



Complete Summary

GUIDELINE TITLE

Adjuvant systemic chemotherapy for stage II and III colon cancer following complete resection: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Jonker D, Spithoff K, Maroun J, Gastrointestinal Cancer Disease Site Group. Adjuvant systemic chemotherapy for stage II and III colon cancer following complete resection: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 Apr 17. 48 p. (Evidence-based series; no. 2-29). [104 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Stage II and III colon cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations regarding the use of adjuvant systemic chemotherapy in the treatment of resected stage II and III colon cancer

TARGET POPULATION

Adult patients with stage II or III colon cancer who have undergone resection with curative intent as primary therapy

INTERVENTIONS AND PRACTICES CONSIDERED

1. Fluoropyrimidine-based systemic chemotherapy versus observation
2. Intravenous (IV) 5-fluorouracil (FU) versus oral fluoropyrimidines
3. Fluoropyrimidines versus fluoropyrimidines plus oxaliplatin
4. Fluoropyrimidines versus fluoropyrimidines plus irinotecan
5. Enrollment in clinical trials

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Disease-free survival
- Adverse effects
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The MEDLINE (1987 through September 2007), EMBASE (1987 through week 38 2007), CANCELIT (1987 through October 2002), and Cochrane Library (through Issue 2, 2007) databases were searched using the medical subject heading

(MeSH) "colonic neoplasms", "colorectal neoplasms", "adjuvant chemotherapy", and the text words "colon cancer", "colorectal cancer", and "colonic neoplasms". These terms were then combined with the search terms for the following study designs: practice guidelines, meta-analyses, and randomized controlled trials. In addition, proceedings from the annual meetings of the American Society of Clinical Oncology (ASCO) (1998 to 2007) were searched for reports of newly completed trials. Personal reprint files and reference lists of relevant studies were also searched.

Study Selection Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. They were fully published reports or published abstracts of randomized controlled trials (RCTs) or meta-analyses of RCTs involving patients with stage II or III colon cancer who had undergone surgery with curative intent. The studies had to include at least one of the following comparisons: adjuvant systemic fluoropyrimidine-based chemotherapy versus observation alone, oral fluoropyrimidines versus intravenous 5-fluorouracil (5-FU), fluoropyrimidines plus oxaliplatin versus fluoropyrimidines alone, or fluoropyrimidines plus irinotecan versus fluoropyrimidines alone.
2. The primary outcome of interest was disease-free survival (DFS). Secondary outcomes of interest were overall survival (OS), treatment toxicity, and quality of life. Articles had to report data for one of these outcomes.
3. They were English-language publications.
4. The clinical trials were published after 1987. Buyse et al summarized the results of randomized trials of adjuvant therapy for colorectal cancer up to 1987.

NUMBER OF SOURCE DOCUMENTS

Meta-analysis of Adjuvant Therapy (randomized controlled trials [RCTs] to 1987)

In 1988, Buyse et al conducted a meta-analysis of all English trials of adjuvant therapy for colorectal cancer (all stages included). Seventeen trials compared adjuvant chemotherapy with surgery alone in patients with colorectal cancer.

Literature Search Results (Post 1987)

The literature search identified 38 relevant reports, representing 31 RCTs and 13 meta-analyses of RCTs published after 1987.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The evidence-based series (EBS) guidelines developed by the Cancer Care Ontario (CCO) Program in Evidence-based Care (PEBC) use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one member of the PEBC Gastrointestinal Cancer DSG and methodologists.

Individual patient data were not available for review. No data pooling was conducted in this review due to the availability of published meta-analyses comparing adjuvant chemotherapy with observation alone in both stage II and stage III colon cancer and the limited trial data available for the comparisons of oral fluoropyrimidines versus intravenous 5-fluorouracil (5-FU), fluoropyrimidines plus irinotecan versus fluoropyrimidines alone, or fluoropyrimidines plus oxaliplatin versus fluoropyrimidines alone.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Report Approval Panel

Prior to the submission of this evidence-based series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel included:

- For the comparison of fluoropyrimidines versus surgery alone, the authors should highlight which data are new since the original publications, and indicate how the conclusions have changed. The authors should consider which components can be historical narrative and removed from the Results section.
- The authors should consider summarizing the published meta-analyses in tabular form.
- The document would benefit from better framing the hypothesis of oral fluoropyrimidines versus intravenous fluoropyrimidines in terms of efficacy non-inferiority, ease of administration, quality of life, and potential cost. A more definitive conclusion about which option, oral or intravenous, is preferred, or what trade-offs exist, would be helpful.

- The authors should more specifically indicate what constitutes "high-risk" and which stage II patients should be treated.
- Summary statements of conclusions for stage II and III patients should be added to each component of the Results section. The information should be reframed along the lines of disease stage in the Discussion section.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External Review by Ontario Clinicians

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base in the original guideline document of this evidence-based series (EBS) and review and approval of the report by the Program in Evidence-based Care (PEBC) Report Approval Panel, the Gastrointestinal Cancer Disease Site Group (DSG) circulated Sections 1 and 2 of the original guideline document to external review participants in Ontario for review and feedback.

Methods

Feedback was obtained through a mailed survey of 78 external review participants in Ontario (28 medical oncologists and 50 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey was mailed out on December 10, 2007. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal Cancer DSG reviewed the results of the survey.

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Gastrointestinal Cancer DSG and the Report Approval Panel of the PEBC.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Stage II Colon Cancer

- The routine use of adjuvant chemotherapy for all patients with stage II colon cancer is not recommended. However, the subset of patients with high-risk stage II disease who should be considered for adjuvant therapy includes patients with inadequately sampled nodes, T4 lesions, perforation, or poorly differentiated histology.
- The ultimate clinical decision should be based on discussions with the patient about the nature of the evidence supporting treatment, the anticipated morbidity of treatment, the presence of high-risk prognostic features on individual prognosis, and patient preferences.
- When treated with adjuvant therapy, high-risk stage II patients should receive similar regimens to those recommended for stage III patients.
- The enrolment of resected high-risk stage II patients in clinical trials is encouraged. Additional trials comparing adjuvant therapy with observation are needed and are ethically acceptable in stage II colon cancer.

Stage III Colon Cancer

- The Gastrointestinal Cancer Disease Site Group (DSG) recommends that patients with completely resected stage III colon cancer should be offered adjuvant chemotherapy and that this treatment should start within eight weeks of surgery. Treatment should depend on factors such as patient suitability and preference, and patients and clinicians must work together to determine the optimal course of treatment. The recommended treatment option is:
 - 5-fluorouracil (5-FU) given intravenously in combination with leucovorin (LV) and oxaliplatin in the regimens known as FOLFOX or FLOX. These 5-FU/LV/oxaliplatin regimens have demonstrated superior disease-free survival (DFS) when compared with 5-FU plus LV and are the recommended regimens. Oxaliplatin administration is associated with a 1% risk of persistent grade 3 neuropathy that needs to be considered in conjunction with expected benefits of therapy.
- Some patients would not be considered appropriate for oxaliplatin regimens. Examples include patients with underlying neurologic conditions or at increased risk of neuropathy, patients at increased risk for infections, and patients likely to poorly tolerate infections as a result of chemotherapy. For these patients, the treatment options are:
 - Oral capecitabine administered for six months, which has equivalent efficacy to intravenous 5-FU/LV. Capecitabine results in significantly less diarrhea, stomatitis, neutropenia, nausea/vomiting, and alopecia but significantly more hand-foot syndrome when compared with 5-FU/LV.
 - 5-FU in combination with LV administered for six months using either the weekly or monthly schedule.
- Suitable patients should be offered entry into clinical trials testing new adjuvant treatments for resected stage III colon cancer.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by meta-analyses and randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Published meta-analyses of randomized controlled trials (RCTs) comparing adjuvant chemotherapy with observation alone generally demonstrated superior disease-free survival (DFS) and overall survival (OS), particularly for stage III patients. Although hazard ratios (HRs) also favoured chemotherapy for stage II patients, these were not statistically significant.
- Two RCTs reported at least equivalent DFS and OS results for oral fluoropyrimidines (capecitabine and oral tegafur-uracil [UFT]) compared with intravenous 5-fluorouracil/leucovorin (5-FU/LV). In the Xeloda for the Adjuvant Therapy for Colon Cancer (X-ACT) study, patients in the capecitabine arm experienced significantly less grade 3/4 stomatitis, grade 3/4 neutropenia requiring intervention, febrile neutropenia/sepsis, diarrhea, nausea and vomiting, and alopecia than did patients in the 5-FU/LV arm, but more hand-foot syndrome. Quality of life did not differ significantly between treatment arms in either RCT.
- Two RCTs compared 5-FU/LV plus oxaliplatin with 5-FU/LV alone in patients with resected stage II and III colon cancer.
 - Multicentre International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC):
 - The MOSAIC RCT reported a significant benefit in DFS after five years of follow-up for stage II and III patients who received 5-fluorouracil + leucovorin + oxaliplatin (FOLFOX4) compared with patients who received 5-FU/LV (HR, 0.80; $p=0.003$). Five-year DFS was 73.3% in the FOLFOX4 group and 67.4% in the 5-FU/LV group. A subgroup analysis by disease stage demonstrated a significant benefit in DFS for FOLFOX4 compared with 5-FU/LV in stage III patients (HR, 0.78; $p=0.005$; 5-year DFS, 66.4% versus [vs] 58.9%) but not in stage II patients (HR, 0.84; $p=0.258$; 5-year DFS, 83.7% vs 79.9%). In an exploratory analysis, HRs suggested a possible benefit in DFS for oxaliplatin in patients with high-risk stage II disease (HR, 0.74; $p>0.05$) but not for low-risk stage II patients (HR, 1.22; $p>0.05$). These data are available only in abstract form and as a publicly available online presentation.
 - After six years of follow-up, overall survival was not significantly different between treatment arms in the overall analysis of stage II and III patients (HR 0.85; $p=0.057$) or in the subgroup analysis of stage II patients (HR, 1.00; $p=0.996$; 6-year OS, 86.9% vs 86.8%); however, analysis of stage III patients demonstrated a significant benefit for the addition of oxaliplatin (HR, 0.80; $p=0.029$; 6-year OS, 73.0% vs 68.6%).

- National Surgical Adjuvant Breast and Bowel Project (NSABP C-07):
 - The NSABP C-07 RCT demonstrated a significant benefit in DFS for the overall analysis of stage II and III patients (HR, 0.80; $p=0.0034$; 4-year DFS, 73.2% versus 67.0%).
- None of the four RCTs comparing fluoropyrimidines with irinotecan to fluoropyrimidines alone detected a significant benefit in DFS for the addition of irinotecan. Two RCTs reported no significant difference in OS between treatment groups, although one was small and underpowered. Three of the four RCTs are available as abstracts and publicly available online presentations only.

POTENTIAL HARMS

- Neurotoxicity with 5-fluorouracil/leucovorin (5FU/LV)/oxaliplatin may be severe, and, although it has a significant reversible component, may leave patients with prolonged, and rarely, severe numbness and paresthesias.
- Capecitabine results in significantly less diarrhea, stomatitis, neutropenia, nausea/vomiting, and alopecia than 5-FU/LV but significantly more hand-foot syndrome when compared with 5-FU/LV.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 Aug 25 (revised 2008 Apr 17)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Gastrointestinal Cancer Disease Site Group (DSG) who were involved in the development of this systematic review were polled for potential conflicts of interest. One author (JM) reported receiving more than \$5,000 in a single year as a guest speaker sponsored by Roche during the past two years. One author (DJ) was a co-investigator on the AVANT, National Surgical Adjuvant Breast and Bowel Project (NSABP C-07) and Xeloda for the Adjuvant Therapy for Colon Cancer (X-ACT) trials.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995 Feb;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 5, 1999. The information was verified by the guideline developer as of February 22, 1999. This NGC summary was updated by ECRI on December 3, 2001. The updated information was reviewed by the guideline developer as of January 10, 2002. This summary was updated again by ECRI on May 14, 2004. The information was verified by the guideline developer on June 2, 2004. This summary was updated by ECRI Institute on August 11, 2008. The updated information was verified by the guideline developer on August 25, 2008.

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