



Complete Summary

GUIDELINE TITLE

Adjuvant therapy for stage III colon cancer following complete resection.

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Figueredo A, Fine S, Maroun J, Walker-Dilks C, Wong S. Adjuvant therapy for stage III colon cancer following complete resection [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2000 Dec [online update]. 34 p. (Practice guideline report; no. 2-2). [81 references]

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT
CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Colon cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations regarding the use and kind of adjuvant therapy in the treatment of patients with resected stage III colon carcinoma

TARGET POPULATION

Adult patients with stage III colon cancer following complete resection

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

Adjuvant therapy for stage III colon cancer following complete resection including the following regimens:

1. 5-fluorouracil and leucovorin for six months
2. 5-fluorouracil and low dose leucovorin plus levamisole for six months
3. 5-fluorouracil and levamisole for one year

Note: Details of regimens are provided in Appendix 2 of the original guideline document.

MAJOR OUTCOMES CONSIDERED

- Overall survival (primary outcome of interest)
- Disease-free survival (secondary outcome)
- Adverse effects of treatment regimens (secondary outcome)

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

Original Guideline: August 1997

MEDLINE was searched (1966 to March 1997) using the terms "colonic neoplasms", "adjuvant chemotherapy", "immunotherapy", "radiotherapy", "Duke(s)", "clinical trial", "review", "meta-analysis", "double-blind method", "random allocation", "guideline". Personal reprint files were searched and the relevant studies from bibliographies were reviewed.

December 2000 Update

The original literature search has been updated using MEDLINE (through December 2000), CANCELIT (through November 2000), the Cochrane Library

(Issue 4, 2000), and the 1998 to 2000 proceedings of the annual meeting of the American Society of Clinical Oncology (ASCO) and the American Society for Therapeutic Radiology and Oncology.

Inclusion Criteria

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

1. They were randomized controlled trials (RCTs) comparing adjuvant treatments with observation or other treatments after curative surgery in patients with stage III colon cancer.
2. The main outcome of interest was survival. Secondary outcomes of interest were disease-free survival and adverse effects of the chemotherapy regimens.
3. This review considered clinical trials published after 1987. Buyse et al summarized results of randomized trials of adjuvant therapy for colorectal cancer up to that year. Results of this meta-analysis will be discussed in the original guideline document in the section titled "Interpretative Summary."

NUMBER OF SOURCE DOCUMENTS

Original Guideline: August 1997

Three meta-analyses, 32 published randomized controlled trials (RCTs), and one consensus statement were reviewed.

December 2000 Update

Four meta-analyses and new or updated reports of 23 randomized controlled trials were reviewed.

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

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Original Guideline: August 1997

Individual patient data were not available for review. In some trials the actual number of patients and events in stage III patients was reported (actual data). If not reported, the number of patients and deaths, as well as survival and disease-free survival, were estimated from published tables and graphs (estimated data). For pooled analysis, these data did not allow statistical adjustments for covariates. Data on survival were combined at the time of follow-up reported in each study; the length of follow-up differed across studies. Combining data in this manner assumes a constant hazard ratio of risks between the groups being compared. Data across studies were combined using the meta-analysis software, Metaanalyst^{0.988} (Dr. Joseph Lau, Boston, MA). Results are expressed as the odds ratio (OR) for death and its 95% confidence intervals (CI). An OR <1.0 favours the experimental treatment (reduction in the odds of death for the experimental treatment group compared with the control group), and an OR >1.0 favours the control group. Data were analyzed by both fixed effects (Mantel-Haenszel) and random effects models. The results were similar for both methods, and the results for the random effects model are shown, which better takes into account possible heterogeneity of treatment effects. For calculation of the OR and 95% CI, the number of patients randomized was used in the denominator rather than the number of patients at risk at the time of follow-up, which will overestimate the precision of the confidence intervals. These narrower intervals do not alter the conclusions in this case.

December 2000 Update

New evidence that has emerged since the completion of the original guideline report was not added to the meta-analysis.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Original Guideline: August 1997

The members of the Gastrointestinal Cancer Disease Site Group (DSG) agreed unanimously that patients with stage III colon cancer should be offered adjuvant therapy. The benefits in survival and disease-free survival seem to outweigh any toxic harm, but patients need to be consulted. Treatment should commence within five weeks of surgery. There was debate about which treatment regimen to recommend, but because of the therapeutic equivalence of the regimens available, most members preferred 5-fluorouracil (5-FU) plus low-dose leucovorin for six months mainly because the shorter duration of therapy is expected to be more acceptable to patients and caregivers; whether levamisole should be added remained unresolved. However, this choice may be less favourable for elderly patients, particularly women, in whom the toxicity of 5-FU plus leucovorin is more significant than 5-FU plus levamisole. There was a strong feeling that, although present adjuvant therapy of stage III colon cancer has produced significant benefits in survival, there is room for more improvements. Further testing of currently available chemotherapy regimens and the use of short-term chemotherapy by portal vein infusion (PVI) and immunotherapy with monoclonal

antibodies or tumour vaccines is needed. Patients with stage III colon cancer should be encouraged to participate in clinical trials testing such approaches.

December 2000 Update

A summary of the new evidence that emerged since the completion of the original guideline report was reviewed by the Gastrointestinal Cancer DSG members. The DSG members agreed that the new evidence is consistent with the data used to inform the initial practice guideline and that the recommendations of the original report should remain unchanged.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

- In 1990, a National Institutes of Health (NIH) Consensus Conference reviewed the available evidence and recommended that one year of 5-fluorouracil (5-FU) plus levamisole be offered to all patients with resected stage III colon cancer. Since then, adjuvant trials have abandoned the no-treatment control and have substituted the 5-FU plus levamisole regimen. Through a computer-simulated model it has been estimated that this adjuvant therapy costs \$2,094 US per year of life saved.
- The recently presented trials by the National Surgical Adjuvant Breast and Bowel Project (NSABP), Intergroup, and North Central Cancer Treatment Group (NCCTG)/National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) demonstrated almost equivalent activity for 5-FU plus levamisole and 5-FU plus leucovorin regimens. The major differences were related to treatment duration, toxicity, and cost. Treatment duration for six months seemed as effective as 12 months but with different regimens: 5-FU and levamisole for 12 months is as effective as 5-FU plus high- or low-dose leucovorin for six months. Clearly, halving treatment duration without loss of effectiveness will improve quality of life and cost. Cost is also a major consideration in the use of 5-FU plus leucovorin.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After preparation of an initial guideline report in 1995, practitioner feedback was obtained through a mailed survey of 100 practitioners in Ontario. 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 practice guideline. Written comments were invited. Those not responding received a follow-up reminder at four weeks (telephone) and six weeks (mail). The results of the survey were reviewed by the Gastrointestinal Cancer Disease Site Group (DSG).

This practice guideline was also reviewed by two external reviewers prior to publication in the journal *Cancer Prevention and Control*.

December 2000 Update

The new information from review and updating activities was not subject to external review because the new evidence is consistent with the data used to inform the original guideline.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Patients with resected stage III colon carcinoma should be offered adjuvant therapy.
- Several adjuvant therapy regimens offer similar reduction in the rates of relapse and mortality (30% to 40%). These regimens, described in Appendix 2 of the original guideline document, include:
 1. 5-fluorouracil and leucovorin for six months
 2. 5-fluorouracil and low-dose leucovorin plus levamisole for six months
 3. 5-fluorouracil and levamisole for one year
- Selection of treatment regimen should be discussed with the patient and the final decision should be based on the preferred schedule, toxicity, and the age and sex of the patient, which will influence toxicity. 5-fluorouracil and low-dose leucovorin for six months is recommended as the preferred option because of its therapeutic equivalence with other choices and shorter duration of treatment.
- Treatments should start within five weeks of surgery (the standard in most studies).
- The enrollment of patients in clinical trials of other currently studied treatments is encouraged.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Original Guideline: August 1997

The guideline is based on three meta-analyses, 32 published randomized controlled trials (RCTs), and one consensus statement. The Gastrointestinal Cancer Disease Site Group pooled data from ten of the 32 randomized controlled trials that provided data which allowed for the analysis.

December 2000 Update

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

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

December 2000 Update

Three published meta-analysis and 32 randomized controlled trials were reviewed in the original guideline report. The updated literature search identified four published meta-analyses and new or updated reports of 23 randomized controlled trials. Most clinical trials have detected benefits in disease-free and overall survival for treated patients versus controls. The Gastrointestinal Cancer Disease Site Group pooled data for stage III patients available from 10 trials included in the original guideline report. The meta-analysis indicated a significant decrease in the odds of death for treated versus untreated patients (odds ratio, 0.69; 95% confidence interval, 0.57 to 0.85; $p=0.00032$). When stratified for treatment type, systemic 5-fluorouracil plus levamisole or leucovorin were the only treatments with a significant effect (levamisole odds ratio, 0.61; 95% confidence interval, 0.46 to 0.80; leucovorin odds ratio, 0.51; 95% confidence interval, 0.36 to 0.73). Randomized controlled trials demonstrated almost equivalent activity for 5-fluorouracil plus levamisole and 5-fluorouracil plus leucovorin regimens. Treatment duration for six months seemed as effective as 12 months but with different regimens: 5-fluorouracil and levamisole for 12 months is as effective as 5-fluorouracil plus high- or low-dose leucovorin for six months. The new evidence that emerged since the release of the original guideline report confirms the recommendations for adjuvant therapy in resected stage III colon cancer. Chemotherapy with 5-fluorouracil and levamisole for one year and 5-fluorouracil plus leucovorin for six months remain the standard adjuvant therapies.

POTENTIAL HARMS

Original Guideline: August 1997

Toxicity of 5-fluorouracil with both levamisole and leucovorin was mild to moderate including stomatitis, diarrhea, and leukopenia, with only 5% of patients requiring hospitalization. Portal vein infusion was associated with rare occurrences of hematologic and gastrointestinal toxicity. Monoclonal antibody administration was associated with no hematologic toxicity but about 6% of patients had allergic reactions.

December 2000 Update

There is no additional information on potential harms in the guideline update.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Results of adjuvant treatment for stage III colon cancer often derive from clinical trials which include stage II and, occasionally, stage I colon as well as rectal cancer. Therefore, results for stage III colon cancer are sometimes based on subgroup analysis and, thus, the generalizability of results is open to some interpretation. These circumstances require consideration of the overall trial results and subgroup analyses of patients with stage III colon cancer.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines 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 warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their 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

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Figueredo A, Fine S, Maroun J, Walker-Dilks C, Wong S. Adjuvant therapy for stage III colon cancer following complete resection [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2000 Dec [online update]. 34 p. (Practice guideline report; no. 2-2). [81 references]

ADAPTATION

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

DATE RELEASED

1997 Aug 25 (updated online 2000 Dec)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), 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

Provincial 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 disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, 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.

GUIDELINE AVAILABILITY

Electronic copies: Available from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Adjuvant therapy for stage III colon cancer following complete resection. Toronto (ON): Cancer Care Ontario, 1997 Aug 25 (updated online 2000 Dec). Electronic copies: Available from the [Cancer Care Ontario Web site](#).
- 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 17, 2001. The updated information was reviewed by the guideline developer as of January 10, 2002. The information was updated again by ECRI on May 14, 2004. The information was verified by the guideline developer on June 2, 2004.

COPYRIGHT STATEMENT

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions. Please refer to the [Copyright and Disclaimer Statements](#) posted at the Program in Evidence-Based Care section of the Cancer Care Ontario Web site.

© 1998-2004 National Guideline Clearinghouse

Date Modified: 11/8/2004

The logo for 'FIRST GOV' features the word 'FIRST' in blue and 'GOV' in red, with a small red star above the 'I' in 'FIRST'.

