CURRENT ONCOLOGY
A Canadian Cancer Research Journal

PRACTICE GUIDELINE

Adjuvant systemic chemotherapy for stages II and III colon cancer after complete resection: a clinical practice guideline

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ABSTRACT

Background Updated practice guidelines on adjuvant chemotherapy for completely resected colon cancer are lacking. In 2008, Cancer Care Ontario's Program in Evidence-Based Care developed a guideline on adjuvant therapy for stages II and III colon cancer. With newer regimens being assessed in this patient population and older agents being either abandoned because of non-effectiveness or replaced by agents that are more efficacious, a full update of the original guideline was undertaken.

Methods Literature searches (January 1987 to August 2015) of MEDLINE, EMBASE, and the Cochrane Library were conducted; in addition, abstracts from the American Society of Clinical Oncology, the European Society for Medical Oncology, and the European Cancer Congress were reviewed (the latter for January 2007 to August 2015). A practice guideline was drafted that was then scrutinized by internal and external reviewers whose comments were incorporated into the final guideline.

Results Twenty-six unique reports of eighteen randomized controlled trials and thirteen unique reports of twelve meta-analyses or pooled analyses were included in the evidence base. The 5 recommendations developed included 3 for stage II colon cancer and 2 for stage III colon cancer.

Conclusions Patients with completely resected stage III colon cancer should be offered adjuvant 5-fluorouracil (5FU)–based chemotherapy with or without oxaliplatin (based on definitive data for improvements in survival and disease-free survival). Patients with resected stage II colon cancer without "high-risk" features should not receive adjuvant chemotherapy. For patients with "high-risk" features, 5FU-based chemotherapy with or without oxaliplatin should be offered, although no clinical trials have been conducted to conclusively demonstrate the same benefits seen in stage III colon cancer.

Key Words Adjuvant treatment, chemotherapy, colon cancer, practice guidelines

Curr Oncol. 2016 Dec;23(6):418-424 www.current-oncology.com

INTRODUCTION

In Canada, colorectal cancer (CRC) is second only to lung cancer as a cause of cancer death, with an estimated 9300 deaths in 2015. Colorectal cancer is the 2nd most common cancer site when both sexes are combined, representing 12.7% of estimated new cancer cases, with approximately 25,100 new cases in 2015[1]. In men, CRC is the 2nd most common site; in women, it is the 3rd most common site[1].

Several guidelines on the use of adjuvant therapy for patients with stage II or III colon cancer after complete resection have been published in the past. In 1990, a U.S. National Institutes of Health consensus conference reviewed the available evidence and recommended adjuvant treatment with 5-fluorouracil (5FU) and levamisole for patients with curatively resected stage III colon cancer[2]. Many questions remained about other therapies. In 2008, Cancer Care Ontario's Gastrointestinal Disease Site Group (GI DSG) developed a systematic review and clinical practice guideline on adjuvant systemic chemotherapy for stages II and III colon cancer after complete resection. The guideline recommended adjuvant chemotherapy for

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stage III patients[3]. For patients with stage II disease, adjuvant chemotherapy was to be an option considered for the subset of patients with high-risk features such as inadequately sampled nodes, T4 lesions, perforation, or poorly differentiated histology. Recommended regimens included 5FU–leucovorin (LV) given intravenously in combination with oxaliplatin (FOLFOX or FLOX). Since the publication of that guideline in 2008, newer regimens have been assessed in this patient population, and some older agents have either been abandoned because of non-effectiveness or been replaced by agents that are more efficacious. The GI DSG therefore determined that a full update of the original guideline was warranted.

RESEARCH QUESTIONS

- What is the impact of adjuvant fluoropyrimidine-based systemic chemotherapy compared with observation on disease-free survival (DFS) and overall survival (OS) in patients with stage II or III colon cancer who have undergone complete resection with curative intent?
- What is the impact of adjuvant intravenous (IV) 5FU compared with oral fluoropyrimidines on DFS and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?
- What is the impact of adjuvant fluoropyrimidines compared with fluoropyrimidines plus oxaliplatin on DFS and OS in patients with
  - stage II or III colon cancer who have undergone complete resection with curative intent?
  - stage II colon cancer who have undergone complete resection with curative intent?
  - stage III colon cancer who have undergone complete resection with curative intent?
- What is the impact on DFS and OS of the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy in patients with stage II or III colon cancer who have undergone complete resection with curative intent?
- What is the impact of the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy on DFS and OS in younger compared with older (≤70 years vs. >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?
- What is the impact of adjuvant fluoropyrimidine monotherapy on DFS and OS in younger compared with older (≤70 years vs. >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?
- What is the impact of microsatellite instability status on DFS and OS with the addition of adjuvant chemotherapy in stage II patients with colon cancer who have undergone complete resection with curative intent?

METHODS

The GI DSG of Cancer Care Ontario's Program in Evidence-Based Care (PEBC) developed the present guideline. The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle[4,5]. The PEBC guidelines include an evidence review (typically a systematic review), an interpretation of that evidence and consensus agreement by its DSGs or panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant.

Search for Systematic Reviews

An overall search strategy was developed and implemented that captured both existing systematic reviews and primary literature in these databases: MEDLINE, EMBASE, the American Society of Clinical Oncology meeting abstracts, the European Society for Medical Oncology meeting abstracts, and the European Cancer Congress meeting abstracts. Identified systematic reviews were further evaluated based on their clinical content and the similarity of the questions they addressed to the questions and objectives of the present guideline. Systematic reviews that were found to be directly relevant and therefore potential foundations for the present evidence review were assessed using the AMSTAR tool[6].

Search for Primary Literature

The methods to be used for locating and evaluating the primary literature if no existing systematic reviews were to be identified, or if identified reviews were incomplete in some fashion, are described in the subsections that follow. Risk of bias was also assessed for each included primary study [see the Cochrane Handbook for Systematic Reviews of Interventions (http://handbook.cochrane.org/, part 2, section 8.5)].

Literature Search Strategy

Original: The MEDLINE (1987 through September 2007), EMBASE (1987 through week 38, 2007), CANCERLIT (1987 through October 2002), and Cochrane Library (through Issue 2, 2007) databases were searched. In addition, proceedings from the annual meetings of the American Society of Clinical Oncology (1998–2007) were searched for reports of newly completed trials. Personal reprint files and reference lists of relevant studies were also searched.

Updated: The MEDLINE (September 2007 to August 2015), EMBASE (week 38, 2007, to week 34, 2015), and Cochrane Library (since Issue 2, 2007) databases were searched to update the evidence found in the original PEBC guideline on adjuvant chemotherapy for stages II and III colon cancer. In addition, the American Society of Clinical Oncology, the European Society for Medical Oncology, and the European Cancer Congress meeting abstracts were searched for the period since September 2007. Reference lists of included studies were also searched.

Internal Review

All PEBC guidelines are reviewed by a panel of content experts (the Expert Panel) and a methodology panel [the Report Approval Panel (RAP)]. Both panels must approve the document. The Working Group was responsible for incorporating the feedback from both the panels and the required changes.

External Review

The PEBC external review process is two-pronged: a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content

experts, and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

RESULTS

Literature Search Results

Meta-analyses of Randomized Controlled Trials of Adjuvant Therapy, Version 1 (to 1987)

In 1988, Buyse *et al.*[7] conducted a meta-analysis of all English-language trials of adjuvant therapy for CRC (all stages included). Seventeen trials compared adjuvant chemotherapy with surgery alone in 6791 patients with CRC. The pooled results detected no significant differences in the odds of death (mortality odds ratio for treatment compared with control: 0.96; 95% confidence interval: 0.87 to 1.06). Stage could not be examined because of the lack of standardized staging methods. The comparison of untreated controls with the subgroup of patients treated with 5FU for at least 1 year detected a significant decrease in the odds of death (odds ratio: 0.83; 95% confidence interval: 0.70 to 0.98; $p = 0.03$).

Literature Search Results, Version 1 (1987–2007)

The literature search identified thirty-eight relevant reports representing thirty-one randomized controlled trials (RCTs) and thirteen meta-analyses of RCTs published after 1987. Where multiple reports were published for a single RCT, only the most recent report was included, unless older reports contained data that were not available in the most recent publication.

Literature Search Results, Version 2

The updated literature search identified publications containing more mature data of full publications included in version 1 of the present guideline and full publications of abstract data included in version 1. Publications of regimens no longer in use were excluded from the present version of the guideline. New trials were also identified that were published after 2007. The present version of the guideline includes twenty-six unique reports[8–33] representing eighteen RCTs that reflect the complete evidence base considered relevant by the Working Group. In addition, twelve meta-analyses or pooled analyses reported in thirteen publications[7,34–45] were included. One other new meta-analysis was identified. It was excluded because a number of the treatment modalities were pooled, and the contribution from systemic chemotherapy alone was unclear. Table I summarizes all studies included in the present update (that is, version 2).

Internal Review

Expert Panel Review and Approval

The GI DSG acted as the Expert Panel for this document. For a guideline to be approved, 75% of the GI DSG membership must cast a vote or abstain, and of those voting, 75% must approve the document. Of the 29 members of the GI DSG eligible to vote on the present guideline, 23 members cast votes and none abstained, for a total response rate of 79.3%. Of members who cast votes, 23 approved the document (100%).

RAP Review and Approval

Three RAP members reviewed the present document in March and April 2015. The RAP approved the document on 12 April 2015.

External Review

Targeted Peer Review

Five targeted peer reviewers from Ontario, Alberta, and British Columbia who are considered to be clinical or methodology experts on the topic (or both) were identified by the Working Group. Four agreed to be reviewers. Four responses were received.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals and other stakeholders who are the intended users of the guideline. All medical oncologists in the PEBC database with an interest in gastrointestinal cancers were contacted by e-mail to inform them of the survey. Of 120 identified stakeholders, 19 (16%) responded.

RECOMMENDATIONS AND KEY EVIDENCE: STAGE II COLON CANCER

Recommendation 1

The routine use of adjuvant chemotherapy for all patients with stage II colon cancer is not recommended. However, adjuvant therapy is a reasonable option for the subset of patients with high-risk stage II disease. Although there is controversy about the tumour features that denote "high risk" in stage II patients, this subset includes patients with inadequately sampled nodes, T4 lesions, perforation at the site of the tumour, or poorly differentiated histology in the absence of microsatellite instability. In those cases, the available treatment options are

- 5FU–LV–oxaliplatin (that is, FOLFOX, XELOX, or FLOX);
- capecitabine;
- 5FU–LV.

Qualifying Statements for Recommendation 1

- The clinical decision should be based on discussions with the patient about the nature of the evidence supporting treatment, the anticipated morbidity, the presence of high-risk prognostic features (individual prognosis), and patient preferences.
- No single RCT has been powered to demonstrate OS data for stage II or for high-risk compared with low-risk stage II disease. However, a clinical rationale, coupled with the methodologic limitations of the existing studies, led the Working Group to conclude that there might potentially be a role for adjuvant chemotherapy in a limited group of high-risk individuals.
- The enrolment of resected 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.

TABLE I Studies selected for inclusion

Study type	Trials (papers) in category (*n*)	References (not mutually exclusive)
Randomized controlled trials		
Fluoropyrimidine-based systemic chemotherapy vs. observation	10 (10)	8–11, 15, 16, 22–25
Oral fluoropyrimidines vs. intravenous 5FU	5 (8)	17–21, 27, 29, 32
Fluoropyrimidines–oxaliplatin vs. fluoropyrimidines	3 (7)	12–14, 28, 30, 31, 33
Fluoropyrimidines–oxaliplatin in stage II vs. stage III	1 (1)	12
Effect of chemotherapy in those ≤70 vs. >70 years of age	4 (4)	13, 17, 26, 31
Meta-analyses of randomized controlled trials		
Fluoropyrimidine-based chemotherapy vs. observation	11 (12)	7, 35–45
Microsatellite instability status of stage II patients	1 (1)	34

5FU = 5-fluorouracil.

- If adjuvant chemotherapy is considered, the following qualifying statements also apply:
  - 5FU–LV can be given intravenously in combination with oxaliplatin in the regimens known as FOLFOX or FLOX, or capecitabine may be given orally in combination with IV oxaliplatin in the regimen known as XELOX. Compared with 5FU–LV alone, these oxaliplatin-containing regimens have demonstrated superior OS and are the recommended regimens. Oxaliplatin administration is associated with a 12.5% risk of severe neuropathy that is permanent in 1% of patients, which has to be considered in conjunction with the expected benefits of therapy.
  - Owing to the toxicity profile of FLOX, that regimen is used less frequently than are the other oxaliplatin-containing regimens.
- Some patients would not be considered appropriate for oxaliplatin-containing regimens. Examples include patients with underlying neurologic conditions and those at increased risk of neuropathy. For such patients, the treatment options are
  - oral capecitabine, whose efficacy is equivalent to that of IV bolus 5FU–LV. Compared with bolus 5FU–LV, capecitabine results in significantly less diarrhea, stomatitis, neutropenia, nausea or vomiting, and alopecia, but significantly more hand–foot syndrome. Although not compared head-to-head with bolus 5FU–LV in clinical trials, infusional 5FU–LV is associated with fewer gastrointestinal side effects and less neutropenia; it has essentially become the standard route of 5FU administration.
  - 5FU–LV.

Key Evidence for Recommendation 1

None of the four adjuvant fluoropyrimidine-based trials that reported comparative OS data for patients with stage II colon cancer demonstrated a benefit for adjuvant chemotherapy compared with observation alone[8–11]. No separate OS data for high-risk and lower-risk stage II patients have been reported. The studies have an unclear risk of bias: all domains in the Risk of Bias assessment were rated as having either a low or unclear risk of bias.

Recommendation 2

When treated with adjuvant therapy, high-risk stage II patients should receive a fluoropyrimidine. The data in support of oxaliplatin providing additional benefit to all high-risk individuals are insufficient.

Qualifying Statements for Recommendation 2

- It would be reasonable to consider FOLFOX for high-risk patients as part of an informed discussion between the patient and the medical oncologists about treatment options.

Key Evidence for Recommendation 2

The addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy demonstrated no difference with respect to OS in stage II patients in both the MOSAIC[12] and NSABP C-07[13] trials. The MOSAIC subgroup analysis of low-risk and high-risk stage II patients demonstrated no significant OS benefit for fluoropyrimidine–oxaliplatin compared with 5FU–LV alone. However, the MOSAIC trial was underpowered for that comparison. Both studies have an unclear risk of bias: almost all domains in the Risk of Bias assessment were rated as having either a low or unclear risk of bias.

Recommendation 3

Adjuvant 5FU monotherapy after surgery in patients who have microsatellite instability (MSI) is not recommended. Testing for MSI should be performed for all stage II patients for whom adjuvant chemotherapy is being considered. In stage II patients who do not require adjuvant chemotherapy (in the absence of high-risk features), MSI testing is not recommended because it will not influence that decision.

Qualifying Statements for Recommendation 3

- In patients with high-risk stage II colon cancer (T4, for instance) and high MSI status (a low-risk factor), the choice of treatment is either observation or FOLFOX; however, data to guide this decision are lacking.

Key Evidence for Recommendation 3

One pooled analysis[34] demonstrated that OS was significantly worse in patients with MSI receiving adjuvant chemotherapy than in those who underwent surgery alone.

RECOMMENDATIONS AND KEY EVIDENCE: STAGE III COLON CANCER

Recommendation 4

It is recommended that patients with completely resected stage III colon cancer be offered adjuvant chemotherapy. Treatment should depend on factors such as patient suitability and preferences. Patients and clinicians must work together to determine the optimal course of treatment. The available treatment options are

- 5FU–LV–oxaliplatin (that is, FOLFOX, XELOX, or FLOX);
- capecitabine;
- 5FU–LV.

Qualifying Statements for Recommendation 4

- 5FU–LV can be given intravenously in combination with oxaliplatin in the regimens known as FOLFOX or FLOX, or capecitabine can be given orally in combination with IV oxaliplatin in the regimen known as XELOX. Compared with 5FU–LV, these oxaliplatin-containing regimens have demonstrated superior OS and are the recommended regimens. Oxaliplatin administration is associated with a 12.5% risk of severe neuropathy that is permanent in 1% of patients, which has to be considered in conjunction with the expected benefits of therapy.
- Owing to the toxicity profile of FLOX, that regimen is used less frequently than other oxaliplatin-containing regimens.
- Some patients would not be considered appropriate for oxaliplatin-containing regimens. Examples include patients with underlying neurologic conditions or those at increased risk of neuropathy. For such patients the treatment options are
  - oral capecitabine, whose efficacy is equivalent to that of IV bolus 5FU–LV. Compared with bolus 5FU–LV, capecitabine results in significantly less diarrhea, stomatitis, neutropenia, nausea or vomiting, and alopecia, but significantly more hand–foot syndrome. Although not compared head-to-head with bolus 5FU–LV in clinical trials, infusional 5FU–LV is associated with fewer gastrointestinal side effects and less neutropenia, and has essentially become the standard route of 5FU administration.
  - 5FU–LV.
- Suitable patients should be offered entry into clinical trials testing new adjuvant treatments for resected stage III colon cancer.
- In the adjuvant randomized controlled trials of resected colon cancer, patients have begun their adjuvant treatment within 4–9 weeks of surgery.

Key Evidence for Recommendation 4

The addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy demonstrated a significant benefit with respect to OS in stage III patients in both the MOSAIC[12] and XELOXA[14] trials. Those studies have an unclear risk of bias: almost all domains in the Risk of Bias assessment were rated as having either a low or unclear risk of bias.

Two of the four[8,10,15,16] adjuvant fluoropyrimidine-based trials that reported comparative OS data for patients with stage III colon cancer demonstrated a benefit for 5FU (with or without LV) compared with observation alone[10,15]. Those studies have an unclear risk of bias: almost all domains in the Risk of Bias assessment were rated as having either a low or unclear risk of bias.

With respect to OS, oral capecitabine has efficacy equivalent to that for IV 5FU–LV[17]. The other studies looking at this comparison did not report *p* values[18–20] or did not report on stage III patients separately[21]. These studies have an unclear risk of bias: almost all domains in the Risk of Bias assessment were rated as having either a low or unclear risk of bias.

Recommendation 5

- Although *post hoc* analyses of studies have not shown a clear benefit of adjuvant fluoropyrimidine–oxaliplatin regimens in patients more than 70 years of age, it is reasonable to consider oxaliplatin-containing regimens for patients more than 70 years of age as part of an informed discussion between the patient and the medical oncologist about treatment options.

Key Evidence for Recommendation 5

- No OS benefit of adjuvant fluoropyrimidine–oxaliplatin regimens was observed in patients more than 70 years of age in any of three trials that performed this *post hoc* subgroup analysis[12–14]. These studies have an unclear risk of bias: almost all domains in the Risk of Bias assessment were rated as having either a low or unclear risk of bias. Caution must be exercised when interpreting *post hoc* subgroup analyses.

CONCLUSIONS

Stage II

The routine use of adjuvant chemotherapy for all patients with stage II colon cancer is not recommended. However, adjuvant therapy is an option for the subset of patients with high-risk stage II disease. The choice of chemotherapy (fluoropyrimidine with or without oxaliplatin) has to take into account a number of pathologic and patient factors. Patients 70 years of age and younger might derive greater DFS and OS benefit from adjuvant chemotherapy than do patients more than 70 years of age (based on subgroup analyses from the MOSAIC and NSABP C-07 trials). Stage II patients with MSI might experience an OS detriment if given adjuvant chemotherapy.

Stage III

Patients with completely resected stage III colon cancer should be offered adjuvant chemotherapy. The recommended treatment options include the numerous variations of fluoropyrimidine with and without oxaliplatin as discussed here. This recommendation is based on evidence for improved DFS and OS at 5 years with oxaliplatin regimens compared with 5FU–LV alone. For patients with a contraindication to oxaliplatin or for whom the adverse effects of oxaliplatin are unacceptable, the treatment options are oral capecitabine or IV 5FU–LV. Patients 70 years

of age and younger might derive greater DFS and OS benefit from adjuvant chemotherapy than do patients more than 70 years of age.

ACKNOWLEDGMENTS

The PEBC GI DSG and the Working Group thank Melissa Brouwers, Bill Evans, Donna Maziak, Sheila McNair, and Hans Messersmith for providing feedback on draft versions. They also thank Judy Brown for conducting the document assessment and review of the original version of this guidance document, and Kristy Yiu for conducting the data audit.

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

This clinical practice guideline is an update of a guideline published in 2011[3].

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: BMM has previously published abstracts of meta-analyses of adjuvant 5FU chemotherapy compared with observation in stage II colon cancer patients. All the other authors declare that they have no conflicts to disclose.

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