



## Complete Summary

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### GUIDELINE TITLE

Postoperative adjuvant radiotherapy and/or chemotherapy for resected stage II or III rectal cancer.

### BIBLIOGRAPHIC SOURCE(S)

Cancer Care Ontario Practice Guideline Initiative (CCOPGI). Postoperative adjuvant radiotherapy and/or chemotherapy for resected stage II or III rectal cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2001 Dec. Various p. (Practice guideline; no. 2-3). [51 references]

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## SCOPE

### DISEASE/CONDITION(S)

Resected stage II or III rectal cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

### CLINICAL SPECIALTY

Gastroenterology  
Internal Medicine  
Oncology  
Radiation Oncology  
Surgery

### INTENDED USERS

Physicians

#### GUIDELINE OBJECTIVE(S)

To make recommendations on the use of postoperative adjuvant radiotherapy and/or chemotherapy for adult patients with resected stage II or III rectal cancer

#### TARGET POPULATION

Adult patients with resected stage II or III rectal cancer

#### INTERVENTIONS AND PRACTICES CONSIDERED

Postoperative adjuvant radiotherapy and/or chemotherapy:

1. Radiotherapy
2. Systemic chemotherapy
3. Combined treatment (chemotherapy and radiotherapy)
4. Portal vein infusion chemotherapy
5. Choice of chemotherapeutic agent (i.e., 5-fluorouracil, semustine)

#### MAJOR OUTCOMES CONSIDERED

Overall survival and local control were the primary endpoints. Disease-free survival was a secondary endpoint. Adverse effects were also evaluated.

## 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

##### September 1998 Guideline

MEDLINE, CANCERLIT and the Cochrane Library (1997, Issue 4) searches were conducted for the years from 1966 to April 1997 using the MeSH terms rectal neoplasm, colorectal neoplasm, drug therapy, adjuvant radiotherapy, randomized controlled trials, meta-analysis and practice guidelines, and the text word adjuvant. The MEDLINE searches were limited to the publication types of randomized controlled trial or practice guideline. Personal reprint files were also searched and citations from retrieved articles were reviewed. The Physician Data Query database was searched for relevant ongoing clinical trials. The literature search was updated in April 1998. When results were reported or updated in more than one publication, only the most recent publication is listed.

##### December 2001 Update

The original literature search has been updated using MEDLINE (through July 2001) CANCERLIT (through May 2001), the Cochrane Library (Issue 2, 2001) and the proceedings of the 1999, 2000, and 2001 annual meetings of the American Society of Clinical Oncology. The Physician Data Query database was searched for relevant ongoing clinical trials.

#### Inclusion Criteria

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

1. Syntheses of evidence in the form of evidence-based practice guidelines, or systematic overviews and randomized controlled trials with appropriate comparison groups
2. Studies that enrolled patients with stage II or III rectal carcinoma who had undergone rectal resection with the intent to cure. Information on tumour staging is found in Appendix 1 of the original guideline. Many studies were identified that included patients with colorectal cancer; these studies were included in the review only if the report presented data for patients with rectal carcinoma separately from the data for patients with colon cancer.

#### NUMBER OF SOURCE DOCUMENTS

##### September 1998 Guideline

Fifteen published randomized controlled trials (RCTs), two meta-analyses, and one evidence-based consensus statement 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  
Systematic Review with Evidence Tables

#### DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

This guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle (see companion document by Browman et al). Evidence was selected and reviewed by four members of the Cancer Care Ontario Practice Guidelines Initiative's Gastrointestinal Cancer Disease Site Group (DSG) and methodologists.

## September 1998 Guideline

Pooling of data: The data were pooled to estimate the overall effect on survival and local control of radiotherapy, chemotherapy or combined modality versus each other or observation. The results for patients with stage II and III rectal cancer were combined in the meta-analysis performed for this report in keeping with the manner in which data were presented in the published reports. Individual patient data were not available for this analysis. When survival and disease-free survival were not reported, they were estimated from published graphs (estimated data). When the actual number of events (deaths or disease recurrence) was reported, the reported data were used in the pooled analyses (actual data). Such data do not allow for statistical adjustments for covariates. Data on local control reported at the time of follow-up in each study were pooled even though follow-up times were different across studies. Combining data in this way assumes a constant hazard ratio of risks between the groups being compared.

Data across studies were combined using the meta-analysis software package, Metaanalyst<sup>0.988</sup> (J. Lau, Boston, MA). Results are expressed as odds ratios (OR), where OR <1.0 favors the experimental treatment and OR >1.0 favors control.

## December 2001 Update

No additional pooling has been performed.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

### September 1998 Guideline

In deliberating about this recommendation, the members of the Gastrointestinal Disease Site Group (DSG) recognized:

1. Combined chemo-radiotherapy (CT+RT) is conventional practice and patients who refuse systemic chemotherapy (CT) are offered radiotherapy (RT) alone.
2. Based on the evidence presented, the use of adjuvant RT alone in stage II and III rectal cancer should be questioned: it does not improve survival although emerging data suggest improved local control. Some DSG members felt the radiation doses used in most of the studies reviewed were lower than in ongoing trials; the development of a recommendation will depend on the results of these studies.
3. The role of CT alone needs to be clarified. The members of the DSG felt it is crucial to support clinical trials addressing this issue.
4. Chemotherapy by portal vein infusion (PVI) is currently rarely used in Ontario and, therefore, treatment recommendations should concentrate on systemic chemotherapy.

5. Some members felt that local recurrence rates after surgery in the reviewed trials were much higher than those rates expected by current standards which include total mesorectal excision.
6. The survival advantage of adjuvant treatments for rectal cancer is small and the side effects significant; further improvements in effective therapy are needed.
7. There was unanimous agreement that patients should be informed of the emerging data on adjuvant therapy, and that they should be encouraged to participate in clinical trials.
8. Current data do not justify a recommendation to alter conventional practices that include combined CT+RT.

December 2001 Update

The information above remains current.

#### 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

September 1998 Guideline

Practitioner feedback was obtained through a mailed survey of 85 practitioners (53 surgeons, 11 gastroenterologists, 15 medical oncologists, 3 radiation oncologists and 3 others) 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. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Gastrointestinal Cancer Disease Site Group.

The practice guideline reflects the integration of the draft recommendations in the External Review process and has been approved by the Gastrointestinal Cancer Disease Site Group and the Practice Guideline Coordinating Committee.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

- Patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of radiotherapy and chemotherapy.
- If the goal of adjuvant therapy is to improve survival, there is no evidence to support the use of radiotherapy alone.
- There is evidence that chemotherapy should include 5-fluorouracil (5-FU), but not semustine.
- During the concurrent component of combination therapy, intravenous infusion with 5-FU is more effective than bolus injection.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

#### September 1998 Guideline

Two meta-analyses, one evidence-based consensus statement, and 15 randomized controlled trials were identified in the original search (April 1997) and were eligible for review. The trials are grouped according to treatment modality (radiotherapy [RT], systemic chemotherapy [CT], combined chemo-radiotherapy [CT+RT], or chemotherapy by portal vein infusion [PVI]) and the nature of the control comparison (see Table 1a in the original guideline). Details of the specific chemotherapy and radiotherapy regimens from each trial are presented in Appendix 2 of the original guideline.

#### December 2001 Update

Since the release of the 1998 guideline, the following reports have been published: three meta-analyses, an evidence-based consensus statement, reports of six randomized trials, two reports of additional analyses of adverse effects from two previously reported randomized trials and a review of the adverse effects of adjuvant radiotherapy and chemotherapy (see Table 1b in the guideline document).

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Radiotherapy versus observation: The pooled results of seven randomized controlled trials of radiotherapy alone versus observation detected a benefit in local control for radiotherapy (odds ratio [for local failure], 0.73; 95% confidence interval, 0.55 to 0.96;  $p=0.022$ ), but there was no significant survival benefit (odds ratio [for death], 0.92; 95% confidence interval, 0.77 to 1.11;  $p=0.40$ ).

Preliminary analysis of an eighth randomized controlled trial, published recently in abstract form, indicated no significant survival benefit for radiotherapy versus observation (hazard ratio, 0.95; 95% confidence interval, 0.69 to 1.31;  $p=0.69$ ).

Chemotherapy versus observation: The pooled results of three studies comparing chemotherapy with observation revealed a significant survival benefit for chemotherapy (odds ratio [for death], 0.65; 95% confidence interval, 0.51 to 0.83;  $p=0.0006$ ), but no benefit in local control (odds ratio [for local failure], 0.71; 95% confidence interval, 0.44 to 1.16;  $p=0.17$ ). All three of the randomized controlled trials located during updating found no significant survival benefit, but one found a significant improvement disease-free survival for chemotherapy versus observation. A published meta-analysis found significant survival benefit favouring adjuvant chemotherapy (odds ratio, 0.64; 95% confidence interval, 0.48 to 0.85), but one of the three randomized controlled trials included in this meta-analysis compared chemotherapy + radiotherapy versus radiotherapy. A published meta-analysis of individual patient data from 2310 patients with rectal cancer found that the mortality risk ratio was 0.857 (95% confidence interval, 0.734 to 0.999;  $p=0.049$ ) and the disease-free survival risk ratio was 0.767 (95% confidence interval, 0.656 to 0.882;  $p=0.0003$ ) favouring adjuvant chemotherapy with oral fluoropyrimidines compared with observation.

Chemotherapy versus radiotherapy: None of the three randomized controlled trials of chemotherapy versus radiotherapy found a benefit for overall survival or disease-free survival. The pooled results of the three randomized controlled trials confirmed no survival benefit (odds ratio [for death], 0.80; 95% CI, 0.58 to 1.10;  $p=0.17$ ).

Chemotherapy by portal vein infusion versus observation: A published meta-analysis of individual patient data from 673 patients with rectal cancer revealed a 4% reduction in the annual odds of death at five years treated with portal vein infusion ( $p$ -value not reported).

Chemotherapy + radiotherapy versus observation: A covariate-adjusted comparison of chemotherapy + radiotherapy compared with observation revealed significantly improved time to recurrence with chemotherapy + radiotherapy in one trial ( $p=0.005$ ). A second randomized controlled trial found a significant decrease in local recurrence rates (12% versus 30%;  $p=0.01$ ) as well as improvement in 5-year overall survival (64% versus 50%;  $p=0.05$ ) and 5-year recurrence-free survival rates (64% versus 46%;  $p=0.01$ ) favouring chemotherapy+ radiotherapy.

Chemotherapy + radiotherapy versus radiotherapy: Pooled analysis of three trials of chemotherapy + radiotherapy versus radiotherapy revealed a benefit for chemotherapy + radiotherapy for both survival (odds ratio, 0.58; 95% confidence interval, 0.37 to 0.92;  $p=0.019$ ) and local control (odds ratio, 0.50; 95% confidence interval, 0.27 to 0.92;  $p=0.025$ ).

Chemotherapy + radiotherapy versus chemotherapy: Pooled results from two trials showed no significant survival benefit for chemotherapy + radiotherapy versus chemotherapy (odds ratio=0.80; 95% confidence interval, 0.48 to 1.32;  $p=0.37$ ). In a third trial, the addition of radiotherapy to chemotherapy did not significantly improve disease-free survival (hazard ratio, 0.99; 95% confidence

interval, 0.80 to 1.22; p=0.90) or overall survival (hazard ratio, 0.98; 95% confidence interval, 0.78 to 1.24; p=0.89).

Comparison of chemotherapy + radiotherapy regimens: When chemotherapy with 5-fluorouracil was given concurrently with radiotherapy, continuous intravenous infusion (CII) was more effective than the drug administered by bolus. The addition of semustine to 5-fluorouracil was ineffective. Two trials found no improvement in survival when levamisole or leucovorin was added to 5-fluorouracil. Preliminary results of two randomized trials have been published in abstract form. In the first, the addition of interferon alfa-2b to adjuvant 5-fluorouracil, leucovorin and radiotherapy was not associated with significant improvements in recurrence or survival rates. The second trial failed to show a significant difference between six and 12 months of 5-fluorouracil plus medium-dose folinic acid in terms of relapse rates, disease-free survival and overall survival.

#### POTENTIAL HARMS

Enteritis, diarrhea, bowel obstruction or perforation, and fibrosis within the pelvis were associated with radiotherapy. Delayed adverse effects from radiotherapy included radiation enteritis (4%), small bowel obstruction (5%) and rectal stricture (5%). A greater number of hematological and non-hematological reactions were associated with chemotherapy + radiotherapy than with chemotherapy, radiotherapy or observation. Postoperative chemotherapy + radiotherapy was associated with acute gastrointestinal and hematologic adverse effects that may be severe or life-threatening.

### 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

### IDENTIFYING INFORMATION AND AVAILABILITY

#### BIBLIOGRAPHIC SOURCE(S)

Cancer Care Ontario Practice Guideline Initiative (CCOPGI). Postoperative adjuvant radiotherapy and/or chemotherapy for resected stage II or III rectal cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2001 Dec. Various p. (Practice guideline; no. 2-3). [51 references]

#### ADAPTATION

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

#### DATE RELEASED

1998 Sep 5 (updated online 2001 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 members, please see the [Cancer Care Ontario Web site](#).

#### FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Provincial 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:

- Postoperative adjuvant radiotherapy and/or chemotherapy for resected stage II or III rectal cancer. Summary. Toronto (ON): Cancer Care Ontario, 1998 Sep 5 (updated online 2001 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;13(2):502-12.

## PATIENT RESOURCES

None available

## NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 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 on July 30, 2003. The updated information was verified by the guideline developer on September 2, 2003.

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