Eastern Canadian Colorectal Cancer Consensus Conference: setting the limits of resectable disease

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ABSTRACT

The annual Eastern Canadian Colorectal Cancer Consensus Conference was held in Montreal, Quebec, October 22–24, 2009. 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 colorectal cancer, such as the management of hepatic and pulmonary metastases, the role of monoclonal antibodies to the epidermal growth factor receptor, and the benefits and safety of chemotherapy in elderly patients. The management of gastrointestinal neuroendocrine tumours and gastric cancer are also discussed.

KEY WORDS

Consensus guideline, colorectal cancer, gastrointestinal neuroendocrine tumour, gastric cancer

1. INTRODUCTION

The Eastern Canadian Colorectal Cancer Consensus Conference was held in Montreal, Quebec, October 22–24, 2009. The 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 selected gastrointestinal cancers.

1.1 Terms of Reference

The participants were oncology professionals from across Ontario, Quebec, and the Atlantic provinces invited to attend the consensus meeting.

The target audience for this report is primarily health professionals involved in the care of patients with CRC and selected gastrointestinal cancers.

This report is intended to provide information about the standard of care to administrators responsible for program and funding decisions—key players in the implementation of best practice.

While not specifically targeted to patients, this report also provides information that may be useful to patients in guiding their decisions regarding care.

1.2 Basis of Recommendations

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

These were the levels of evidence used in the presentations [1]:

I Evidence from randomized controlled trials
II-1 Evidence from controlled trials without randomization
II-2 Evidence from cohort or case–control analytic studies, preferably from more than one centre or research group
II-3 Evidence from comparisons between times or places with or without the intervention (dramatic results in uncontrolled experiments could be included here)

III Opinions of respected authorities, based on clinical experience; descriptive studies; or reports of expert committees

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. HEPATIC RESECTION IN METASTATIC CRC

Question: What are the principles involved in defining patients with metastatic CRC for hepatic resection?

- Hepatic metastases from CRC can be thought of as "resectable," "not optimally resectable," and "never resectable" (level III) [2].
- Patients should be operative candidates for a major laparotomy and liver resection (level III).
- In general, patients should have no extrahepatic disease; however, selected cases could be considered if resectable extrahepatic disease is present (level III).
- The intent of hepatic resection should be to resect all liver disease (at least grossly) with preservation of adequate liver function (level III).
- The primary CRC must be resectable (level III).

Question: Is there a role for liver biopsy in patients with suspected liver metastases from metastatic CRC?

- Routine biopsy of a suspected liver metastasis is not warranted if the patient has had a pathologic diagnosis of CRC in the preceding 5 years (level III).
- Avoidance of liver biopsy in this setting avoids the risk of complications such as tumour seeding, infection, and bleeding (level II-3) [3–5].

3.1 Unresectable CRC Liver Metastases

Question: What is the role of conversion strategies in the management of CRC patients with unresectable liver metastases?

- Conversion strategies are strategies used in an attempt to convert unresectable CRC liver metastases to a resectable state.
- Patients with potentially resectable liver metastases from metastatic CRC should be assessed by a multidisciplinary team including hepatobiliary surgery, medical oncology, radiation oncology, and radiology (level II-3) [6].
- Patients with initially unresectable CRC liver metastases should be reassessed by a hepatobiliary surgeon (in a timely fashion) if they have a favourable response to conversion therapy (level II-3) [6].
- In patients with unresectable CRC liver metastases, strategies for conversion to resectability may include portal vein embolization, radiofrequency ablation, staged resection, and systemic therapy (level II-3) [6].
- Patients with metastatic CRC should have access (in a timely fashion) to magnetic resonance imaging and computed tomography imaging, where indicated, to assess resectability (level III).
- The role of positron-emission tomography (PET) in evaluating patients before liver resection is currently under investigation.
- Combination chemotherapy should be selected to maximize response rate and to facilitate an R0 resection (level III) [7].
- Biologic therapy (bevacizumab or an epithelial growth factor receptor inhibitor in *KRAS* wild-type tumours) in combination with chemotherapy may have benefit as a conversion strategy (level III) [8–10].
- Bevacizumab, if discontinued 5 weeks before the time of operation, is not associated with excessive operative morbidity and mortality in patients undergoing hepatic resection (level II-1) [11].
- Optimal timing of a hepatic resection is after fewer than 6 cycles of systemic therapy—an approach that minimizes postoperative morbidity (level II-3) [12].
- Further studies investigating conversion therapy are warranted (level III).

4. RADIOTHERAPY FOR CRC LIVER METASTASES

Question: What is the role of radiotherapy in the management of CRC liver metastases?

- If radiation to liver metastases is being considered, use of stereotactic body radiotherapy (SBRT—high-dose radiation therapy delivered very conformally in a few fractions) or conformal radiation therapy are required to safely irradiate and control liver metastases (level II-1) [13,14].
- Radiation treatments for CRC liver metastases should be performed by radiation oncologists with experience in treating liver metastases (level III).
- No randomized phase III trials involving SBRT for the treatment of CRC liver metastases have been

conducted; however, high-dose radiotherapy can be safely delivered to focal unresectable liver metastases, and sustained local control is a possibility (level II-1) [13,14].

- The most ideal setting for SBRT is that of small, unresectable liver metastases (<8 cm in the maximum diameter) that are located away from the small bowel and stomach and that allow for an adequate non-radiated hepatic reserve of at least 700 mL (level III) [13,14].
- If SBRT is used for the treatment of CRC liver metastases, systemic therapy should be discontinued 2 weeks before the SBRT and restarted no sooner than 4 weeks after SBRT completion (level III).
- There is strong biologic rationale for the combination of SBRT and systemic therapies. Further study of combination therapy, with external quality assurance evaluation, is required (level III).

5. PULMONARY RESECTION IN METASTATIC CRC

Question: What is the role of pulmonary resection in patients with metastatic CRC involving lungs?

- Patients with potentially resectable lung metastases from CRC should be assessed by a multidisciplinary team including thoracic surgery, medical oncology, radiation oncology, and radiology (level III).
- Pulmonary resection should be considered in patients who have undergone successful treatment of the primary site, who have adequate cardiopulmonary reserve, who can tolerate surgery, and in whom an R0 resection is expected (level III).
- Wedge resection or resections by video-assisted thoracoscopic surgery is the ideal surgery for unilateral disease with 3 or fewer pulmonary lesions (level II-2) [15].
- Evidence of involved mediastinal lymph nodes (from CRC) is a contraindication for pulmonary resection (level II-3) [16,17].
- Biopsy (including immunohistochemistry) of the pulmonary lesion or lesions to distinguish a solitary metastasis from a primary lung carcinoma should be considered if clinically indicated (level III).
- Comprehensive staging before pulmonary resection includes the use of PET imaging to rule out distant unresectable disease, hilar and mediastinal disease, and recurrence at the primary site (level III) [18].
- Perioperative chemotherapy (pre- or postoperative, or both) is appropriate (level III).
- Outcome is best in patients in whom the metastases are solitary (or few), isolated to the lung, and occurring after a long disease-free interval [19].

6. MONOCLONAL ANTIBODIES AGAINST EPIDERMAL GROWTH FACTOR RECEPTOR IN METASTATIC CRC

Question: What is the role of cetuximab or panitumumab as monotherapy in the treatment of patients with chemo-refractory metastatic CRC (mCRC)?

- Monoclonal antibodies against epidermal growth factor receptor (EGFR) should be available to patients with chemo-refractory wild-type *KRAS* mCRC not previously exposed to such monoclonal antibodies, based on these factors:
  - Cetuximab significantly prolongs overall survival in patients with wild-type *KRAS* chemo-refractory mCRC (level I) [20].
  - Panitumumab significantly prolongs progression-free survival (PFS) in patients with wild-type *KRAS* chemo-refractory mCRC (level I) [21].
- Testing for *KRAS* should be widely available (locally and in a timely fashion) as part of routine pathologic evaluation for mCRC patients who are candidates for EGFR monoclonal antibody therapy (level III) [22].
- There should be equity of access to EGFR monoclonal antibody therapy and *KRAS* testing in all provinces and territories in Canada (level III).

Question: What is the role of cetuximab and panitumumab in combination with chemotherapy in the treatment of patients with mCRC?

- Monoclonal antibodies against EGFR, in combination with chemotherapy, are an acceptable option for patients with wild-type *KRAS* mCRC who have not previously been exposed to such monoclonal antibodies, based on these factors:
  - Use of EGFR monoclonal antibodies (cetuximab, panitumumab) with combination chemotherapy significantly improves response rate in patients with wild-type *KRAS* mCRC in the first- and second-line settings (level I) [10,23–25].
  - Cetuximab in combination with FOLFIRI chemotherapy [5-fluorouracil (5FU), irinotecan, leucovorin], as compared with FOLFIRI chemotherapy alone, significantly improves overall survival as initial therapy for wild-type *KRAS* mCRC (level I) [26].
  - Cetuximab in combination with irinotecan improves response rate and PFS in irinotecan-refractory mCRC (level I) [27].

7. MANAGEMENT OF ELDERLY PATIENTS WITH CRC

Question: What is the effect of increasing age on the benefit of adjuvant chemotherapy for CRC?

- Advancing age is a risk factor for the development of CRC (level II-1) [28].
- Evidence is conflicting regarding the benefit of adjuvant FOLFOX chemotherapy (5FU, leucovorin, oxaliplatin), as compared with 5FU monotherapy, in patients over the age of 70 years (level II-1) [29–31].
- Chemotherapy should be offered to fit elderly patients in the adjuvant setting (level III).
- The use of adjuvant FOLFOX chemotherapy is appropriate in patients with resected high-risk stage II and stage III CRC (level III).

Question: What is the effect of increasing age on the benefits and safety of palliative chemotherapy for MCRC?

- It is appropriate to use combination systemic therapy in older fit patients as first-line therapy (level II-1) [30,32–35].
- It is also appropriate to treat fit elderly patients with capecitabine monotherapy and then to change to combination chemotherapy or single-agent irinotecan upon progression (level I) [36,37].
- Bevacizumab in combination with systemic chemotherapy is appropriate to use in elderly patients without contraindications to bevacizumab (level II-1) [38].
- Cetuximab can be offered to older patients (level II-2) [39].

8. LINES OF THERAPY

Question: Should access to therapies for MCRC be limited by "lines of therapy" or an arbitrary number of cycles?

- Treatment of MCRC is complex and should not be restricted to a certain number of "lines" of therapy (level III).
- Therapy with bevacizumab in combination with chemotherapy in patients with MCRC should continue as long as the patient is deriving clinical benefit; this therapy should not be restricted to an arbitrary number of cycles (level I) [8,40,41].

9. GASTROINTESTINAL NEUROENDOCRINE TUMOURS

Question: What role do biomarkers for gastrointestinal neuroendocrine tumours (NETS) play?

- Optimal routine assessments for a patient with a NET include (level III) [42]:
  - Chromogranin A (available in a timely fashion)
  - Urinary 5-hydroxyindoleacetic acid
  - Other tests to investigate functionality

Question: What is optimal imaging for NETS?

- Optimal imaging for NETS includes (level III) [42]:
  - Octreotide scan (completed 6 months after resection, because imaging before this point may produce a false-positive result)
  - Computed tomography imaging (every 6 months after curative resection, every 3 months in metastatic disease)
  - Echocardiogram at presentation, and then annually (functional NETS)

Question: What is the optimal pathology reporting for NETS?

- Pathology reporting of NETS should include (level III) [43,44]:
  - TNM stage
  - Size and anatomic location
  - Ki-67 proliferation index
  - Mitotic count

Question: What is the optimal medical therapy ("biotherapy") for patients with well-differentiated metastatic midgut NETS?

- Octreotide in a long-acting release (LAR) formulation should be considered, because it has been shown to improve PFS for symptomatic and asymptomatic, functional and non-functional, well-differentiated midgut NETS (level I) [45].
- Interferon alfa (in combination with octreotide LAR) could be considered for patients who have experienced progression despite therapy with octreotide LAR in NETS with a Ki-67 index of 2% or less (level III) [46].

Question: What is the role of cytotoxic chemotherapy for NETS?

- Cytotoxic chemotherapy should be considered only in patients with a high (Ki-67 above 2%) proliferation index (level III).
- Suggested chemotherapy for an intermediate-grade NET involves the combination of 5FU with streptozocin or doxorubicin (level III) [47].
- Suggested chemotherapy for a high-grade NET (Ki-67 above 20%) is cisplatin combined with etoposide (level III) [48,49].

Question: What is the optimal therapy for progressive pancreatic NETS?

- Sunitinib malate should be considered, because compared with placebo, it has been shown to

improve PFS in progressive well-differentiated pancreatic islet cell tumours (level I) [50].
- Suggested chemotherapy involves the combination of doxorubicin, streptozotocin, and 5FU (level II-1) [51].

10. GASTRIC CANCER

Question: Does chemotherapy provide a clinical benefit to patients with advanced gastric cancer?

- Compared with best supportive care alone, palliative chemotherapy combined with best supportive care improves overall survival in patients with advanced gastric cancer and good performance status (level I) [52].
- Combination palliative chemotherapy is superior to monotherapy for overall survival (level I) [52].

Question: Is there a standard chemotherapy for initial use in advanced gastric cancer?

- Combination chemotherapy with epirubicin, cisplatin, and 5FU is an acceptable standard for initial use in advanced gastric cancer (level I) [53,54].
- Combination chemotherapy with docetaxel, cisplatin, and 5FU is an acceptable standard for initial use in advanced gastric cancer; however, this regimen has a significant toxicity profile (level I) [55].
- Capecitabine is an acceptable substitute for infusional 5FU when used in combination with epirubicin and a platinum agent (cisplatin or oxaliplatin) (level I) [56,57].
- Oxaliplatin is an acceptable substitute for cisplatin when used in combination with epirubicin and a fluoropyrimidine (5FU or capecitabine) (level I) [57].

Question: Does trastuzumab offer clinical benefit to patients with advanced gastric cancer?

- In patients with a good performance status and tumours that overexpress the human epidermal growth factor receptor 2 [HER2/*neu* (approximately 22% of patients)], trastuzumab in combination with chemotherapy, as compared with chemotherapy alone, improves overall survival (level I) [58].
- Testing for HER2/*neu* should be available (in a timely fashion) to patients with advanced gastric cancer who are candidates for trastuzumab therapy (level III).

Question: Is there a role for second-line chemotherapy in patients with advanced gastric cancer?

- Second-line chemotherapy may offer an overall survival benefit in patients with a good performance status and without previous exposure to the proposed chemotherapy agents (level II-1) [59–65].

11. CONFLICT OF INTEREST DISCLOSURES

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