Predictive oncology comes to colorectal cancer

REPORT OF THE EASTERN CANADIAN COLORECTAL CANCER CONSensus CONFERENCE 2008
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TERMS OF REFERENCE

Purpose
• This report is a consensus opinion produced by oncologists and other allied health professionals invited from across Eastern Canada for the purpose of recommending management strategies for patients with colorectal cancer (CRC).

Participants
• Oncology professionals from across Ontario, Quebec and the Atlantic provinces were invited to attend this consensus meeting.

Target audience
• The target audience of this report is primarily health professionals involved in the care of patients with colorectal cancer.
• This report is intended to provide information on the standards 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.

Basis of recommendations
• These recommendations were based on presentation and discussion of best available evidence. Where applicable, references are cited.

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OPENING STATEMENTS

Application of recommendations
Statements apply to broad populations of patients, and may therefore not apply to the unique circumstances of each patient. Individual decisions for care are always made within a doctor–patient relationship.

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

POPULATION SCREENING FOR COLORECTAL CANCER

Question: What is the role of colorectal cancer screening for average-risk Canadian men and women?

• CRC represents a serious Canadian public health issue, with approximately 21,500 new cases and over 8900 deaths expected in 2008.2
• Population fecal occult blood testing (FOBT) screening results in a 15% to 33% relative reduction in mortality and is recommended for average-risk men and women between 50 and 74 years of age. This is based on results from three RCTs (Level I).3-5
• Population-based CRC screening programs are an urgent priority.
• To ensure quality screening that maximizes benefits and minimizes potential risks, screening should be within an organized and structured program that includes:
  – High sensitivity FOBT (Level I) or fecal immunohistochemical testing (FIT) (Level II–2) at least every two years6-7
  – Timely access to colonoscopy for individuals with a positive screening test
  – Education programs for patients and family physicians to encourage population uptake of screening programs8-10
• There is currently insufficient evidence to recommend the routine use of screening computed tomography (CT) colonography.

BEVACIZUMAB IN THE MANAGEMENT OF CRC

Question: What is the role of bevacizumab in the management of advanced CRC?

• Bevacizumab is recommended in combination with fluoropyrimidine-based chemotherapy for either first-line (chemotherapy naive) or second-line therapy of advanced CRC. This is the standard of care (Level I).11-14
• This recommendation is based on results from randomized controlled trials in both chemotherapy naive and pretreated patients, where the addition of bevacizumab improved progression-free survival and overall survival when added to chemotherapy alone.

• Continuation of bevacizumab until progression is recommended, without arbitrary duration limits.11-14
• There is currently insufficient data for or against the use of second-line bevacizumab in patients who have progressed on a first-line regimen containing bevacizumab (Level III).
• Outside of a clinical trial, combination chemotherapy with both bevacizumab and an EGFR monoclonal antibody (cetuximab or panitumumab) is not recommended.15-16

PANITUMUMAB AND CETUXIMAB IN CHEMOTHERAPY-REFRACTORY ADVANCED CRC

Question: What are the roles of panitumumab and cetuximab in the management of chemorefractory advanced CRC?

• Recommended options for chemotherapy-refractory patients include cetuximab (Level I), panitumumab monotherapy (Level I) or cetuximab in combination with irinotecan (Level II). These agents improve progression-free and/or overall survival in this setting, and should be made available.17-19
• KRAS testing is mandatory for patients being considered for panitumumab or cetuximab therapy, with treatment reserved for patients with tumours expressing wild-type KRAS (Level II).20-21
• Steroid plus antihistamine premedication is recommended with cetuximab to reduce hypersensitivity reactions (Level II–3).22 This is not required for panitumumab.
• Early initiation of minocycline, doxycycline or tetracycline should be considered for prophylaxis of skin toxicity (Level I).23-24

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**MANAGEMENT OF ADVANCED CRC**

**Question:** What is the best management of Stage IV CRC in an era of increasing surgical resection of metastases?

- Surgery should be considered for CRC patients in whom all metastases can be completely excised with clear margins, regardless of site or sites of disease (e.g. liver, lung) (Level II–1).25-27
- While a valuable strategy, it is unknown if radiofrequency ablation (RFA) results in equivalent disease control compared to surgical resection of metastases.28-30
- Multidisciplinary discussion is essential for management of patients with potentially resectable disease.
- Suggested preoperative evaluation includes contrast-enhanced angiography (CEA), CT or magnetic resonance imaging (MRI) as well as consideration of functional imaging with positron emission tomography (PET) scan.
- For patients with initially unresectable disease, but for whom a reduction in disease burden might be predicted to promote conversion to resectability, combination chemotherapy is recommended (Level II–3).31-33
- Perioperative (post and/or preoperative) chemotherapy in resectable cases is recommended, based on randomized trials that demonstrated consistent trends toward improved outcome (Level III).33,34
- A complete radiographic response to chemotherapy does not imply complete pathologic response—warranting caution to not overtreat in the neoadjuvant setting, because of the risk of obscuring lesions that require resection (Level II–2).35 Duration of treatment is governed by resectability rather than best response. Surgical excision should ideally include all sites of pretreatment disease.

**Question:** Is there a role for intermittent therapy (rather than treatment to progression) for the management of advanced CRC?

- Intermittent oxaliplatin is reasonable to avoid cumulative toxicities and reduced quality of life related to chemotherapy effects (Level I).36-39
- Continuing some form of low-intensity (maintenance) chemotherapy compromises survival to a lesser extent than does complete chemotherapy-free periods (Level I).36-39
- In the setting of disease control following six months of chemotherapy, a chemotherapy-free interval may not compromise outcome (Level III).
- If intermittent therapy is being contemplated, patients must have close followup with prompt reinitiation of therapy at the time of progression.

**ADJUVANT THERAPY FOR COLON CANCER**

**Question:** What is the role of adjuvant chemotherapy in patients with curatively resected Stage III and high-risk Stage II colon cancer?

- Six months of postoperative adjuvant oxaliplatin plus fluororacil + leucovorin (5FU/LV) are recommended for patients with Stage III colon carcinoma (Level I).40-42
- Use of fluoropyrimidine monootherapy as adjuvant therapy is a reasonable alternative for treated patients for whom concern exists regarding use of FOLFOX (Level I).43
- Subgroup analysis of the MOSAIC trial suggests an incremental benefit of oxaliplatin plus 5FU/LV over the use of fluoropyrimidines alone (HR 0.74; 7.2% increase in 5-year disease-free survival) for patients with high-risk Stage II colon cancer. However, overall survival is not different. Treatment remains controversial in this subgroup, but there is consensus that either FOLFOX or fluoropyrimidine monotherapy is reasonable in this population after careful discussion with the patient (Level I).40-42,44
- The definition of high-risk Stage II CRC may include clinical (e.g. insufficient node sampling, T4, high-grade, lymphovascular invasion, obstruction, perforation of tumour) and molecular parameters (e.g. MSI status, 18q deletions) (Level II).
- Fluoropyrimidine monotherapy in patients with MSI-high status is not recommended, since this is both a good prognostic factor and a predictor of lack of benefit from chemotherapy. If risk is sufficient for therapy, FOLFOX might be more appropriate, although no data are available to determine this (Level III).45,46
- Because of the risk of permanent neuropathy, trials to address duration and prevention studies are warranted.

**PHARMACOECONOMICS OF CRC**

**Question:** How should the Canadian healthcare system approach access to new effective therapies in CRC?

- Approval of funding for CRC interventions must be determined on an equal footing with other interventions in other diseases. Approval processes should be:
  - transparent, with published criteria and rationale for decisions
  - based on standardized pharmacoeconomic analysis methodology
  - inclusive of patient input
- The principle of universality must be maintained for all therapies found within an appropriate cost-effectiveness threshold, and governments should ensure access is not dependent on a patient’s demographics, financial means or province of residence.
- For therapies where the cost-effectiveness exceeds appropriate thresholds but clinical benefit has been established, governments must allow access to these therapies.

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through private-pay or insurance mechanisms.

- Physicians should inform patients regarding the most effective therapies, but are not obliged to provide or arrange such therapies where not publicly funded.
- Pharmacoeconomic analysis should be encouraged in the design of clinical trials.
- Pharmaceutical companies have a duty to price drugs responsibly.
- Healthcare providers, governments and pharmaceutical companies should work together to ensure that access to therapies is timely, and that prices are affordable and sustainable within the public reimbursement system.

**CRC GENETICS SERVICES**

**Question:** What is the role of genetic services for patients with CRC and their families?

- The goal of genetic testing for CRC is to identify individuals and families with hereditary cancers to reduce cancer incidence and mortality.
- Hereditary conditions of interest include Familial Adenomatous Polyposis (FAP), Hereditary Non-Polyposis CRC (HNPPC) and other syndromes.
- Provincial cancer programs and ministries of health should develop and sustain dedicated cancer genetic programs, which include:
  - timely access to genetic services which include genetic counselors with expertise in colon cancer genetics
  - development of guidelines for referral to cancer genetic services, criteria for genetic testing, and guidelines for prevention strategies in carriers. [12]

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**References**

1. Levels of evidence as defined by the Canadian Task Force on Preventive Health Care. Accessed November 1, 2008 at www.ctfphc.org > History & Methods. Table 2. Levels of Evidence — Research Design Rating:
CONSENSUS


