Eastern Canadian Colorectal Cancer Consensus Conference: application of new modalities of staging and treatment of gastrointestinal cancers

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ABSTRACT

The annual Eastern Canadian Colorectal Cancer Consensus Conference was held in Ottawa, Ontario, October 22–23, 2010. Health care professionals involved in the care of patients with colorectal cancer participated in presentation and discussion sessions for the purpose of developing the recommendations presented here. This consensus statement addresses current issues in the management of colorectal cancer, such as the use of epidermal growth factor inhibitors in metastatic colon cancer, the benefit of calcium and magnesium with oxaliplatin chemotherapy, the role of microsatellites in treatment decisions for stage II colon cancer, the staging and treatment of rectal cancer, and the management of colorectal and metastatic pancreatic cancers.

KEY WORDS

Consensus guideline, colorectal cancer, rectal cancer, pancreatic cancer, microsatellites, EGFR1

1. INTRODUCTION

The Eastern Canadian Colorectal Cancer Consensus Conference was held in Ottawa, Ontario on October 22–23, 2010. The conference is held annually, and some of the terms of reference and opening statements are taken directly 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 2010 Eastern Canadian Colorectal Cancer Consensus Conference consisted of oncology professionals from across Ontario, Quebec, and the Atlantic provinces. A few invited participants also came from Western Canada.

The target audience for the present report is primarily health care professionals involved in the care of patients with CRC and other selected gastrointestinal cancers. The report is intended to provide 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, this 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 presentations 2:

- i: Evidence from randomized controlled trials
- ii-1: Evidence from controlled trials without randomization
• 11-2: Evidence from cohort or case–control analytic studies, preferably from more than one centre or research group
• 11-3: Evidence from comparisons between times or places with and without the intervention (dramatic results in uncontrolled experiments could be included here)
• 11-3: 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. THE OPTIMAL USE OF EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS IN FIRST-LINE METASTATIC CRC

Question: What is the optimal use for epidermal growth factor receptor (EGFR) inhibitors (EGFRi) in the treatment of metastatic CRC (mCRC)?

- The activity of EGFRi is limited to patients that are found to have a KRAS wild-type (wt) tumour on pathology analysis (level i) 3.
- Monoclonal antibodies (“Moabs”) against EGFR are indicated in the treatment of mCRC in patients with KRAS wt tumours (level i).
- The use of an EGFRi with chemotherapy is a reasonable option in the treatment of patients with KRAS wt tumours (level i).
- The EGFRi do not have activity in patients with KRAS mutant tumours and thus should not be used in that patient population (level i).
- KRAS testing should be available at mCRC diagnosis if use of an EGFRi is being considered (level i).
- An EGFRi is not indicated in the adjuvant treatment of resected CRC (level i).
- Rash is a known side effect of EGFRi. The degree of severity of the rash has been found to directly correlate with tumour response to these agents and with survival (level ii).
- Appropriate treatment of EGFRi skin rash is recommended (level iii) 4.
- In the metastatic setting:
  • Compared with FOLFIRI alone, the addition of cetuximab to FOLFIRI improved progression-free survival, relapse rate, and overall survival in patients with KRAS wt tumours 5,6 (level i).
  • The biologic agent (bevacizumab, cetuximab, or panitumumab) that is superior in combination with systemic therapy is unknown; more study in this area is required (level iii).

4. THE USE OF CALCIUM AND MAGNESIUM WITH OXALIPLATIN CHEMOTHERAPY

Question: Should Ca and Mg (Ca/Mg) be given concomitantly with oxaliplatin chemotherapy?

- Oxaliplatin chemotherapy is associated with both acute and chronic neuropathy (level i) 7–10.
- Neuropathy that develops during therapy leads both to reduced dose intensity and to early discontinuation of therapy with oxaliplatin-containing regimens (level i) 11–13.
- When given with oxaliplatin-containing regimens, Ca/Mg reduces neurotoxicity (level ii) 14,15.
- Given the uncertainty about whether Ca/Mg reduces the efficacy of oxaliplatin in the adjuvant setting, the evidence is insufficient to recommend the routine use of Ca/Mg to prevent or reduce neurotoxicity associated with oxaliplatin-containing chemotherapy (level iii).
- More study is required before firm recommendations can be made about the use of Ca/Mg. Studies examining strategies to reduce oxaliplatin neuropathy are encouraged [for example, CRC6, neuroprotectants (glutamate oxidase), and biomarkers].

5. MICROSATELLITES AND TREATMENT DECISIONS IN STAGE II COLON CANCER

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

- All patients with stage ii colon cancer should be referred to medical oncology for an opinion regarding adjuvant systemic therapy.
- Microsatellite instability high (MSI-H) phenotypes of CRC arise from the epigenetic silencing of the mismatch repair genes (d-MMR) or from germline deficiencies (Lynch syndrome). These tumour phenotypes occur in 20%–25% of stage ii CRC.
- Testing for MSI should be available in patients with resected high-risk stage ii CRC. Immunohistochemistry is an acceptable method to test for this mutation.
- MSI-H is a good prognostic marker in stage ii CRC16–19.
- Fluoropyrimidine monotherapy should be avoided in patients with resected stage ii CRC with MSI-H, because fluoropyrimidine treatment is not as effective in patients of that disease subtype (level ii) 16,17.
• If a patient’s tumour is classified as being clinically high-risk stage II and MSI-H, an oxaliplatin-based treatment regimen can be considered (level III) [16]. However, the overall survival 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.

• Consider genetics referral for patients less than 60 years of age with MSI-H.

6. RECTAL CANCER

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

• The standard of care for the treatment of T3, T4, or N1 rectal cancer includes neoadjuvant chemoradiation.

• Magnetic resonance imaging (MRI) is the preferred preoperative imaging test for regional staging of T3 and T4 rectal cancer (level III).

• Endoscopic rectal ultrasonography can be considered complementary to MRI for local staging of rectal cancer.

• Computed tomography (CT) imaging should not routinely be used for local staging of rectal cancer (level III). Imaging by CT is, however, useful for the detection and staging of distant metastases (level III).

Question: What are the requirements for MRI to be adequate for the staging of rectal cancer?

• For an MRI scanner to be used for the staging of rectal cancer, it must meet these minimal quality criteria (level III):
  • It must produce high-resolution oblique T2 images.
  • It must be a 1.5T or 3T scanner.
  • It must have a torso phase array with multi-channel coil.
  • The information gained from MRI will provide prognostic features of the tumour and assist in surgical and radiation treatment planning (level III).

• Compared with tumour T stage, MRI is more accurate in predicting resection margin status (level I).

• When MRI is used for the staging of rectal cancer, the jurisdiction should implement synoptic reporting, and the synoptic reporting should include these data:
  • Tumour localization
  • Extramural spread
  • Extramural vascular invasion
  • Circumferential radial margin
  • Lymph node status (including spiculated or indistinct margin)
  • Presence and location of metastases

Question: What is the role of brachytherapy in the treatment of rectal cancer?

• External-beam radiotherapy is the standard of care in the treatment of rectal cancer (level I).

• Options for external-beam radiotherapy (level I) include either of:
  • short-course treatment (25 Gy in 5 fractions)
  • long-course treatment (45 Gy plus 5.4–9 Gy in 28–30 fractions)

• When used for the treatment of rectal cancer, brachytherapy can be delivered interstitially or endoluminally.

7. COLORECTAL CANCER

Question: What is the optimal adjuvant treatment for patients with resected stage II colon cancer?

• Patients with resected stage II and stage III colon cancer should be evaluated by a medical oncologist within 4–6 weeks of surgery to determine whether they are candidates for adjuvant chemotherapy (level III).

• For resected stage II disease, the highest risk factors for recurrence include (level II) [20]
  • T4 disease.
  • fewer than 12 lymph nodes sampled at time of surgery.

• Adjuvant chemotherapy is indicated in patients with high-risk resected stage II colon cancer.

• Appropriate regimens for the adjuvant treatment of high-risk stage II colon cancer include capecitabine and FOLFOX.

The de Gramont schedule of continuous venous infusion is favored over bolus treatments such as Mayo or Roswell Park because of the relative excess toxicity associated with bolus regimens (level III).

Question: What is the optimal adjuvant treatment for patients with resected stage III colon cancer?

• FOLFOX and XELOX chemotherapy improve disease-free survival in patients with resected stage III colon cancer (level I).

• FOLFOX chemotherapy improves disease-free survival and overall survival in stage III colon cancer (level I).

• In the elderly, FOLFOX should be reserved for patients with a good performance status.

• Capecitabine improves disease-free survival and overall survival when given as adjuvant treatment for stage III colon cancer.
• Capecitabine is preferred over 5-fluorouracil–leucovorin when monotherapy is used (level i).

**Question:** Which therapies are *not* indicated in the adjuvant treatment of stage ii and iii colon cancer?

• The addition of bevacizumab or cetuximab to chemotherapy has failed to provide benefit in the adjuvant setting (level i).
• Irinotecan-containing regimens are not indicated in the adjuvant setting (level i).

**Question:** What lifestyle recommendations should be made to colon cancer survivors?

• Survivors of colon cancer should be advised to engage in regular exercise, to follow the Canada Food Guide, to stop smoking, and to limit alcohol to moderate consumption (level iii)
• Patients with mCRC should be evaluated in a multidisciplinary fashion, including review of the patient’s case by medical oncology, radiation oncology, surgical oncology, and hepatobiliary (HPB) surgery, if needed.
• Perioperative or pseudo-adjuvant therapy should be considered in patients with resectable disease.
• Of non-resectable patients, 10%–20% can be converted to resectability with neoadjuvant treatment (level iii).
• Hepatobiliary surgery should be performed only in a large-volume center (level ii).
• The optimal treatment of patients with mCRC requires more study.

8. METASTATIC Pancreatic CANCER

**Question:** What is the recommended first-line systemic therapy for metastatic pancreatic cancer?

• Gemcitabine is one of the standard chemotherapies for the first-line treatment of metastatic pancreatic cancer (level i).
• Other first-line options include gemcitabine and erlotinib (level i), gemcitabine and capecitabine (level ii).

**Question:** What are the options for second-line therapy for metastatic pancreatic cancer?

• In patients who progress on gemcitabine and have a good performance status, oxaliplatin-containing regimens are appropriate second-line therapies (level i).
• Capecitabine, irinotecan, 5-fluorouracil–leucovorin, taxanes, gemcitabine, erlotinib, mitomycin–cisplatin are also appropriate second-line therapies in patients with a good performance status, if they have not previously been exposed to those agents (level iii).

9. CONFLICT OF INTEREST DISCLOSURES

The author has no financial conflicts of interest to declare.

10. REFERENCES

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*a* Petrelli NJ. Plenary program discussion. Presented at the 43rd Annual Meeting of the American Society of Clinical Oncology; Chicago, IL; June 4, 2007.


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