancer outcomes (level II/III).
  - They improve communication between colleagues.
  - They allow for the continuing education of physician participants.

Question: Are there standards that should be in place for the conduct of MCCS[24,25]?

- There are standard criteria that have to be met for a meeting to be considered an MCC. Those criteria include ensuring that
  - all appropriate diagnostic tests and treatment options are discussed for each patient.
  - meetings occur at regularly scheduled intervals (a minimum of every 2 weeks for at least an hour is suggested).
  - appropriate recognition (remuneration and endorsement) is given for the time and expertise provided by participants.
  - space and audiovisual equipment are designated for the meetings.
  - a coordinator and chair are designated for the meetings.
  - the coordinator and chair receive administrative support.
  - questions for review by the radiologists and pathologists are defined in advance.
  - key radiologists and pathologists are appointed to attend.

10. PROGNOSTIC AND PREDICTIVE TOOLS FOR ADJUVANT THERAPY DECISION-MAKING IN STAGE II COLON CANCER

Question: What is the role of adjuvant chemotherapy in stage II CRC?

- Level I evidence has shown a 3% survival benefit for 5FU chemotherapy administered in stage II CRC.

However, consensus statements indicate that treating all stage II colon cancer cases leads to overtreatment of a significant number of patients[26].

- Historical prognostic factors used to determine increased risk of recurrence in patients with stage II CRC include these[27]:
  - Inadequate staging
  - Clinical or pathologic features (level II):
    - T4 lesions
    - Obstruction or perforation
    - Inadequate lymph node sampling (<12 nodes)
  - Lymphovascular invasion and tumour differentiation are poorly validated as features prognostic for risk and should not be used.
  - Additional prognostic and predictive factors are needed.

Question: Does microsatellite instability (MSI) play a role in the choice of treatment administered to patients with stage II CRC?

- Testing for MSI should be available for patients with resected stage II CRC in which knowledge of MSI will influence a treatment decision or approach. Immunohistochemistry is an acceptable method to test for this mutation[28].
- High MSI (MSI-H) is a good prognostic marker in stage II CRC.
- The use of 5FU monotherapy should be avoided in patients with resected stage II CRC with MSI-H, because this treatment is not as effective in this subtype of patients (level II)[29].
- If a patient's tumour is classified as clinically high-risk stage II and MSI-H, an oxaliplatin-based treatment regimen can be considered (level III). However, the OS benefit of adjuvant chemotherapy in stage II colon cancer is modest. The decision to treat should be made after an appropriate discussion between the patient and the physician[29,30].

Question: What is the role of loss of heterozygosity 18q in selecting treatment for adjuvant stage II CRC?

- We do not endorse use of loss of heterozygosity 18q as a prognostic or predictive marker in stage II CRC.
- Loss of heterozygosity 18q has been shown to be prognostic in stage III CRC, but evidence for its use in stage II CRC is lacking[31,32].

Question: What is the role of *KRAS* or *BRAF* for prognostication in stage II CRC?

- Because of lack of evidence, we do not endorse the use of *KRAS* as a prognostic factor in the setting of stage II CRC.
- *BRAF* may be prognostic; however, the data have been confounded by MSI status (level II)[33–35].

Question: What is the role of gene expression profiling in stage II CRC?

- Multiple gene expression signatures are currently in development for CRC. Currently, Oncotype DX Colon (Genomic Health, Redwood City, CA, U.S.A.) and ColoPrint (Agendia, Amsterdam, Netherlands) are the most advanced in terms of clinical validation. These tools may help in the decision-making process for treating stage II CRC[36].
- Two large retrospective validation studies in stage II CRC patients showed good correlation of Oncotype DX score with risk of recurrence (level I/II)[37]. In cases where the tumour is MSI-H, the Oncotype DX test should not be used. Evidence suggests that Oncotype DX may work best in T3, N0, microsatellite-stable patients[38,39].
- ColoPrint has been validated in a smaller study in stage II CRC patients and performs well for recurrence risk (level II)[40]. That finding is being tested in a prospective study.
- Oncotype DX treatment score is not predictive.
- Given the current level of evidence, we do not recommend routine use of gene expression profiling in the clinical setting.

11. NEW DEVELOPMENTS IN THE TREATMENT OF GASTROINTESTINAL STROMAL TUMOURS

Question: What factors should be used in selecting patients with gastrointestinal stromal tumour (GIST) for treatment with imatinib in the adjuvant setting?

- According to the modified consensus criteria, high risk of recurrence in patients with GIST includes[41]
  - tumour diameter exceeding 10 cm, *or*
  - tumour mitosis count exceeding 10 in 50 high-power microscopy fields, *or*
  - size exceeding 5 cm and mitosis count exceeding 5 in 50 high-power microscopy fields, *or*
  - tumour rupture occurring spontaneously or at surgery.

Question: What is the role of imatinib as adjuvant therapy for high-risk patients with resected GIST?

- Imatinib has been shown to improve recurrence-free survival.
- It is not certain whether imatinib given in this setting delays or actually prevents recurrence.
- An OS benefit has been documented in high-risk patients (level I)[42].
- For non-high-risk patients, a discussion about whether to undertake adjuvant treatment with imatinib should take place with the physician.

Question: What is the recommended duration of treatment with imatinib in the adjuvant setting?

- Because of documented improvements in recurrence-free survival and OS in patients with a high risk of recurrence, 3 years is preferred compared with 1 year[43].

Question: What is the role of imatinib therapy for patients with advanced (metastatic or localized unresectable) GIST?

- Imatinib is recommended as first-line treatment for advanced GIST, in which it has a high level of activity (level I)[44].

Question: What is the recommended imatinib dose in advanced GIST?

- An oral dose of 400 mg daily is recommended.
- If patients progress on 400 mg, dose escalation to 600–800 mg imatinib daily may be considered[44,45].
- A patient with an exon 9 *KIT* mutation may benefit from a starting dose of 800 mg daily. In this situation, a higher dose has been shown to increase PFS, but not OS[46–49].

Question: What is the recommended length of treatment with imatinib in metastatic GIST?

- A daily regimen with imatinib is recommended (level I).
- Discontinuation of imatinib is not recommended if the patient is tolerating the treatment well.

Question: What treatment options are available in imatinib-resistant or -intolerant GIST?

- Sunitinib is recommended for imatinib-resistant or -intolerant advanced GIST (level I)[50,51].
- There is no standard third-line treatment.

12. NEW DEVELOPMENTS IN THE TREATMENT OF PANCREATIC NEUROENDOCRINE TUMOURS

Question: What is the optimal first-line systemic treatment for patients with advanced nonsurgical pancreatic neuroendocrine tumours (PNETS)?

- For advanced progressive low- or intermediate-grade PNETS, an improved PFS was demonstrated for everolimus and sunitinib compared with placebo (level I). Functional and nonfunctional PNETS were both included in the clinical trials[52,53].
  - Based on the current level of evidence, we cannot endorse one drug over the other.
- It may be reasonable to consider somatostatin analogues; however, no randomized controlled trials have been conducted, especially for PNETS (level II).
- For low- and intermediate-grade poorly differentiated PNETS, chemotherapy is an option as first-line treatment. Potential options include
  - streptozocin plus 5FU (level II)[54], and
  - capecitabine plus temozolomide (level II)[55].
- For high-grade, poorly differentiated PNETS, chemotherapy with cisplatin–etoposide would be the preferred first-line treatment (level II)[56].

13. THE ROLE OF FOLFIRINOX IN THE TREATMENT OF PANCREATIC CANCER

Question: What is the role of FOLFIRINOX is the treatment of metastatic pancreatic cancer?

- FOLFIRINOX (leucovorin, 5FU, irinotecan, oxaliplatin) is the preferred chemotherapy regimen in patients with metastatic pancreatic cancer who have a good performance status (Eastern Cooperative Oncology Group 0–1) and a bilirubin value less than 1.5 times the upper limit of normal (level I)[57].
- Compared with gemcitabine, FOLFIRINOX has been shown to be associated with improved response rate, PFS, and OS, and improved quality-of-life parameters.
- FOLFIRINOX is associated with increased toxicity and should therefore be used in the context of the eligibility criteria of the clinical trial. Those criteria include[57]
  - Eastern Cooperative Oncology Group performance status 0 or 1,
  - bilirubin less than 1.5 times the upper limit of normal,
  - adequate bone marrow function, and
  - age less than 76 years.
- Granulocyte colony–stimulating factor should be available for secondary prophylaxis in dose-limiting or complicated neutropenia during FOLFIRINOX treatment (level III).

14. CONFLICT OF INTEREST DISCLOSURES

The authors have no affiliations that might represent a conflict of interest or that might directly or indirectly influence the content of this article.

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