



Treatment of colorectal cancer

REPORT OF THE EASTERN CANADIAN COLORECTAL CANCER CONSENSUS CONFERENCE 2005
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Editor's note:

Over the last decade combination therapies have contributed significantly to progress in the treatment of metastatic colorectal cancer. In adjuvant treatment, data in the last 3 years have increasingly demonstrated the efficacy of new chemotherapy combinations, so that several options are now available to manage Stage II–III colon cancers. These options are associated, however, with new toxicities and increasing costs. Optimizing therapy requires selection of the most effective combination tailored to a patient's needs. The Eastern Consensus Conference in Colorectal cancer was convened to evaluate the evidence and recommend appropriate choices tailored to a variety of clinical settings.

Oncology Exchange is pleased to publish the consensus statement reached at the 2005 meeting held in Ottawa. A similar initiative in the western provinces reached the same conclusions in 2005.

This document thus presents national recommendations for the treatment of this common cancer. We hope that the dissemination of this information will assist physicians in their choice of optimal treatment for their patients. We also hope to publish such statements on a regular basis and to broaden the scope to all types of malignancies.

TERMS OF REFERENCE

Purpose

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

Participants

- Academic cancer centres from across Ontario, Quebec and the Atlantic provinces were invited to send representatives to 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 guide 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 recommendation

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

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.

ADJUVANT TREATMENT OF COLON CANCER

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

Evidence-based recommendation

- Based on Level I evidence (see box), 6 months of post-operative adjuvant oxaliplatin plus fluorouracil/leucovorin (5FU/LV) are recommended for patients with high-risk colon carcinoma. This represents the current standard of care.^{2,3}
- This recommendation is based on Phase III trials involving the follow regimens:
 - FOLFOX results in superior disease-free survival compared to the previous standard 5FU/FA (4-year DFS 75.9% vs 69.1%, HR = 0.76, $p < 0.0008$).²
 - FLOX results in superior disease-free survival compared to the previous standard 5FU/FA (3-year DFS 76.5% vs 71.6%, HR = 0.79, $p < 0.004$).³
- Oxaliplatin must be accessible and funded for all eligible patients.

Qualifying statements

- Definition of high risk for Stage II patients includes inadequate node dissection (evaluation of insufficient number lymph nodes in the resected specimen), T4 status, perforation and poorly differentiated tumours. Other factors that may be considered include perineural invasion, lymphovascular invasion, symptomatic obstruction or

tumours defined as high-risk using molecular markers (e.g. MSI, 18q del, TGF β).

- The ideal minimum number of nodes for evaluation is 12 nodes.
- Adjuvant therapy is not routinely recommended for low-risk Stage II colon cancer.
- Adjuvant chemotherapy is ideally commenced within 8 weeks of surgery.
- All patients with Stage II and III colon cancer should be referred for the opinion of a medical oncologist.

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

Evidence-based recommendation

- Six months of capecitabine is recommended for patients with curatively resected Stage III and high-risk Stage II colon cancer who have contraindications to oxaliplatin or who have barriers (e.g. physical, social, geographic) to the use of combination therapies.⁴
- Capecitabine is as effective as, and has fewer toxicities than 5FU/LV, which is no longer recommended for patients who are appropriate candidates for oxaliplatin-based combination therapy or capecitabine.⁵
- This recommendation is based on Level I evidence from the X-ACT trial, in which the starting dose was 2500 mg/m²/day.⁴
- Capecitabine must be accessible and funded for all eligible patients.

Qualifying statements

- Capecitabine may be associated with increased risk of toxicity in patients with renal dysfunction.
- Patients must be capable of compliance with oral medication and must both be able and educated to seek and have access to expert advice in the event of toxicity during a cycle of capecitabine.
- Capecitabine may be associated with drug interactions (e.g. warfarin, phenytoin).
- There may be a small subset of patients for whom the prior standard therapy 5FU/FA is still appropriate.

POST-THERAPY SURVEILLANCE FOR COLORECTAL CANCER

Question: What is appropriate surveillance for patients with curatively resected Stage II and III colorectal cancer who would tolerate potentially curative therapy in the event of recurrence?

Evidence-based recommendation

- Based on Level I evidence from 6 randomized trials summarized in a meta-analysis, a program of surveillance is recommended.⁶⁻¹³

- Based on expert opinion, 5 years of surveillance for recurrence of the prior colon cancer from the time of surgery is recommended. This is based on the recurrence pattern.
- Based on expert opinion, secondary screening of the colon is recommended indefinitely as long as a patient remains in good health.
- Based on expert opinion, visits are recommended every 3 to 6 months for 3 years, then every 6 months for 2 additional years. At each of these visits, the following is recommended: history, physical exam and carcinoembryonic antigen (CEA) with investigation of any abnormalities.
- There was no clear consensus regarding the routine use of CT scan, ultrasound and chest x-ray.
- There is currently insufficient evidence to recommend the routine use of PET scanning in surveillance.
- Based on expert opinion, colonoscopy is recommended within 1 year of surgery or at the completion of chemotherapy for those without adequate colonoscopy preoperatively. If abnormalities are identified, a repeat colonoscopy is recommended at 1 year. In the case of a normal colonoscopy a repeat is recommended every 3 to 5 years.

Qualifying statements

- There is no evidence that outcomes are superior if surveillance occurs with a specialist vs a primary care physician.
- There is inadequate evidence to make a recommendation regarding surveillance for recurrence for patients with Stage I colon cancer, although screening colonoscopy recommendations still apply.

MANAGEMENT OF LIMITED METASTATIC DISEASE

Question: What is the role of local therapies (e.g. surgery, radiofrequency ablation, chemoembolization, hepatic arterial infusion) for localized metastatic disease?

Evidence-based recommendation

- Based on Level II-3 evidence of outcomes, patients with limited metastatic disease are potentially curable.¹⁴⁻¹⁵
- Consensus is that these patients should have their case discussed within the context of a multidisciplinary team.

ADVANCED COLORECTAL CANCER

Question: What is recommended for patients with locally advanced or metastatic disease not amenable to curative therapy?

Evidence-based recommendation

- All patients should have access to and funding for fluoropyrimidines, irinotecan, oxaliplatin and bevacizumab in the course of their management, as there is Level I evidence that each of these agents contributes to improved survival.¹⁶⁻²⁷

Levels of evidence

Several different systems are in use for rating levels of evidence,¹ with slight variations among them. The system used by many Canadian consensus guideline groups, including the Eastern Canadian Colorectal group, is as follows (available at www.ctfphc.org > History & Methods. Table 2. Levels of Evidence — Research Design Rating):

- I Evidence from randomized controlled trial(s).
- II-1 Evidence from controlled trial(s) 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.

Question: What is the optimal sequencing of chemotherapy?


Evidence-based recommendation

- Combination chemotherapy incorporating fluoropyrimidines with either irinotecan or oxaliplatin in combination with bevacizumab is the standard of care for first-line therapy.²⁵⁻²⁷
- On progression after first-line therapy, the alternative agent (irinotecan vs oxaliplatin) is recommended.²³ When oxaliplatin is used as second-line therapy, it should be given in combination with 5FU/LV (Level I).²² When irinotecan is used second-line there is evidence for use either as a single agent or in combination with 5FU/LV.^{17,18,23}
- Level I evidence demonstrates that for patients who did not receive first-line bevacizumab, second-line bevacizumab in combination with fluoropyrimidines improves survival.²⁷
- There is currently insufficient data to recommend second-line bevacizumab for patients who have progressed on a first-line regimen containing bevacizumab.
- Sequential monotherapy may be an appropriate option for selected patients.²⁸

Question: What is the role of cetuximab?

Evidence-based recommendation

- Based on a randomized Phase II trial, cetuximab plus irinotecan is a reasonable option for patients with EGFR-positive, chemotherapy-resistant colon cancer.²⁹

- When cetuximab is to be administered to patients who have progressed while on irinotecan, it is recommended that the irinotecan be continued or restarted. Compared to cetuximab alone, the combination results in a significant increase in response rate (22.9% vs 10.8%) and time to progression (4.1 vs 1.5 months).
- At this time there is insufficient data to recommend the use of cetuximab in patients who remain chemotherapy-sensitive.
- The role of cetuximab in patients with EGFR-negative tumours is less clear, but there is Level II-3 evidence that cetuximab may also be active in these patients.^{30,31}
- The best available evidence suggests that EGFR testing by immunohistochemistry may not be important in selecting patients for cetuximab therapy.³² 

Participant disclosure of potential conflicts of interest

Scott Berry: BMS (honoraria < \$2000), Roche (advisory board \$2,000-\$9999); Jim Biagi: Roche (research funds \$10,000-\$99,999); Bruce Colwell: Sanofi-Aventis (advisory board < \$2000); Christine Cripps: BMS (honoraria < \$2000), Roche (advisory board < \$2000); Mark Dorreen: BMS (advisory board), Roche (advisory board), Sanofi-Aventis (consultant and advisory board), all < \$2000; Anthony Fields: BMS (honoraria and advisory board), Ortho Biotech (honoraria), Roche (honoraria and advisory board), all \$2000-\$9999; Colin Germond: Amgen, Novartis (honoraria, both < \$2000); Rakesh Goel: Novartis, Pfizer and Roche (advisory boards < \$2000); Derek Jonker: BMS (research funds < \$2000), Roche (honoraria and advisory board, both < \$2000); Jennifer Knox: Bayer (advisory board < \$2000) and Roche (honoraria < \$2000); Jean Maroun: AstraZeneca (honoraria < \$2000), Pfizer (honoraria and advisory board, both < \$2000), Roche (honoraria and advisory board, both \$2000-\$9999); Lucille Robillard: Novartis (honoraria, < \$2000); Marlene Sellon: BMS, Pfizer, Roche (advisory boards, all < \$2000); Michael Thirlwell: AstraZeneca (advisory board < \$2000), Novartis (advisory board \$2000-\$9999); Kiran Virik: AstraZeneca, BMS, Roche, (advisory boards), all < \$2000.

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